UNITED STATES
CONSUMER PRODUCT SAFETY COMMISSION
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Memorandum

Date: October 25, 2010

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SUBJECT : Toxicity Review of **Diethyl phthalate (DEP)**

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 **DEP**.

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

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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 DIETHYL PHTHALATE (DEP)

Contract No. CPSC-D-06-0006
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LIST OF ABBREVIATIONS AND ACRONYMS

ACP	Acid phosphatase
AGD	Anogenital distance
AGI	Anogenital index
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
DBP	Dibutyl phthalate
DBT	Dibutyl terephthalate
DEP	Diethyl phthalate
DMBA	7,12-dimethylbenzanthracene
DNA	Deoxyribonucleic acid
FEV_1	Forced expiratory volume at 1 second
FVC	Forced vital capacity
GD	Gestation day
LDH	Lactate dehydrogenase
LOAEL	Lowest-observed-adverse-effect level
LD_{50}	Median lethal dose
MEP	Monoethyl phthalate
NHANES	National Health and Nutrition Examination Survey
NOAEL	No-observed-adverse-effect level
NTP	National Toxicology Program
PND	Postnatal day
SD	Standard deviation
SE	Standard error
TPA	12-O-tetradecanoylphorbol-13-acetate
TWA	Time-weighted average

EXECUTIVE SUMMARY

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

Oral exposure to DEP resulted in oral LD_{50}s > 5,500 – 31,000 mg/kg in rat studies, 6,172 – 8,600 mg/kg in mice studies, > 4,000 – 8,600 mg/kg in guinea pig studies, and 5,000 mg/kg in a dog study. Dermal exposure to DEP resulted in dermal LD_{50}s > 11,000 mg/kg in rats and >22,000 mg/kg in guinea pigs. Acute inhalation exposure resulted in an inhalation LC_{50} of > 4.64 mg/L in a poorly documented rat study. Dermal application of DEP to human test subjects in multiple studies did not induce any irritation. Dermal exposure to DEP in rabbits, guinea pigs, and rats resulted in moderate to no irritation. Ocular exposure to DEP in multiple rabbit studies resulted in slight to no ocular irritation. Three human studies and two guinea pig studies were negative for sensitization following standard induction and challenge protocols.

Sufficient animal data supported the conclusion that oral exposure to DEP induced toxicity in a variety of organ systems such as the liver and kidney. Maternal exposure to DEP also induced developmental effects (i.e. increased number of variations) in litters not affected by maternal toxicity. In addition, DEP exposure altered reproductive parameters in some studies (i.e. gestation length). Additional items of questionable significance following chronic dermal exposure included changes in brain weight, erythrocytes, hematocrit and hemoglobin, and other organ systems.

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 estimated for DEP relevant exposure durations for the general population and for other sensitive subpopulations because data on toxicological endpoints were corroborated in multiple quality studies.

In summary, data supports the conclusion that DEP can be considered "toxic" under the FHSA due to its toxicity following short- and long-term exposures. This conclusion was based on the sufficient evidence in animals of DEP-induced toxicity to the liver and other tissues.

When considering FHSA criteria, products that contain DEP may be considered "hazardous" if long-term exposures to the general population during "reasonably foreseeable handling and use" exceed the long-term ADI for the general population (0.33 mg DEP/kg bw-day).

In addition, products that contain DEP may be considered "hazardous" if short-term exposures during "reasonably foreseeable handling and use" exceed the short-term ADI for reproductive effects (1.47 mg DEP/kg bw-day).

In addition, products that contain DEP may be considered "hazardous" if exposures to reproductively viable female populations (13 to 49 years of age) during "reasonably foreseeable handling and use" exceed the ADI for developmental effects (3.82 mg DEP/kg bw-day).

Insufficient evidence (hazard data) precluded the generation of ADI's for inhalation or dermal exposures or for cancer endpoints.

TOXICITY REVIEW FOR DIETHYL PHTHALATE (DEP, CASRN 84-66-2)

1. INTRODUCTION

This report summarizes available data on the identity, physicochemical properties, manufacture, supply, use, toxicity, and exposure associated with diethyl phthalate (DEP). This assessment was prepared from a variety of review articles (NICNAS, 2008; EPA, 2010; ECB, 2006) as well as supplemental independent studies retrieved from literature searching.

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

2. IDENTITY and PHYSICOCHEMICAL CHARACTERISTICS

This section highlights the identity and key physico-chemical properties of DEP. DEP is comprised of a pair of 2-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*).

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

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

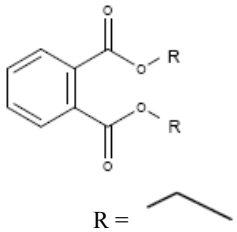
Table 2.1 Names, Structural Descriptors, and Molecular Formulas of DEP (NICNAS, 2008)	
CAS Number:	84-66-2
Chemical Name:	1,2-Benzenedicarboxylic acid, diethyl ester
Common Name:	Diethyl phthalate (DEP)
Molecular Formula:	C12H14O4
Structural Formula:	
Molecular Weight:	222.30
Synonyms:	Diethyl phthalate; Phthalate, diethyl; Ethyl phthalate; Phthalic acid, diethyl ester; o-Benzenedicarboxylic acid diethyl ester, o-Bis(ethoxycarbonyl)benzene
Purity/Impurities/Additives:	Purity: ≥ 99.70 – 99.97 % w/w; Impurities: isophthalic, terephthalic acid and maleic anhydride; Additives: none

Table 2.2 Physicochemical Properties of DEP	
Property	**Value**
Physical state	Clear, colorless, odorless liquid (NICNAS, 2008)
Melting point	-40.5°C (HSDB, 2009); -40°C (U.S. EPA, 2010)
Boiling point	298°C (295°C-302°C; NICNAS, 2008); 295°C (HSDB, 2009; U.S. EPA, 2010)
Density	1120 kg/m^3 (25°C; NICNAS, 2008; HSDB, 2009)
Vapor pressure	2.19 x 10^{-4} kPa (25°C; NICNAS, 2008)
Water solubility	1 g/L (25°C; NICNAS, 2008)
Partition coefficient n-octanol/water (log Kow)	2.47-2.51 (NICNAS, 2008); 2.47 (HSDB, 2009); 2.21-3.27 (U.S. EPA, 2010)
Henry's law constant	7.9x10^{-5} kPa.m^3/mol (25ºC; NICNAS, 2008); 6.1x10^{-7} atm-m^3/mole (25ºC; HSDB, 2009; U.S. EPA, 2010)
Flash point (open cup)	161°C (HSDB, 2009)

3. MANUFACTURE, SUPPLY, AND USE

Manufacture

In general, DEP is manufactured commercially in a closed system by esterifying phthalic anhydride with ethanol using a concentrated sulfuric acid catalyst. As with other phthalates, the unreacted alcohols are recovered and reused, and the DEP mixture is purified by vacuum distillation or activated charcoal. The purity of DEP can achieve 99% or greater using current manufacturing processes (HSDB, 2009). The remaining fraction of the DEP commercial mixture can also contain impurities such as isophthalic, terephthalic acid, and maleic anhydride (Harris et al., 1997; ATSDR, 1995).

Eastman Chemical Company recently announced that they will no longer manufacture DEP after December 31, 2011 (Eastman, 2011). According to Eastman, the company intends to substitute DEP with benzoate plasticizers and a non-phthalate plasticizer known as dibutyl terephthalate (DBT). BASF has previously marketed DEP as Palatinol® A for use as with cellulose acetate and nitrate blister films or surface coatings. Moreflex, Inc., a subsdiary of Reilly Industries, currently markets DEP online and Huls America, Inc. has been reported in other federal publications as one of the four manufacturers of DEP in the United States (ATSDR, 1995).

Supply

U.S. production of DEP declined to approximately 5,000 metric tons in 1995 after peaking at 12,000 metric tons in 1988. Since 1995, production has remained relatively stable with only a slight decrease happening from 2005-2008 (to 4,500 metric tons). DEP's proportion of the total phthalate production market has been projected to remain stable at 0.8% into 2013, but this projection is questionable considering Eastman's plans to discontinue manufacture at the end of 2011 (Bizzari, 2007, 2009).

U.S. consumption (in metric tons) of DEP has historically been about 1,000 metric tons higher than production and DEP's proportion of the total phthalate consumption market has been projected to remain stable at 1.0% into 2013 (this estimation does not consider Eastman's

discontinuation of DEP). Historical numbers suggest that most DEP produced in the U.S. is utilized locally. Other DEP is primarily imported from India and Italy and used to some extent in perfumery, flavor, and fragrance applications.

Use

LMWPE's (i.e. DEP) are used primarily as solvents or in cellulose acetate polymers, and not in PVC manufacture because of their high volatility (ECB, 2006; Godwin, 2010). In fact, approximately 5,200 of the 5,800 metric tons consumed in 2008 was utilized to make cellulose acetate, cellulose acetate butyrate, and cellulose acetate proprionate for film materials, tool handles and adhesives (ATSDR, 1995). The non-confidential industrial processing and uses reported in the 2006 Inventory Update Rule submission for DEP included chemical product and preparation manufacturing and soap and cleaning compound manufacturing (U.S. EPA, 2010). The non-confidential commercial and consumer use included adhesives and sealants, rubber and plastic products, soaps, and detergents (U.S. EPA, 2010). DEP has been used in epoxy resins, cosmetics, pharmaceutical and personal care products, and children's toys (NICNAS, 2008). According to the Cosmetic Ingredient Review Expert Panel, the highest reported concentration of DEP in perfumes is 11% (CIR, 2003). Other uses noted in HSDB (2009) and ATSDR (1995) include solvent for manufacturing cellulose acetate, plasticizer, alcohol denaturant, fragrance and cosmetic ingredients (≤ 0.1% to 25-50%; bath preparations (oils, tablets, and salts), eye shadows, toilet waters, perfumes and other fragrance preparations, hair sprays, wave sets, nail polish and enamel removers, nail extenders, nail polish, bath soaps, detergents, aftershave lotions, and skin care preparations), photograph sheets, blister packages, adhesive tapes, toothbrushes, auto components, toys, tool handles, insecticidal sprays and repellents, in solid rocket propellents, in dye applications, aspirin coatings, dental impression materials, and in other adhesives and surface lubricants used in food and pharmaceutical products.

DEP has also been reported from a variety of food items including cranberries, baked potatoes, roasted filberts, oysters, clams, and fish (NTP, 1995).

4. TOXICOKINETICS

Available in vivo and in vitro animal and human data indicate that orally-administered DEP is rapidly absorbed, metabolized, and excreted in the urine predominantly as monoethyl phthalate (MEP). Rats and mice were administered [^{14}C]-DEP orally and assessed for at least 48 hours postadministration for radioactivity in tissues, urine, and feces (Ioku et al., 1976, as reported in Api, 2001). Maximum concentrations of radioactivity were observed within 20 minutes postadministration and were highest in kidney and liver, followed by blood, spleen, and fat. By 24 hours postadministration, only trace levels of internal radioactivity were found. Urinary and fecal excretion were 47 and 0.7%, respectively, for the first 12 hours and reached 90 and 2.7% by 48 hours postadministration. In Wistar rats administered DEP (10 or 100 mg) by gavage, daily urine collections revealed that for both doses, >75% of the administered dose was excreted in the urine within the first 24 hours as MEP (67–70%), phthalic acid (8–9%), and parent compound (0.1–0.4%); between 83 and 90% of the administered dose had been excreted in the urine by 1 week postadministration (Kawano, 1980).

Hydrolysis of DEP to MEP has been demonstrated in vitro in preparations from gastrointestinal tissues of rats, baboons, ferrets, and humans (Lake et al., 1977; Rowland et al., 1977); liver of rats, mice, baboons, and ferrets (Kayano et al., 1997; Lake et al., 1977; Rowland et al., 1977), mouse kidney and lung (Kayano et al., 1997), and rat and human skin (Hotchkiss and Mint, 1994). DEP induced carboxylesterases from human, rat, and mouse liver (Mentlein and Butte, 1989; Ashour et al., 1987) and rat and mouse kidney (Ashour et al., 1987). Kayano et al. (1997) isolated an esterase from mouse hepatic microsomes that hydrolyzed DEP to MEP, but further hydrolysis of MEP was not observed even after prolonged incubation.

Dermally-applied DEP is readily absorbed, metabolized, and excreted in the urine. In a 2-week single-blinded study, 26 healthy Caucasian male subjects received whole-body applications of a basic cream formulation once per day for 5 consecutive days (control week 1) followed by five daily topical applications (treatment week 2) of the basic cream formulation containing 2% (v/v) DEP (as well as 2% dibutyl phthalate and 2% butyl paraben). Each subject was administered the cream at 2 mg/cm^2 of body surface area. Blood samples (Janjua et al., 2007) were collected just prior to the start of the control (week 1) and treatment (week 2) periods, and at 1, 2, 3, 4, 24, 96, and 120 hours following the first application on weeks 1 and 2. All urine was collected during weeks 1 and 2 (Janjua et al., 2008). Blood and urine were analyzed for levels of MEP.

Levels of MEP were measurable in all serum samples and 24-hour urine samples (Janjua et al., 2008, 2007). Serum MEP levels were 12 ± 1 µg/L (mean ± standard error [SE]) for week 1 and 7 ± 1 µg/L just prior to the initial application of test material on week 2; these values represented baseline MEP levels prior to the initiation of dermal DEP treatment. At 2 hours following the initial application of test material, the serum MEP level peaked at 1,001 ± 81 µg/L and decreased thereafter to 22 µg/L by 24 hours postapplication. Serum MEP was 60 µg/L on treatment day 5. Urinary MEP excretion was 565 ± 42 µg for week 1 and 40,996 ± 1,889 µg for week 2. The majority of urinary MEP was excreted during the first 8 hours postapplication. Total urinary MEP consisted of approximately 80% in free form and 20% in glucuronidated form. The study authors estimated that 5.79% of the dermally-administered DEP had been absorbed based on urinary recovery of MEP.

Elsisi et al. (1989) applied [^{14}C]-DEP to the skin of male F344 rats (n=3) at 5–8 mg/cm^2 (30–40 mg/kg) under occluded conditions for 7 days, during which time urine and feces were collected for analysis of radioactivity. Rats were sacrificed on day 7 and radioactivity was measured in major organs and tissues. In the first 24 hours postapplication, 24 and 1% of the administered radioactivity was recovered in urine and feces, respectively. During the 7-day postapplication period, urine and feces accounted for 50% of the administered radioactivity. At sacrifice, 34% of the administered radioactivity was found on the application site, 4% in the occlusion material, and <1% in body organs and tissues.

Following application of an unspecified dose of [^{14}C]-DEP to rabbit skin, approximately 49 and 1% was recovered in the urine and feces, respectively, during 4 days postapplication; <1% of the radioactivity was found in liver, kidney, and blood combined (RIFM, 1973; as cited in NICNAS, 2008).

In vitro studies demonstrate that rat skin is more permeable to DEP than human skin. Mint et al. (1994) applied [^{14}C]-DEP (neat) to rat and human skin samples for 72 hours and found absorption to be 35.9 ± 2.9 and 38.4 ± 2.5% (mean ± standard deviation [SD]) for occluded and unoccluded rat dorsal skin, respectively, and 3.9 ± 1.2 and 4.8 ± 0.7% for occluded and unoccluded human breast skin, respectively. Using in vitro test conditions similar to those employed by Mint et al. (1994), Scott et al. (1987) measured steady-state absorption rates of 41.37 ± 9.28 and 1.27 ± 0.11 µg/cm^2/hour (mean ± SE) for the rat and human skin, respectively. Lag times for the rat and human skin preparations were 1.1 and 6.0 hours, respectively. Frasch et al. (2007) assessed the absorption of DEP across hairless guinea pig skin in vitro and

calculated steady-state absorption rates of 11.77 ± 4.14 μg/cm^2/hour (mean ± SD) for DEP neat and 22.74 ± 9.32 μg/cm^2/hour for saturated DEP in aqueous solution.

Silva et al. (2004) reported detectable levels of MEP and other monoester metabolites of phthalates in >75% of 2,540 urine samples collected from U.S. participants (≥6 years of age) of the National Health and Nutrition Examination Survey (NHANES) 1999–2000. Non-Hispanic blacks exhibited significantly higher levels of MEP than Mexican-Americans and non-Hispanic whites and children had significantly lower concentrations of MEP than adolescents and adults. MEP levels were significantly higher in women than men. In subsets of urine (n=262) and serum (n=93) samples from the U.S. population, Silva et al. (2003) found that approximately 71% of the urinary MEP was in its free form, the remainder was MEP-glucuronide. MEP has been detected in human breast milk (Main et al., 2006).

Singh et al. (1975) detected radioactivity in maternal blood, fetal tissue, amniotic fluid, and placenta following intraperitoneal administration of [^{14}C]-DEP to pregnant rats on gestation day (GD) 5 or 10.

5. HAZARD INFORMATION

This section contains brief hazard summaries of the adverse effects of DEP 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 DEP resulted in oral LD_{50}s > 5,500 – 31,000 mg/kg in rat studies, 6,172 – 8,600 mg/kg in mice studies, > 4,000 – 8,600 mg/kg in guinea pig studies, and 5,000 mg/kg in a dog study. Dermal exposure to DEP resulted in dermal LD_{50}s > 11,000 mg/kg in rats and >22,000 mg/kg in guinea pigs. Acute inhalation exposure resulted in an inhalation LC_{50} of > 4.64 mg/L in a poorly documented rat study. Dermal application of DEP to human test subjects in multiple studies did not induce any irritation. Dermal exposure to DEP in rabbits, guinea pigs, and rats resulted in moderate to no irritation. Ocular exposure to DEP in multiple rabbit studies resulted in slight to no ocular irritation. Three human studies and two guinea pig studies were negative for sensitization following standard induction and challenge protocols.

Sufficient animal data supported the conclusion that oral exposure to DEP induced toxicity in a variety of organ systems such as the liver and kidney. Maternal exposure to DEP also induced developmental effects (i.e. increased number of variations) in litters not affected by maternal toxicity. In addition, DEP exposure altered reproductive parameters in some studies (i.e. gestation length). Additional items of questionable significance following chronic dermal

exposure included changes in brain weight, erythrocytes, hematocrit, and hemoglobin, and other organ systems.

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 estimated for DEP relevant exposure durations for the general population and for other sensitive subpopulations because data on toxicological endpoints were corroborated in multiple quality studies.

In summary, data supports the conclusion that DEP can be considered "toxic" under the FHSA due to its toxicity following short- and long-term exposures. This conclusion was based on the sufficient evidence in animals of DEP-induced toxicity to the liver and other tissues.

When considering FHSA criteria, products that contain DEP may be considered "hazardous" if long-term exposures to the general population during "reasonably foreseeable handling and use" exceed the long-term ADI for the general population (0.33 mg DEP/kg bw-day).

In addition, products that contain DEP may be considered "hazardous" if short-term exposures during "reasonably foreseeable handling and use" exceed the short-term ADI for reproductive effects (1.47 mg DEP/kg bw-day).

In addition, products that contain DEP may be considered "hazardous" if exposures to reproductively viable female populations (13 to 49 years of age) during "reasonably foreseeable handling and use" exceed the ADI for developmental effects (3.82 mg DEP/kg bw-day).

Insufficient evidence (hazard data) precluded the generation of ADI's for inhalation or dermal exposures or for cancer endpoints.

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

Groups of male and female albino rats (5/sex/dose) were administered DEP at 0.5, 1.0, 2.0, or 5.0 mL/kg by gavage (neat) and observed for 14 days following dosing; two separate DEP samples were tested (CPTC, 1978a). In one test, a single high-dose male exhibited slight depression at 24 hours following dosing; the depression persisted through posttreatment day 4 and the rat was found dead on posttreatment day 5. In the other test, mortality occurred in a single female of the 1.0 mL/kg dose group. There were no other mortalities in either test. The median lethal dose (LD_{50}) was >5.0 mL/kg (5,500 mg/kg based on a density of 1.1 g/mL for DEP).

Secondary sources list acute oral LD_{50} values of >5,500–31,000 mg/kg for rats; 6,172–8,600 mg/kg for mice; >4,000–8,600 mg/kg for guinea pigs; and 5,000 mg/kg for dogs (U.S. EPA, 2010; NICNAS, 2008; WHO, 2003; SCCNFP, 2001; European Commission, 2000). A report of an oral LD_{50} of 1,000 mg/kg for rabbits was attributed to a 1934 Dissertation by Kemp (given name and dissertation title not available) from Würzburg (as cited in Peakall, 1975). An unspecified number of rabbits administered DEP by gavage at 3 mL/kg (3,300 mg/kg based on a density of 1.1 g/mL) daily for 8 consecutive days and observed for 2 weeks following the last dosing survived and appeared normal except for what was described as "temporary distress" (Blickensdorfer and Templeton, 1930).

Sufficient information is provided in animal studies to conclude that the majority of DEP LD_{50}s in a variety of animal species 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 DEP 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

Groups of male and female albino rats (3/sex/group) received a single 24-hour occluded dermal application of DEP at 1.0, 2.0, 5.0, or 10.0 mL/kg and were observed for 14 days; two separate DEP samples were tested (CPTC, 1978b). There were no mortalities in either test. The dermal LD_{50} was >10 mL/kg (11,000 mg/kg based on a density of 1.1 g/mL for DEP).

Guinea pigs (1/group) receiving single 24-hour occluded dermal application of DEP at 0, 5, 10, or 20 mL/kg (0–22,000 mg/kg based on a density of 1.1 g/mL) survived a 14-day posttreatment period (U.S. EPA, 2010). A guinea pig dermal LD_{50} of 3,000 mg/kg was reported by SCCNFP (2001); however, the primary source was not located.

Sufficient information is provided in the referenced animal studies to demonstrate 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. DEP, 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 deaths occurred in rats (3/group) exposed whole body to DEP as a mixture of aerosol and vapor at 0 or 4.64 mg/L (nominal) for 6 hours and observed for 14 days following exposure (U.S. EPA, 2010; Eastman Kodak, 1978). Secondary sources list inhalation LC_{50} values of 4.9 in mice and 7.5 mg/L in rats for DEP, but no details were provided and the reliability of these data cannot be assessed (NICNAS, 2008; SCCNFP, 2001; European Commission, 2000).

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

5.4. Primary Skin Irritation

Api (2001) reported no signs of skin irritation in summarizing information from several studies of volunteers who were exposed to DEP (undiluted) by single or repeated occluded dermal application. This includes a closed patch test using 0.5 mL of undiluted DEP in 45 adult subjects, a 10-day occluded patch test featuring daily application of 0.05 mg/cm^2 of undiluted DEP in 16 volunteers, and a 48-hour closed patch test in 26 volunteers. In all, data were available for 576 individuals exposed to undiluted DEP on the skin with no irritant reactions.

Multiple studies in rabbits, guinea pigs, and rats of skin irritation following single or repeated dermal applications of undiluted DEP to intact or abraded skin under open or occluded conditions for 4–24 hours produced responses ranging from no irritation to slight-to-moderate irritation (Api, 2001; SCCNFP, 2001). The National Toxicology Program (NTP, 1995) found that long-term repeated dermal application of DEP (99% pure) at 100 or 300 μL produced mild dermal acanthosis in rats.

Dermal irritation was not noted in any of 576 human subjects exposed dermally to DEP. No, slight, and moderate irritation was observed following exposure to a variety of laboratory animals. Dermal acanthosis (dermal hyperplasia) was reported following long-term rat dermal exposures to DEP.

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

Sufficient human evidence also supported the conclusion that DEP did not fit the definition of a "primary [dermal] irritant" when considering FHSA criteria (16 CFR §1500.3(c)(4)).

This conclusion did consider that certain animal studies reflected a variety of dermal conditions, some of which included irritation. Animal data were deemed of lesser importance, however, when compared to the large amount of human exposure data that existed for DEP.

5.5. Primary Eye Irritation

Results of multiple studies indicate that undiluted DEP (0.1 mL) is not irritating or only slightly irritating to the rabbit eye following ocular instillation, with or without washing (Api, 2001).

The weight of evidence including sufficient animal data supported the conclusion that DEP did not fit the definition of an ocular "corrosive" as outlined in the FHSA (16 CFR §1500.3(c)(4)).

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

5.6. Sensitization

DEP did not induce sensitization responses in several studies of healthy volunteers receiving repeated dermal applications of DEP (undiluted or in ethyl alcohol solvent) in the induction phase followed by dermal challenge at a naïve site (Api, 2001). This includes a Kligman maximization test with 10% DEP in 25 subjects, a second similar study in 26 subjects, and a third study in which 42 subjects were repeatedly exposed to 0.5 mL of undiluted DEP and another 37 subjects were similarly treated with 50% DEP in ethyl alcohol. DEP did not typically induce sensitization responses in numerous studies featuring patch testing of patients or workers with signs of dermatitis; occasional positive responses may have been the result of cross-sensitization (Api, 2001).

DEP did not induce dermal irritation or sensitization responses in guinea pigs receiving 24-hour occluded dermal applications of 0.5 mL DEP (50% aqueous solution) 3 times weekly for 3 weeks in the induction phase and challenged 2 weeks later on the same area and a naïve area as well (Api, 2001). No sensitization response was elicited in Himalayan white-spotted guinea pigs tested with undiluted DEP using methods that included an open epicutaneous test, the Draize intradermal test, the guinea pig maximization test, and the Freund's complete adjuvant test (Klecak, 1979; Klecak et al., 1977; as cited in Api, 2001).

A sufficient weight of human and animal evidence suggests that DEP does not fit the definition of a “strong sensitizer” as defined in the FHSA (16 CFR §1500.3(c)(5)).

REPEAT DOSE TOXICITY

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

No treatment-related mortality, clinical signs of toxicity, or effects on body weight were observed in repeated-dose studies of rats or mice administered DEP via daily gavage for 1–4 weeks (including periods of gestation and/or lactation in some studies) at dose levels ranging from 500 to 4,500 mg/kg-day (Kwack et al., 2009; Gray et al., 2000; Hardin et al., 1987). Significantly depressed body weight (15–25% less than controls) was noted in rats administered DEP in the diet for 16 weeks at a concentration of 5% (3,160 and 3,710 mg/kg-day for the males and females, respectively) (Brown et al., 1978). Significantly depressed terminal body weight (8–12% lower than controls) was reported in F1 (but not F0) parental CD-1 mice administered DEP in the diet during premating, mating, and gestation periods at a concentration of 2.5% (4,509 and 4,878 /kg-day for the males and females, respectively) (Lamb et al., 1987; NTP, 1984). In another two-generation reproductive toxicity study, no clinical signs or toxicologically significant effects were seen in Sprague-Dawley rats administered DEP in the diet at concentrations up to 15,000 ppm (1,016–1,375 mg/kg-day) (Fujii et al., 2005).

No toxicologically significant effects on clinical signs or body weight were seen in rats or mice administered DEP by repeated dermal applications for 4 weeks at doses up to 3,227 mg/kg-day (rats) or 6,340 mg/kg-day (mice) or in other rats and mice dosed for up to 105 weeks at up to 1,170 mg/kg-day (rats) or 834 mg/kg-day (mice) (NTP, 1995).

5.8. Respiratory

Hoppin et al. (2004) reported a significant association ($p < 0.05$) between urinary MEP levels and decreased forced vital capacity (FVC) and forced expiratory volume at 1 second (FEV_1) within a group of 100 males selected from 289 participants of the NHANES III) whose urine was analyzed for levels of selected phthalates. No significant association was found among a group of 140 females selected from NHANES III participants. The study authors suggested that MEP may influence pulmonary function among adult males.

5.9. Hepatotoxicity

Increases in liver weight were reported in several oral studies. Increases in absolute and relative liver weight up to 14% were observed in parental F0 and F1 male and female rats receiving DEP from the diet at approximately 1,016 mg/kg-day (males) or 1,375 mg/kg-day (females) for up to 15–17 weeks, although histopathologic evaluations revealed no signs of DEP-induced liver lesions (Fujii et al., 2005). Higher DEP doses caused more marked increases in liver weight (as much as 31–33% higher in rats receiving DEP from the diet at 3,160–3,710 mg/kg-day for 16 weeks in the absence of histopathologic liver lesions) (Brown et al., 1978). An 18–28% increase in liver weight was seen in adult F1 male and female mice treated with 4,509–4,878 mg/kg-day in the diet in a multigeneration study; liver histopathology was not evaluated in this study (Lamb et al., 1987; NTP, 1984). No effect on liver weight was seen in young male rats treated with 500 mg/kg-day of DEP for 4 weeks (Kwack et al., 2009).

Studies by Pereira and co-workers (Pereira et al., 2006, 2007; Pereira and Rao, 2007) reported a host of changes in liver endpoints, including serum and liver chemistry, liver weight, and histopathology, in rats exposed to doses as low as 0.57 mg/kg-day for 5 months. However, it is questionable whether DEP was the cause of the observed effects. The effects reported are generally not consistent with other studies of DEP or other phthalates, and the dose levels are orders of magnitude lower than DEP treatment-related effect levels identified in other repeated-dose oral studies. The one study that included multiple dose levels reported no clear dose-response or the reverse of the usual dose-response pattern (changes were seen at the low dose, but not the mid or high doses) for most altered endpoints.

No effects on liver weight or gross or histopathology of the liver were seen in studies of rats and mice administered DEP by repeated dermal applications at doses as high as 3,227 mg/kg-day (rats) and 6,340 mg/kg-day (mice) for 4 weeks or as high as 1,170 mg/kg-day (rats) and 834 mg/kg-day (mice) for 105 weeks (NTP, 1995).

The weight of evidence from the above studies supported the conclusion that there was "sufficient animal evidence" for the designation of DEP as a "hepatotoxicant".

5.10. Renal Toxicity

Increases in kidney weight were reported in several oral studies. A 7–9% increase in kidney weight was observed in F1 parental female rats receiving DEP from the diet at approximately 1,375 mg/kg-day for up to 17 weeks, but not F0 females or F0 or F1 males; histopathologic evaluations revealed no signs of DEP-induced kidney lesions (Fujii et al., 2005). Higher DEP doses caused more marked increases in kidney weight (as much as 18% higher in male rats receiving DEP from the diet at 3,160 mg/kg-day for 16 weeks in the absence of histopathologic lesions) (Brown et al., 1978). No effect on kidney weight was seen in young male rats treated with 500 mg/kg-day of DEP for 4 weeks (Kwack et al., 2009).

No effects on kidney weight or gross or histopathology of the kidney were seen in studies of rats and mice administered DEP by repeated dermal applications at doses as high as 3,227 mg/kg-day (rats) and 6,340 mg/kg-day (mice) for 4 weeks or as high as 1,170 mg/kg-day (rats) and 834 mg/kg-day (mice) for 105 weeks (NTP, 1995).

5.11. Endocrine Activity

Decreased absolute and relative (i.e., adjusted for body weight by analysis of covariance) pituitary weights (17 and 12%, respectively, lower than controls) were observed in F1 parental female mice receiving DEP from the diet at 4,878 mg/kg-day from weaning through 7 weeks premating and an unspecified cohabitation period; these mice had been exposed to DEP via their mothers as well (Lamb et al., 1987; NTP, 1984). Equivocal decreases in adrenal weight were seen in F0 and F1 adult male rats in a multigeneration reproduction study, but there were no observed changes in F0 or F1 females and no evidence of histopathologic lesions in the adrenals of either sex (Fujii et al., 2005). No effect on adrenal weight was seen in young male rats treated with 500 mg/kg-day of DEP for 4 weeks (Kwack et al., 2009).

Gross and histopathologic evaluations of adrenals, pituitary, and thyroid glands of rats and mice administered DEP by repeated dermal applications at doses as high as 3,227 mg/kg-day (rats) and 6,340 mg/kg-day (mice) for 4 weeks or as high as 1,170 mg/kg-day (rats) and 834 mg/kg-day (mice) for 105 weeks revealed no signs of treatment-related effects (NTP, 1995).

5.12. Reproductive Toxicity

There is some evidence that exposure to DEP may result in alterations within selected biomarkers of male reproductive function in humans. Jönsson et al. (2005) assessed urine, serum, and semen samples from 234 young Swedish men and found that subjects within the highest quartile for urinary MEP had 8.8% (95% confidence interval=0.8–17) fewer sperm, 8.9% (0.3–18) more immotile sperm, and lower serum luteinizing hormone values (0.7 IU/L; 0.1–1.2) compared to those subjects in the lowest quartile for urinary MEP. A dose-response relationship between sperm deoxyribonucleic acid (DNA) damage (as assessed by the comet assay) and urinary MEP levels was reported for two groups of men who presented at a health facility for semen analysis as part of an infertility investigation (Hauser et al., 2007; Duty et al., 2003). Pant et al. (2008) reported a significant ($p < 0.05$) inverse relationship between sperm concentration and level of DEP in the semen of a group of 300 males between the ages of 20 and 40.

No effects on reproductive indices (numbers of fertile pairs, pups per litter, live pups per litter, and live pup birth weight) were seen in mice receiving DEP from the diet for 7 days prior to mating and throughout a 98-day period of cohabitation and 21 days following separation at doses as high as 4,509 mg/kg-day (males) and 4,878 mg/kg-day (females) (Lamb et al., 1987; NTP, 1984). However, when offspring of these mice were administered DEP in their diets at a concentration resulting in doses of 4,509 mg/kg-day (males) and 4,878 mg/kg-day (females) from weaning through 7 weeks premating and an unspecified continuous breeding period, the F1 parental males exhibited 32% increased prostate weight and 30% decreased sperm concentration and there was a 14% lower total number of live pups per litter at birth compared to controls. No effects on fertility or fecundity were seen in a two-generation study of rats receiving DEP from the diet at doses up to 1,016 mg/kg-day (males) and 1,375 mg/kg-day (females) for 10 weeks prior to mating and throughout mating, gestation, and lactation (Fujii et al., 2005). Decreased serum testosterone levels in F0 males and a dose-related increase in the frequency of abnormal (tailless) sperm rate and tailless sperm rate in F1 parental males were observed in the mid- and high-dose groups in this study. Researchers considered these changes to be toxicologically insignificant due to the absence of associated effects on copulation, fertility indices, sperm counts and motility, or histopathology of testis and epididymides. Further reproductive effects (uterine weight, female gestation length, prostate weight) were noted in this study. The author did not attribute decreased gestation length to DEP treatment because all values fell within historical norms for this species, even though similar decrements were seen in both F_0 and F_1 rats.

No gross or histopathologic effects were observed upon examination of reproductive organs and tissue samples from rats or mice administered DEP by repeated dermal applications at doses as high as 3,227 mg/kg-day (rats) and 6,340 mg/kg-day (mice) for 4 weeks or as high as 1,170 mg/kg-day (rats) and 834 mg/kg-day (mice) for 105 weeks.

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

5.13. Prenatal, Perinatal, and Post-natal Toxicity

Swan et al. (2005) reported a significant ($p < 0.05$) association between urinary levels of MEP in prenatal urine samples from pregnant women and age-adjusted anogenital index (AGI=anogenital distance [AGD]/weight) of their postnatal males (n=134) at 2–36 months of age; urinary MEP levels were inversely related to AGI.

No indications of developmental toxicity were seen after repeated gavage dosing of pregnant rats with DEP during gestation at 750 mg/kg-day (Gray et al., 2000) or pregnant mice at 4,500 mg/kg-day (Hardin et al., 1987). In one study of pregnant rats, administration of DEP in the diet at a concentration producing a dose level of 3,210 mg/kg-day during GDs 6–15 resulted in increased incidence of extra ribs, percent of litters with malformed fetuses, and percent of litters with variations, but no DEP-related effects on resorption incidence, live litter size, sex distribution, or fetal body weight; the no-observed-adverse-effect level (NOAEL) was 1,910 mg/kg-day (Field et al., 1993). Reported changes occurred at non-maternally toxic doses. In a two-generation reproductive toxicity study of rats, depressed pup weight at weaning, delayed pinna detachment in male pups, and delayed onset of vaginal opening were noted in offspring of rats receiving DEP from the diet at 1,016 mg/kg-day (males) and 1,375 mg/kg-day (females); these effects were not seen at doses of 197 mg/kg-day (males) and 267 mg/kg-day (females) (Fujii et al., 2005). Depressed body weight at weaning (25% lower than controls) of male F1 pups and decreased total number of live pups per litter in the F2 generation were reported in mice receiving DEP from the diet at 4,509 mg/kg-day (males) and 4,878 mg/kg-day (females) in a continuous breeding study; no effects were seen at the next lower dose level (2,255 mg/kg-day for males and 2,439 mg/kg-day for females), although only a single generation was tested at this dose and it is unclear if F1 pups at this dose were maintained through weaning (Lamb et al., 1987; NTP, 1984).

Pereira and Rao (2007) reported that dietary exposure of male and female rats to 2.85 mg/kg-day DEP for 100 days prior to mating, during 10 days of mating, and throughout gestation and lactation resulted in reduced litter size, sluggishness and reduced activity in pups, and reduced pup body weights at postnatal day (PND) 21. However, the reliability of this report is questionable.

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

5.14. Carcinogenicity

Genotoxicity

Results from mutagenicity testing of DEP in Salmonella are predominantly negative. In several assays, DEP was not mutagenic to *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537 either with or without exogenous metabolic activation at concentrations up to 1,000–10,000 µg/plate (NTP, 1995; BASF Corporation, 1993; Henrich and Munten, 1987; Zeiger et al., 1985) or at 3 µmol/plate (Florin et al., 1980). Blevins and Taylor (1982) reported negative results for DEP-induced mutagenicity in *S. typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 at unspecified DEP concentrations both with and without exogenous metabolic activation. Omori et al. (1976) summarized results from a study by Kurata (1975) in which DEP was negative for mutagenicity in *S. typhimurium* strains TA98 and TA100 and *Escherichia coli* in the presence of exogenous metabolic activation at a DEP concentration of 10 mg/plate. Agarwal et al. (1985) reported a negative response in *S. typhimurium* strain TA1535 both with and without exogenous metabolic activation at DEP concentrations up to and including 2,000 µg/plate. However, positive results were reported by Agarwal et al. (1985) and Kozumbo et al. (1982) for *S. typhimurium* strain TA100 in the absence (but not the presence) of exogenous metabolic activation at concentrations in the range of 500–1,000 µg/plate and by Seed (1982) in the presence and absence of exogenous metabolic activation, albeit at a concentration (3.3 mM) that also caused approximately 50% cytotoxicity.

DEP did not induce chromosomal aberrations in Chinese ovary cells either with or without exogenous metabolic activation at DEP concentrations up to 250–324 µg/mL (NTP, 1995; Ishidate and Odashima, 1977). DEP induced sister chromatid exchanges in Chinese ovary

cells in the presence (but not the absence) of exogenous metabolic activation at DEP concentrations of 167 and 750 μg/plate (NTP, 1995).

Initiation and Promotion

There was no evidence that DEP acted as a skin tumor initiator or promoter in a 1-year dermal initiation/promotion study of male Swiss (CD-1) mice (50/group) (NTP, 1995).

Carcinogenicity Studies

No statistically significant treatment-related increased incidences of neoplastic lesions were found in a 2-year chronic toxicity and carcinogenicity study of male and female F344/N rats administered DEP via dermal applications at 0, 100, or 300 μL/animal-day, 5 days/week for 105 weeks (NTP, 1995). Based on reported mean body weights for the time periods of 1–13, 14–52, and 53–105 weeks (and adjustment for 5 days of treatment/week), approximate time-weighted average (TWA) doses of DEP were 230 and 743 mg/kg-day to the low- and high-dose males and 379 and 1,170 mg/kg-day to the low- and high-dose females. The study authors determined that under the conditions of the study, there was no evidence of carcinogenic activity of DEP in the male or female F344/N rats, but noted that the sensitivity of the male rat portion of the study was reduced due to poor survival in all groups.

Male and female B6C3F1 mice were administered DEP (in acetone) by dermal applications at 0, 7.5, 15, or 30 μL/animal-day, 5 days/week for 105 weeks (NTP, 1995). Based on reported mean body weights for the time periods of 1–13, 14–52, and 53–105 weeks (and adjustment for 5 days of treatment/week), approximate TWA doses of DEP were 191, 387, and 775 mg/kg-day to the low-, mid-, and high-dose males and 209, 415, and 834 mg/kg-day to the low-, mid-, and high-dose females. In male mice, incidences of hepatocellular adenomas and hepatocellular carcinomas of DEP-treated groups were not significantly different from control incidences; however, combined incidences of adenoma or carcinoma were significantly increased at high dose (18/50 versus 9/50 controls; p=0.034). Incidences of hepatocellular adenomas in control, low-, mid-, and high-dose female mice were 4/50, 12/51 (p=0.017), 14/50 (p=0.006), and 10/50, respectively. Although the incidences were significantly increased in low- and mid-dose groups, a significant dose-related trend was not found. Incidences of hepatocellular carcinomas in DEP-treated female mice were not significantly different from controls. Combined incidences of adenoma or carcinoma were significantly increased in low- and mid-dose females and reflected the increases in adenomas. Because the incidence of

hepatocellular adenomas in the high-dose male mice was similar to that of historical controls, and in the absence of a dose-response trend for liver neoplasms in the female mice, the study authors indicated that the marginal increases in hepatocellular neoplasms provided only equivocal evidence of carcinogenic activity.

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

6. EXPOSURE

HSDB (2009) reported that occupational exposure to DEP 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 DEP via inhalation of ambient air, ingestion of food and drinking water, and dermal contact with products containing DEP (HSDB, 2009).

Koo and Lee (2004) measured levels of phthalates, including DEP, in 102 cosmetic products and collected information on frequency and volume of cosmetic use to estimate human exposure to phthalates. The mean, median, and 90th percentile values for frequency of use were used to estimate daily exposure levels using three models based on different assumptions with regards to dermal or inhalation absorption. Total daily exposure levels were calculated by combining exposure estimates for the use of perfume, deodorant, nail polish and hair products. The total mean daily exposure levels for DEP based on the three models used in the study was 5.971 µg/kg/day, 0.183 µg/kg/day, and 24.879 µg/kg/day. Koo and Lee (2004) noted that the estimates generated in this study suggest that exposure to phthalates in cosmetics is small; however, total exposure to phthalates from several sources should be further investigated.

Hubinger and Havery (2006) analyzed 48 cosmetic products, including hair care products, deodorants, lotions, creams, nail products, fragrances and body washes, and found the high levels of phthalate esters in nail enamel (59,815 ppm DBP) and fragrance (38,663 ppm DEP) samples. Phthalates found in nail enamel included DEP, but the level was not quantified. The only phthalate detected in fragrance samples was DEP.

Consumer exposure to eight phthalates, including DEP, was investigated by Wormuth et al. (2006) using a scenario-based risk assessment approach that included various oral, dermal, and inhalation exposure pathways. Included in this analysis was consumer exposure to personal care products resulting from dermal contact and incidental ingestion of the products. Wormuth et al. (2006) calculated total consumer exposure for seven different age and gender groups by adding the single exposure estimates for all the exposure pathways. In addition, the study authors reported on the relative contribution of various sources to the total daily exposure. In all consumer groups investigated, dermal application and incidental ingestion of personal care products were the main sources of exposure to DEP, accounting for at least 65% of the total DEP exposure. In this study, there was considerable variability in the daily exposure estimates.

According to the study authors, this was due to uncertainty and natural variability in the input parameters used in the calculations.

Sathyanarayana et al. (2008) examined the use of infant care products applied to the skin as a potential source of exposure to phthalates in infants and toddlers. Data on urinary phthalate metabolite concentrations and use of infant care products were obtained by Sathyanarayana et al. (2008) for a group of 163 infants born between 2000 and 2005. Through a questionnaire, the infants' mothers provided information on the use of infant powder, talc, cornstarch, diaper creams, shampoo, wipes and lotion during the 24 hours prior to sample collection. Urine samples were collected from wet diapers provided by the mothers and analyzed for 9 phthalate metabolites.

Use of infant wipes was reported by 94% of the mothers while 54% of the mothers reported use of infant shampoo. Only 14% of mothers reported using baby powder prior to sample collection. MEP was one of the most frequently detected metabolites found in 98% of the samples. MEP also had the highest mean (178.2 µg/L) and median (60.9 µg/L) values of all the metabolites detected. The study authors noted that all urine samples had a least 1 phthalate compound above the limit of detection. In this study, multiple linear regression analyses, using data adjusted for infant age and creatinine levels, were conducted to investigate the association between metabolite concentrations and product use. The results of these analyses showed that the reported use of infant lotion, powder and shampoo was significantly associated with increased urinary concentrations of the MEP and other metabolites, especially in infants younger than 8 months. The use of diaper creams or infant wipes, on the other hand, was not strongly associated with urinary concentrations of any of the metabolites detected. Based on the study findings, Sathyanarayana et al. (2008) suggested that dermal exposure may be an important route of exposure to some phthalates for young infants.

Based on a study review by the Cosmetic Ingredient Review Expert Panel, the estimated median exposure level of DEP is 57 µg/kg/day, which is well below the U.S. EPA reference dose of 800 µg/kg/day (CIR, 2003). Even the median exposure levels of the highest exposed group (women aged 20 to 40 years) is well below the references dose (CIR, 2003). The panel indicated that scientific committees with the government of the EU and U.S. have evaluated the human risks of DEP and expressed minimal to no concern over consumer exposure to these compounds (National Toxicology Program's Center for the Evaluation of Risks to Human Reproduction, 2000; Netherlands Organization for Applied Scientific Research and National Institute of Public

Health and the Environmental; Scientific Committee on Cosmetic Products and Non-Food Products, 2002).

7. DISCUSSION

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 DEP, which are derived from the repeated dose oral toxicity studies of Kwak et al. (2009) and Brown et al. (1978) in rats, the reproduction studies of Fujii et al. (2005) in rats and Lamb et al (1987; NTP, 1984) in mice, the developmental toxicity studies of Hardin et al. (1987) in mice and Gray et al. (2007) and Field et al. (1993) in rats, and the dermal short-term and long-term cancer studies of NTP (1995) in rats and mice.

DEP is not a potent developmental toxicant. No evidence for developmental toxicity was found in a developmental toxicity screening study in mice at a dose of 4,500 mg/kg-day or in a study of sexual development 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). A study of standard developmental endpoints in pregnant Sprague-Dawley rats exposed to up 5% DMP in the diet (~3,210 mg/kg-day) on GDs 6–15 found increased incidence of skeletal variations (extra rib) but no other embryotoxic or fetotoxic effects; the NOAEL in this study was 1,910 mg/kg-day (Field, 1993). A multigeneration reproduction study in rats that included assessment of sexual and other developmental milestones in pups found decreased pup weight at weaning in both generations, delayed pinna detachment in F1 male pups, and delayed onset of vaginal opening in F1 female pups at the high dose of 15,000 ppm (1,016–1,375 mg/kg-day), with a NOAEL of 3,000 ppm (197–267 mg/kg-day) (Fujii et al., 2005). A continuous breeding study in mice found a decrease in body weight of F1 male pups at weaning and decreased total number of live pups per litter in the F2 generation at 2.5% in the diet (4,509–4,878 mg/kg-day); there were no effects at 1.25% in the diet (2,255–2,439 mg/kg-day), although only a single generation was tested at this dose and it is unclear if pups at this dose were maintained through weaning (Lamb et al., 1987; NTP, 1984).

Reproductive endpoints were less sensitive than developmental endpoints in the reproduction studies. Fujii et al. (2005) reported only a few toxicologically significant effects on reproductive organs or function (i.e. gestation length) in rats exposed for two generations to doses as high as 15,000 ppm (1,016–1,375 mg/kg-day). Lamb et al. (1987; NTP, 1984) observed no reproductive effects in the first generation breeding in mice, but reported increased prostate

weight and decreased sperm concentration in the F1 parental males and decreased total number of live pups per litter in the F2 generation at 2.5% in the diet (4,509–4,878 mg/kg-day).

Among systemic endpoints, increased liver weight was the most sensitive effect, but still occurred only at LOAELs greater than 1000 mg/kg-day. Increases in liver weight were reported at 1,016–1,375 mg/kg-day in F0 and F1 parental males and females in the multigeneration rat study (Fujii et al., 2005), at 4,509–4,878 mg/kg-day in F1 parental males and females in the multigeneration mouse study (Lamb et al., 1987; NTP, 1984), and at 3,160–3,710 mg/kg-day in rats in a 16-week repeated dose study (Brown et al., 1978). No histological changes in the liver were seen in either of the studies that included pathology examinations (Fujii et al., 2005; Brown et al., 1978). NOAELs for hepatic effects in these and other studies ranged from 197–267 mg/kg-day to 750–770 mg/kg-day (Fujii et al., 2005; Lamb et al., 1987; NTP, 1984; Brown et al., 1978; Kwack et al., 2009).

The dermal toxicity studies performed by NTP (1995) found no evidence of carcinogenic effects of DEP in rats or mice at any dose tested. The mouse bioassay produced equivocal evidence for increased incidence of hepatocellular tumors (adenomas and carcinomas combined), and the rat bioassay was negative. Negative results were also found in the initiation/promotion study by NTP (1995) and in most of the available genotoxicity studies.

Benchmark Dose (BMD) Analysis

The BMD method for generating acceptable daily intake levels (ADI's) is an alternative to methods that use NOAELs and LOAELs. A BMD is a dose at which a specified low incidence (i.e 10%) of health risk occurs over background levels (BMD_{10}). The $BMDL_{10}$ is the 95% lower confidence limit of the BMD_{10}. The BMD approach is thought to more accurately estimate a point of departure (POD) for each effect since it uses the entire dose-response curve and is independent of the doses tested.

To derive a $BMDL_{10}$, experimental data is curve fit with multiple statistical routines in order to estimate an effect dose level. The generated curves and associated statistics for each model routine are reviewed and the most appropriate endpoint chosen based on established criteria. The estimated dose level is then combined with uncertainty factors to generate an ADI.

For this report, toxicity endpoints for short-, intermediate-, and long-term incidental oral exposures to DEP were selected from analysis of a developmental study by Field et al. (1993), a two generation reproduction study by Fujii et al. (2005), and a two-year dermal exposure cancer assessment by the NTP (1995). These data were used in a BMD approach for calculating ADI's. NOAELs and LOAELs from these studies (described above) were compared to the generated $BMDL_{10}$ values.

BMD software designed by EPA (BMDS version 2.1.2) was used for BMD analysis of continuous data on DEP induced changes in body weight (maternal, fetus, pup), organ weight (liver, kidney, brain, testis, prostate, epididymides, etc), and reproduction (gestation length, age at pinna detachment, tailless and abnormal sperm, testosterone production, etc). BMD software was also used for analysis of dichotomous data on DEP-induced changes in development (incidence of visceral, external, skeletal, and other malformations and variations) and other lesions (skin acanthosis, follicular cell hyperplasia of the thyroid, etc). The data sets for these endpoints were thought to be of sufficient quality (dose-related, corroborated in multiple studies) to use in a BMD approach and were used to more accurately estimate a point of departure (POD) from each study for each effect.

BMD continuous models were selected to model data based on continuous variables (e.g. body weight). The $BMDL_{10}$ (95% lower confidence interval of the estimated benchmark dose that results in a 10% change) was estimated for continuous data using Linear, Polynomial, Hill, and Power models. For these endpoints, a 10% change was considered reasonable because most organ or body weight changes that are less than 10% are not associated with adverse effects. Results from each data set were screened to exclude model runs that had obviously misfitted curves, goodness-of fit p-values < 0.1, and a low $BMDL_{10}$ value to high $BMDL_{10}$ value ratio of > 3. Following this screening, model selection preference was given to runs with high p-values, low Akaike's Information Criterion (AIC), and data points near estimated BMD and BMDL levels.

BMD dichotomous models (Gamma, Logistic, Multistage, Probit, and Weibull) were selected to graph data based on quantal variables. As with continuous data, the $BMDL_{10}$ was also estimated for these data. For these endpoints, a 10% change in a parameter was considered reasonable. The $BMDL_{10}$ is different than that used previously by a Chronic Hazard Advisory Panel convened by CPSC (2001; BMD_{05}), and CPSC staff (2002) for setting an ADI based on quantal data (the incidence of spongiosis hepatis in rats) for diisononyl phthalate. Dichotomous results were screened as described above.

Summarized BMD_{10} and $BMDL_{10}$ results and graphs can be seen in Appendix C.

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 estimated for long-term exposure durations for the general population (non-reproductive endpoint) and short-term exposures to maternal animals (reproductive and developmental endpoints).

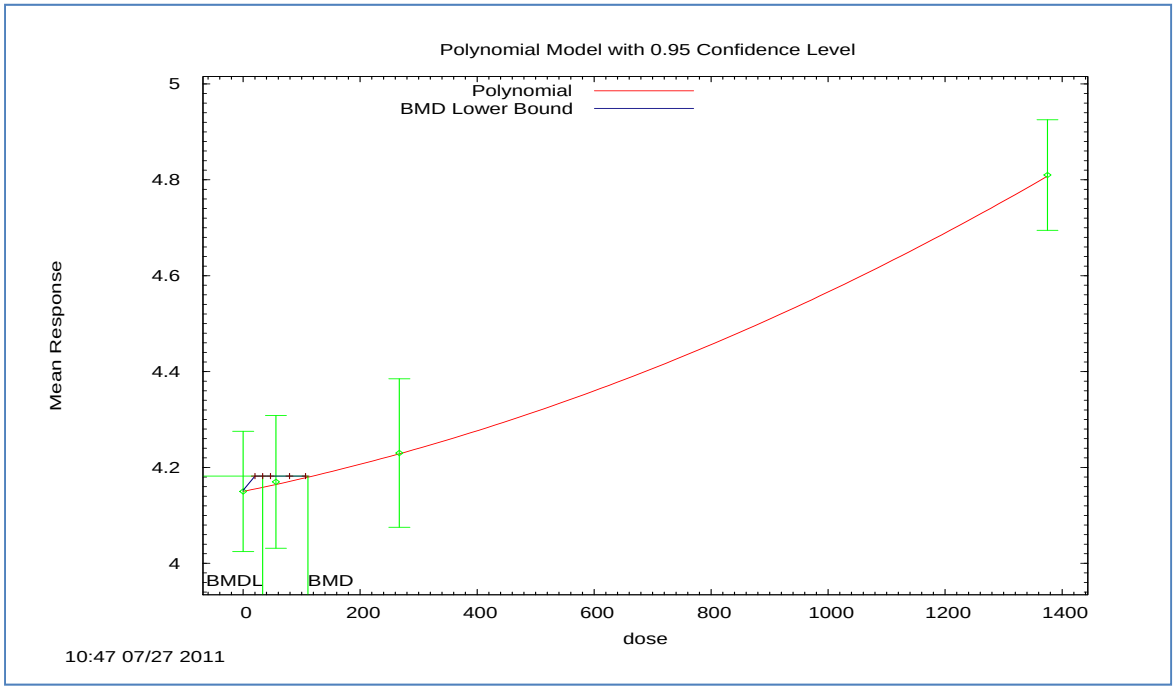
General population ADI's

Long-term oral exposures – general population

For long-duration oral exposures, the $BMDL_{10}$ of 33 mg/kg-day (BMD_{10} = 111 mg/kg-day; Fujii et al., 2005) was chosen as the representative overall hazard endpoint for general toxicity. This endpoint was derived from a reproduction study in which Sprague-Dawley rats were exposed to DEP in the diet for two generations.

DEP doses of 1375 mg/kg-day (LOAEL; NOAEL = 267 mg/kg-day) significantly increased the relative liver weight in female F2 Sprague-Dawley pups. $BMDL_{10}$ model calculations suggested that the increase in relative liver weight was best described by the Polynomial model (AIC = -119.3, model dependency ratio = 1.67 [≤ 3], goodness of fit p-value = 0.95; see Figure 7.1 below).

Figure 7.1 Polynomial Model Plot of Female F2 Pup Relative Liver Weight (Fujii et al., 2005)



Choice of relative liver weight study data for use as a hazard endpoint induced by long-term DEP exposure was supported by additional liver weight data that had slightly higher hazard effect levels. Dietary exposure to DEP increased absolute and relative liver weights in parental F0 and F1 rats up to 14% (LOAELs = 1016 mg/kg-day for males; 1375 mg/kg-day for females; Fujii et al., 2005), in other rats (LOAEL = 3160 to 3710 mg/kg-day; Brown et al., 1978; LOAEL = 1753 mg/kg-day; Moody and Reddy, 1978), and in adult F1 male and female mice from 18-28% (LOAEL = 4509 to 4878 mg/kg-day; Lamb et al., 1987; NTP 1984). Benchmark dose analysis of many of these endpoints resulted in a spread of values from 43 to 1558 mg/kg-day (see Appendix C).

The $BMDL_{10}$ of 33 mg/kg-day was used to generate an Acceptable Daily Intake (ADI) by dividing by an uncertainty factor of 100 (10X for interspecies variation, 10X for intraspecies variation and sensitive populations). This "safety factor" is typically applied by CPSC to the lowest NO[A]EL for animal data in which developmental, reproductive, or neurotoxicological effects have been determined (16 CFR§1500.135(d)(4)(B)). **The long-term exposure oral ADI for the general population was calculated to be 0.33 mg/kg-day.**

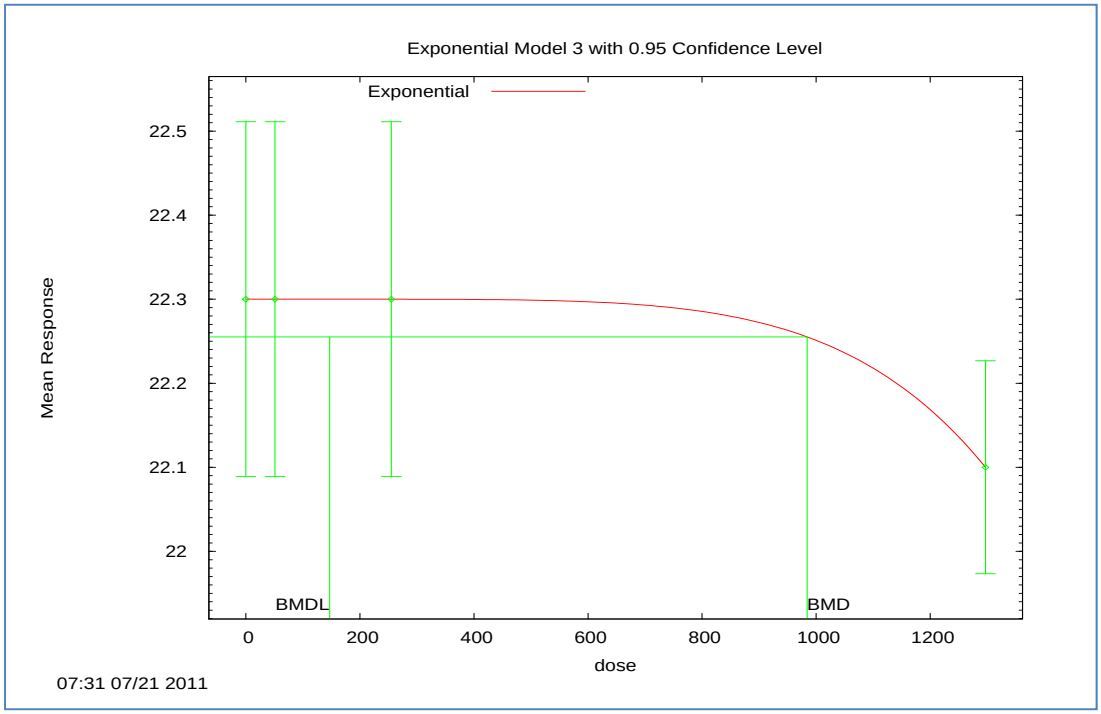
Reproductive ADI

Short-term oral exposures – reproduction

For short-duration oral exposures and reproductive endpoints, the $BMDL_{10}$ of 147 mg/kg-day (BMD_{10} = 984 mg/kg-day; Fujii et al., 2005) was chosen as the representative hazard endpoint. This endpoint was derived from a reproduction study in which Sprague-Dawley rats were exposed to DEP in the diet for two generations.

DEP doses of 1297 mg/kg-day (LOAEL; NOAEL = 255 mg/kg-day) decreased the gestation length in F0 Sprague-Dawley rat females. $BMDL_{10}$ model calculations suggested that the increase in gestation length was best described by the $Exponential_3$ model (AIC = -49.9, model dependency ratio = 3 [≤ 3], goodness of fit p-value = 1.0; see Figure 7.2 below).

Figure 7.2 Polynomial Model Plot of Increased Gestation Length (Fujii et al., 2005)



Choice of decreased gestation length data ($BMDL_{10}$ of 147 mg/kg-day) was supported by additional reproduction-related data with slightly higher hazard effect levels. Significantly decreased gestation index length was observed in F1 generation female rats (LOAEL = 1375; NOAEL = 267 mg/kg-day; Fujii et al., 2005). Decreased absolute and relative uterus weights

(LOAEL = 1297/NOAEL = 255 mg/kg-day; LOAEL = 1375/NOAEL = 267 mg/kg-day; Fujii et al., 2005) and increased incidence of cystic ovaries (LOAEL = not determined; $BMDL_{10}$ = 1010 mg/kg-day) were also reported in female rats.

The decrease in gestation length also occurred at a lower dose than other male rodent reproductive endpoints such as decreased sperm linear motility (LOAEL =500 mg/kg-day) and decreased sperm count (-41%) and motility (-56%) (LOAEL = 250 mg MEP/kg-day; Kwack et al., 2009); and increased rate of abnormal sperm in F1 male rats, 32% increase in prostate weight, and decreased sperm concentration in the F1 male rats (LOAEL = 4,509 to 4,878 mg/kg-day; Lamb et al., 1987).

Benchmark dose analysis of many of these endpoints resulted in a spread of values from 49 to 1010 mg/kg-day (see Appendix C). Benchmark doses of 49, 50, and 132 were not chosen to represent the reproductive endpoint because they were absolute organ weights. Absolute organ weights (excluding the brain) are strongly dependent on body weight, and hence are of less utility than relative organ weights. Benchmark dose levels for relative prostate weight (148 mg/kg-day; LOAEL =nd, Fujii et al., 2005), and relative right testis weight (807 mg/kg-day; LOAEL = nd; NTP, 1995) were not used to generate an ADI because they are higher than that for decreases in gestation length.

The $BMDL_{10}$ of 147 mg/kg-day was used to generate an Acceptable Daily Intake (ADI) by dividing by an uncertainty factor of 100 (10X for interspecies variation, 10X for intraspecies variation and sensitive populations). This "safety factor" is typically applied by CPSC to the lowest NO[A]EL for animal data in which developmental, reproductive, or neurotoxicological effects have been determined (16 CFR§1500.135(d)(4)(B)). **The short-term exposure oral ADI for the general population was calculated to be 1.47 mg/kg-day.**

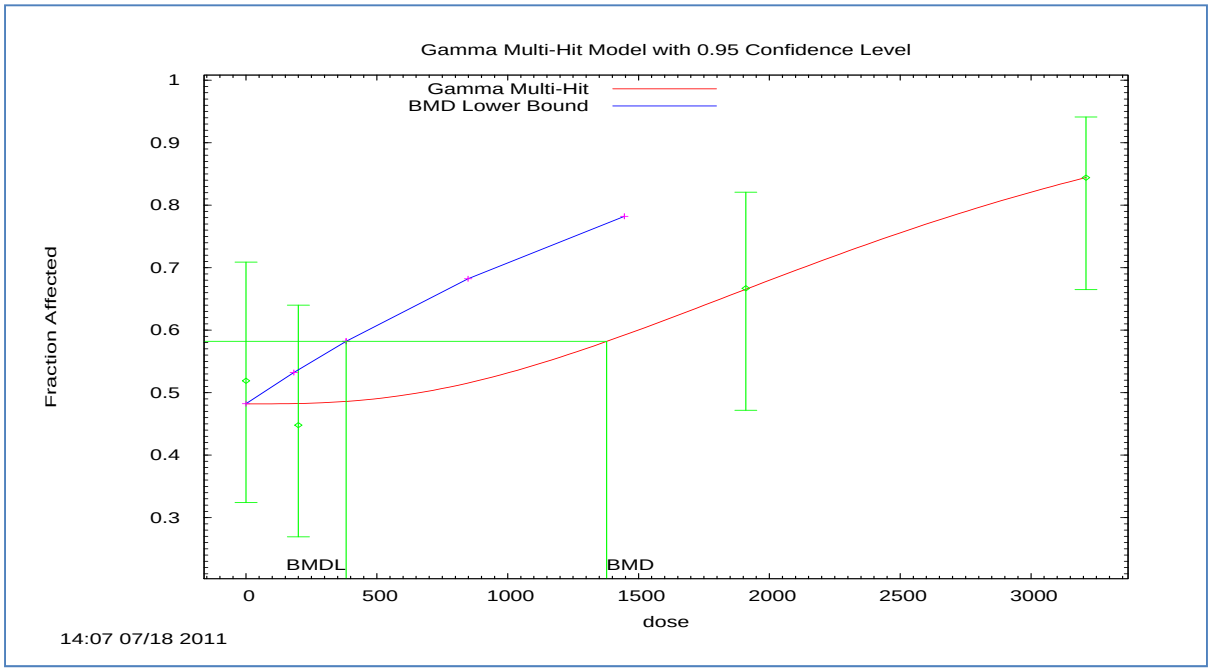
Developmental ADI

Maternal exposures – developmental effects

For developmental effects, the maternal dose $BMDL_{10}$ of 382 mg/kg-day was chosen as the representative overall hazard endpoint (BMD_{10} = 1337 mg/kg-day; Field et al., 1993)**.** This endpoint was derived from a gestational exposure study in which pregnant female Sprague-Dawley rats were dosed with DEP in the diet during gestation days 6 to 15.

DEP doses of 3210 mg/kg-day (LOAEL; NOAEL = 1910 mg/kg-day) significantly increased to percent of litters with variations (in the absence of consistent maternal toxicity evinced as body weight decrements). $BMDL_{10}$ model calculations suggested that the increase in variations was best described by the Weibull model (AIC = 149.5, model dependency ratio = 1.7 [≤3], goodness of fit p-value = 0.59; see Figure 7.3 below).

Figure 7.3 Weibull Model Plot of Increased Developmental Variations (Field et al., 1993)



Choice of increased percentage of variations data was supported by additional developmental-related data with a higher hazard effect levels. In the same study, an increased percentage of litters with extra ribs (LOAEL = 3210; $BMDL_{10}$ = 757 mg/kg-day), litters with malformed fetuses (LOAEL = 3210; $BMDL_{10}$ = 1953 mg/kg-day), and significant trend for the

percent of fetuses with an extra rib/litter (LOAEL = 3210; NOAEL = 1910 mg/kg-day) were described for rat fetuses with mothers treated with DEP on Gd 6-15 (Field et al., 1993). Increased numbers of variations and retardations were also reported in ICR mice pups following percutaneous exposure of dams to DEP on Gd 0-17 (LOAEL = 5600; NOAEL = 1910 mg/kg-day; Tanaka et al., 1987). A dose-related increase in the numbers of unspecified skeletal abnormalities was also seen following IP dosing by Singh et al. (1972). In addition, a significant decrease in the number of live CD-1 mouse pups per litter was reported by Lamb et al., (1987; LOAEL = 4509-4878; NOAEL = nd). All of these developmental health effect levels were higher than that chosen for the generation of an ADI.

A handful of developmental hazard endpoints had lower effect levels than that chosen to generate an ADI. These were not used, however, to generate an ADI for particular reasons.

Significant delays in the onset of vaginal opening in F1 pups (LOAEL = 1375; NOAEL = 267 mg/kg-day) and the age at pinna detachment in F1 male (LOAEL = 1297, $BMDL_{10}$ = 123 mg/kg-day) and F1 female pups (LOAEL = nd; $BMDL_{10}$ = 129 mg/kg-day) were reported by Fujii et al. (2005). Increases in the age of pinna detachment were also observed in male and female F2 pups in the same study. These findings were not reported in other studies, however, and therefore, were not considered for use in generating an ADI. Changes in pup body weights (Fujii et al., 2005; male F1, male F1 at day 21, male F2 at day 21, female F1 at day 4, female F1 at day 21, female F2, female F2 at day 21; BMDs = 73, 63, 45, 123, 55, 104, and 49, respectively) during and before weaning were also not chosen for ADI development, since these may not have represented true developmental changes.

The $BMDL_{10}$ of 382 mg/kg-day was used to generate an Acceptable Daily Intake (ADI) by dividing by an uncertainty factor of 100 (10X for interspecies variation, 10X for intraspecies variation and sensitive populations). This "safety factor" is typically applied by CPSC to the lowest NO[A]EL for animal data in which developmental, reproductive, or neurotoxicological effects have been determined (16 CFR§1500.135(d)(4)(B)). **The developmental ADI was calculated to be 3.82 mg/kg-day.**

Other ADIs

Insufficient evidence (hazard data) precluded the generation of ADI's for inhalation or dermal exposures or for cancer endpoints.

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Appendix A. Summary of Endpoints by Organ System

Table A.1. Summary of NOAELs/LOAELs Identified for DEP by Organ System

Species (Gender)	Exposure Route	Dose (Number of Animals per Dose Group)	Dose Duration	Effect Category	Toxicological Endpoint	Toxicological Basis	Citation
Oral Exposure							
Sprague-Dawley rat (M)	Gavage (in corn oil)	0, 500 mg/kg-day (6 per group)	Once daily for 4 weeks	General	NOAEL=500 mg/kg-day LOAEL=None	No deaths, relevant clinical signs, or body weight effects	Kwack et al., 2009
				Liver	NOAEL=500 mg/kg-day LOAEL=None	No effects on liver weight or associated clinical chemistry	
				Kidney	NOAEL=500 mg/kg-day LOAEL=None	No effects on kidney weight or associated clinical chemistry	
				Endocrine	NOAEL=500 mg/kg-day LOAEL=None	No effects on adrenal weight or associated clinical chemistry	
				Reproduction	NOAEL = nd LOAEL=500 mg/kg-day	18% decreased linear motility of sperm, but no overall effect on sperm motility and no effect on sperm count	
Sprague-Dawley rat (M)	Gavage (in corn oil)	0, 250 mg MEP/kg-day (6 per group)	Once daily for 4 weeks	Reproduction	NOAEL = nd LOAEL=250 mg/kg-day	Decreased sperm motility and sperm count (-56% and -41%, respectively)	
				General	NOAEL=750–770 mg/kg-day LOAEL=3,160–3,710 mg/kg-day	No deaths or clinical signs; depressed terminal body weight in high-dose males (23–25%) and females (15–20%)	Brown et al., 1978
				Liver	NOAEL=750–770 mg/kg-day LOAEL=3,160–3,710 mg/kg-day	Increased liver weight in high-dose males (33%) and females (31%) in the absence of DEP-induced histopatho-logic lesions	
				Kidney	NOAEL=750–770 mg/kg-day LOAEL=3,160–3,710 mg/kg-day	Increased kidney weight in high-dose males (18%) and females (11%) in the absence of DEP-induced histopatho-logic lesions	
				General	NOAEL=1,016–1,375 mg/kg-day LOAEL=None	No deaths in parental mice; no clinical signs and no toxicologically significant effects on body weight	Fujii et al., 2005

Table A.1. Summary of NOAELs/LOAELs Identified for DEP by Organ System

Species (Gender)	Exposure Route	Dose (Number of Animals per Dose Group)	Dose Duration	Effect Category	Toxicological Endpoint	Toxicological Basis	Citation
				Liver	NOAEL=197–267 mg/kg-day LOAEL=1,016–1,375 mg/kg-day	Absolute and relative liver weight increased up to 14% in F0 and F1 parental males and females. No evidence of histopathologic liver lesions.	
				Kidney	NOAEL=1,016–1,375 mg/kg-day LOAEL=None	Small increase (<10%) in kidney weight in F1 adult females, but not F0 females or F0 or F1 males. No evidence of histopathologic kidney lesions.	
				Endocrine	NOAEL=1,016–1,375 mg/kg-day LOAEL=None	Equivocal decreases in adrenal weight in F0 and F1 adult males. No changes in F0 or F1 females. No evidence of histopathologic lesions.	
				Reproduction	NOAEL=1,016–1,375 mg/kg-day LOAEL=None	No toxicologically significant effects on reproductive organs or function.	
				Reproduction	NOAEL = 267 mg/kg-day LOAEL = 1375 mg/kg-day	Significant decrease in gestation index in F1 female rats	
				Development	NOAEL=197–267 mg/kg-day LOAEL=1,016–1,375 mg/kg-day	Decreased F1 and F2 pup weight at weaning, delayed pinna detachment in F1 male pups, and delayed onset of vaginal opening in F1 female pups	

Table A.1. Summary of NOAELs/LOAELs Identified for DEP by Organ System

Species (Gender)	Exposure Route	Dose (Number of Animals per Dose Group)	Dose Duration	Effect Category	Toxicological Endpoint	Toxicological Basis	Citation
CD-1 mouse (M&F)	Dietary (0, 0.25, 1.25, 2.5% in food)	M; 0, 451, 2,255, 4,509 mg/kg-day F; 0, 488, 2,439, 4,878 mg/kg-day (controls: 40 M, 40 F; DEP dose groups: 20 M, 20 F)	7 Days prior to mating and throughout 98 days of cohabitation and 21 days following separation to allow for delivery of final litters (females treated until final litters were weaned at PND 21)	General	NOAEL=4,509–4,878 mg/kg-day LOAEL=None	One mid-dose male and female and two high-dose males died during the study, but causes of deaths were not specified; no clinical signs and no toxicologically significant effects on body weight	Lamb et al., 1987; NTP, 1984
				Reproduction	NOAEL=4,509–4,878 mg/kg-day LOAEL=None	No treatment-related adverse effects on numbers of fertile pairs, pups/litter, live pups/litter, or live pup birth weight	
				Development	NOAEL=2,255–2,439 mg/kg-day LOAEL=4,509–4,878 mg/kg-day	25% depressed male pup body weight at weaning. It is unclear if pups at lower dose levels were maintained through weaning.	
CD-1 mouse (M&F)	Dietary (0 or 2.5% in food)	M: 0, 4,509 mg/kg-day F: 0, 4,878 mg/kg-day (20 M, 20 F)	From weaning at PND 21 for 7 weeks prior to cohabitation and for an unspecified cohabitation period (these mice were F1 offspring from F0 mice treated prior to and during cohabitation to produce the F1 generation)	General	NOAEL=None LOAEL=4,509–4,878 mg/kg-day	Depressed terminal body weight (12 and 8% for males and females, respectively)	Lamb et al., 1987; NTP, 1984
				Liver	NOAEL=None LOAEL=4,509–4,878 mg/kg-day	18–28% increased liver weight in F1 parental males and females (liver histopathology not performed)	
				Endocrine	NOAEL=None LOAEL=4,878 mg/kg-day	12–17% decreased pituitary weight in F1 parental females	
				Reproduction	NOAEL=None LOAEL=4,509–4,878 mg/kg-day	32% increased prostate weight and decreased sperm concentration in F1 parental males; increased rates of abnormal sperm in F1 males	
				Development	NOAEL=None LOAEL=4,509–4,878 mg/kg-day	significantly decreased live pups per litter	
CD-1 mouse (F)	Gavage (in corn oil)	0, 4,500 mg/kg-day (50 F per group)	Once daily on GDs 6–13	General	NOAEL=4,500 mg/kg-day LOAEL=None	No deaths, clinical signs or body weight effects	Hardin et al., 1987
				Development	NOAEL=4,500 mg/kg-day LOAEL=None	No effects on litter size, birth weight, neonatal growth, or survival up to PND 3	

Table A.1. Summary of NOAELs/LOAELs Identified for DEP by Organ System

Species (Gender)	Exposure Route	Dose (Number of Animals per Dose Group)	Dose Duration	Effect Category	Toxicological Endpoint	Toxicological Basis	Citation
Sprague-Dawley rat (F)	Gavage (in corn oil)	0, 750 mg/kg-day (9 controls, 5 DEP-treated)	Once daily from GD 14 to PND 3	General	NOAEL=750 mg/kg-day LOAEL=None	No DEP-related deaths, clinical signs, or maternal body weight effects	Gray et al., 2000
				Development	NOAEL=750 mg/kg-day LOAEL=None	No effects on pup weight at birth, number of live pups, AGD in males, male pup body weight at weaning or terminal sacrifice at 3–5 months of age, age at puberty, malformations, weights of pituitary, adrenal, kidney, liver, reproductive organs, or spermatid head count	
Sprague-Dawley rat (F)	Dietary (0, 0.25, 2.5, or 5.0% in food)	0, 200, 1,910, 3,210 mg/kg-day (31–32 F per group)	GDs 6–15	General	NOAEL=1,910 mg/kg-day LOAEL=3,210 mg/kg-day	No deaths or clinical signs; depressed maternal body weight gain	Field et al., 1993
				Development	NOAEL=1,910 mg/kg-day LOAEL=3,210 mg/kg-day	Increased incidence of extra rib; no effects on resorption incidence, live litter size, sex distribution, or fetal body weight	
Dermal Exposure							
F344/N rat (M&F)	Dermal (0, 37.5, 75, 150, 300 µL/rat-day neat)	M: 0, 282, 559, 1,332, 2,278 mg/kg-day F: 0, 404, 7,830, 1,600, 3,227 mg/kg-day	Once/day, 5 days/ week for 4 weeks	General	NOAEL=2,278–3,227 mg/kg-day LOAEL=None	No deaths; no treatment-related effects on clinical signs or body weights	NTP, 1995
				Liver	NOAEL=2,278–3,227 mg/kg-day LOAEL=None	No toxicologically significant effects	
				Kidney	NOAEL=2,278–3,227 mg/kg-day LOAEL=None	No toxicologically significant effects	
				Reproduction	NOAEL=2,278–3,227 mg/kg-day LOAEL=None	No effects on testis weight or histopathology	

Table A.1. Summary of NOAELs/LOAELs Identified for DEP by Organ System

Species (Gender)	Exposure Route	Dose (Number of Animals per Dose Group)	Dose Duration	Effect Category	Toxicological Endpoint	Toxicological Basis	Citation
B6C3F1 mouse (M&F)	Dermal (0, 12.5, 25, 50, 100 µL/ mouse-day neat)	M: 0, 630, 1,312, 2,594, 5,212 mg/kg-day F: 0, 785, 1,590, 3,196, 6,340 mg/kg-day	Once/day, 5 days/ week for 4 weeks	General	NOAEL=5,212–6,340 mg/kg-day LOAEL=None	No deaths; no treatment-related effects on clinical signs or body weights	NTP, 1995
				Liver	NOAEL=5,212–6,340 mg/kg-day LOAEL=None	No toxicologically significant effects	
				Kidney	NOAEL=5,212–6,340 mg/kg-day LOAEL=None	No effects on kidney weight or histopathology	
				Reproduction	NOAEL=5,212–6,340 mg/kg-day LOAEL=None	No effects on testis weight or histopathology	
F344/N rat (M&F)	Dermal (0, 100, 300 µL/rat-day neat)	M: 0, 230, 743 mg/kg-day F: 0, 379, 1,170 mg/kg-day	Once/day, 5 days/ week for 105 weeks	General	NOAEL=743–1,170 mg/kg-day LOAEL=None	No significant differences in survival among control and DEP-treated groups; no toxicologically significant effects on clinical signs or body weights	NTP, 1995
				Liver	NOAEL=743–1,170 mg/kg-day LOAEL=None	No effects on liver weight at 15-month interim sacrifice; no gross or histopathologic liver effects at interim or terminal sacrifice	
				Kidney	NOAEL=743–1,170 mg/kg-day LOAEL=None	No effects on kidney weight at 15-month interim sacrifice; no gross or histopathologic kidney effects at interim or terminal sacrifice	
				Endocrine system	NOAEL=743–1,170 mg/kg-day LOAEL=None	No gross or histopathologic effects on adrenals, pituitary, or thyroid glands	
				Reproduction	NOAEL=743–1,170 mg/kg-day LOAEL=None	No gross or histopathologic effects on reproductive organs	

Table A.1. Summary of NOAELs/LOAELs Identified for DEP by Organ System

Species (Gender)	Exposure Route	Dose (Number of Animals per Dose Group)	Dose Duration	Effect Category	Toxicological Endpoint	Toxicological Basis	Citation
B6C3F1 mouse (M&F)	Dermal (0, 7.5, 15, 30 µL/ mouse-day in acetone)	M: 0, 191, 378, 775 mg/kg-day F: 0, 209, 415, 834 mg/kg-day	Once/day, 5 days/ week for 105 weeks	General	NOAEL=775–834 mg/kg-day LOAEL=None	No significant differences in survival among control and DEP-treated groups; no toxicologically significant effects on clinical signs or body weights	NTP, 1995
				Liver	NOAEL=775–834 mg/kg-day LOAEL=None	No effects on liver weight at 15-month interim sacrifice and no gross or histopathologic effects on liver at interim or terminal sacrifice; equivocal evidence for increased incidence of hepatocellular tumors (adenomas and carcinomas combined)	
				Kidney	NOAEL=775–834 mg/kg-day LOAEL=None	No toxicologically significant effects on kidney weight at 15-month interim sacrifice; no gross or histopathologic effects on kidney at interim or terminal sacrifice	
				Endocrine system	NOAEL=775–834 mg/kg-day LOAEL=None	No gross or histopathologic effects on adrenals, pituitary, or thyroid glands	
				Reproduction	NOAEL=775–834 mg/kg-day LOAEL=None	No gross or histopathologic effects on reproductive organs	

Appendix B. Critical Study Reviews

Repeated-dose toxicity studies

Kwack et al., 2009

Sexually immature (5-week-old) male Sprague-Dawley rats (n=6/group) were exposed to 0 or 500 mg/kg-day DEP, or 250 mg/kg-day MEP, 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). Body weight was monitored repeatedly throughout the study. Food consumption was measured at the beginning of the study and twice/week during the last week of treatment. Before termination, urine was collected for 12 hours for urinalysis. At termination, the heart, lung, liver, kidneys, adrenal glands, spleen, thymus, thyroid glands, testes, and epididymides were weighed for determination of relative organ weights. Blood was collected at this time for comprehensive hematological and clinical chemistry testing (including electrolytes). The right cauda epididymis was used for sperm count analysis and the left was used for motility analysis. Specific motility parameters measured included percentage of motile sperm, average path velocity, straight-line velocity, curvilinear velocity, amplitude of the lateral head displacement, beat cross frequency, straightness, and linearity. No examination for organ pathology was performed for this study.

There was no mortality during the study (Kwack et al., 2009). Clinical signs were limited to salivation immediately after dosing. Mean terminal body weights in DEP- or MEP-exposed rats were not significantly ($p > 0.05$) different from the control mean, and food consumption was unchanged. Relative organ weights and hematological parameters were also not affected by dosing with DEP or MEP. Serum chemistry analyses showed only a small (8%) significant increase in serum calcium in rats exposed to DEP, but not MEP. Urinalysis showed no differences between treated and control animals. DEP had no effect on sperm count or motility, although among the individual components of motility, linearity was significantly reduced by 18% relative to controls. In contrast, MEP produced significant decreases in sperm count (-41%) and motility (-56%), but with no effect on linearity or any of the other individual components of motility. 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).

Brown et al. (1978)

Groups of male and female Sprague-Dawley rats (15/sex/group) were administered DEP in the diet at 0, 0.2, 1.0, or 5.0% for 16 weeks (Brown et al., 1978). Based on body weight and food consumption data, the study authors estimated mean DEP intakes of 0, 150, 770, and 3,160 mg/kg-day, respectively, for the males and 0, 150, 750, and 3,710 mg/kg-day, respectively, for the females. Additional groups of 5 rats/sex were fed similar diets for 2 or 6 weeks for interim assessments. A paired-feeding portion of the study was performed using 6 rats/sex fed diets containing 0 or 5.0% DEP for 112 days. Each control rat was given the same amount of food that had been consumed by its DEP-treated paired litter-mate the previous day. In each segment of the study, body weights were measured weekly. In the main portion of the study, food and water intakes were measured weekly. Urine was collected during treatment weeks 2, 6, and 13 and examined for cells and other microscopic constituents, protein, glucose, ketones, bile, and blood. Urine concentration and dilution tests were performed as well. At terminal sacrifice (week 16), blood was collected for hematological evaluation and serum samples were evaluated for alanine aminotransferase (ALT), aspartate aminotransferase (AST), and lactate dehydrogenase (LDH) activity. Differential leukocyte counts were also performed on blood samples collected from control and high-dose animals sacrificed after 2 and 6 weeks of treatment. Macroscopic lesions were noted and brain, pituitary, thyroid, heart, liver, kidney, adrenal glands, spleen, gonads, stomach, small intestine, and caecum were weighed. Samples of all major organs and tissues were prepared for histopathologic evaluations.

DEP-treated rats exhibited no treatment-related changes in behavior or clinical signs. High-dose rats of both sexes consumed only 21–27% as much food as their respective controls at the beginning of the treatment period, but reported food consumption was not significantly different from that of controls at other reported time points (days 27, 56, and 112) (Brown et al., 1978). A pattern of more marked decrease in food consumption at the beginning of a treatment period than later may reflect decreased palatability of DEP. Overall mean food consumption in the high-dose male and female rats was 23 and 18%, respectively, lower than that of controls ($p < 0.05$); mid-dose females consumed approximately 11% less food overall than their controls ($p < 0.05$), although there was no significant difference between mid-dose females and controls at days 25, 56, or 112. Mean body weights of the high-dose rats were 23–25% (males) and 15 to 20% (females) lower than those of controls at days 27, 56, and 112 ($p < 0.05$). Mean body weight of mid-dose males was 6% lower ($p < 0.05$) than that of controls on day 27, whereas mean body weight of mid-dose females was 5–8% lower ($p < 0.05$) than that of controls at days 27, 56, and 112. Although pair-fed high-dose male and female rats consumed slightly more food

during the 112 days of treatment than their corresponding controls, mean body weights and body weight gains in the high-dose groups were 7–12% lower than those of their respective controls, indicating that the effects on body weight in the DEP-treated rats of the main study were not solely the result of decreased food consumption, but were partly attributable to decreased food efficiency. There were no significant DEP treatment-related effects on water consumption.

There were no consistent dose-related effects on hematology, serum enzyme (ALT, AST, LDH) activity, or urinary parameters, and no remarkable treatment-related gross or histopathological effects (Brown et al., 1978). The study authors noted a pattern of reduction in absolute weight of brain, heart, spleen, kidneys, adrenal glands, gonads, and pituitary, but increase in relative weight of these organs and the pituitary, particularly at DEP dose levels resulting in depressed body weight; it was suggested that the effects on these organ (and pituitary) weights were the direct result of DEP-induced depressed body weight. Significantly increased relative liver weight was noted in low-, mid-, and high-dose females (6, 8, and 31%, respectively, higher than controls) and in high-dose males (33% higher than controls). High-dose males and females exhibited significantly increased relative kidney weight (18 and 11%, respectively, higher than controls). At week 16, dose-related significantly increased relative weights of stomach and small intestine were noted in all groups of DEP-treated males and females; the study authors postulated that the effects on stomach and small intestine weights may have been a result of unusually low weights in the control animals rather than a direct effect of DEP treatment because it was noted that little or no growth of these organs occurred in the controls between weeks 6 and 16, whereas the body weight increased by 40% in that time period. Histopathologic examinations revealed no evidence of DEP treatment-related lesions in males or females. This study identified a NOAEL of 1% DEP in the diet (750 mg DEP/kg-day for males and 770 mg DEP/kg-day for females) and a lowest-observed-adverse-effect level (LOAEL) of 5% DEP in the diet (3,160 mg DEP/kg-day for males and 3,710 mg DEP/kg-day for females) for decreased mean body weight and increased liver and kidney weight.

NTP (1995)

Groups of F344/N rats (10/sex/group) were administered DEP dermally 5 days/week for 4 weeks at 0, 37.5, 75, 150, or 300 µL neat (0, 46, 92, 184, or 369 mg/animal using a density of 1.23 g/mL for DEP as reported by NTP) to shaved interscapular skin (NTP, 1995). Based on reported body weight data, approximate DEP doses were 0, 282, 559, 1,332, and 2,278 mg/kg-day for males and 0, 404, 783, 1,600, and 3,237 mg/kg-day for females. Animals were observed twice daily; clinical findings and body weights were recorded weekly. At necropsy, kidney,

liver, testis, and thymus weights were measured. Comprehensive gross and histopathologic examinations were performed on all animals. No clinical signs of toxicity were observed. There were no treatment-related effects on body weight or food consumption. Mean relative (but not absolute) liver weights were significantly increased in female rats of the two highest dose levels (7–8% higher than controls; $p \leq 0.05$) and in high-dose male rats (11% higher than controls; $p \leq 0.01$). Mean relative (but not absolute) kidney weights were significantly increased in male rats of the two highest dose levels (9–10%; $p \leq 0.05$) and in females of the second highest dose level (8%; $p \leq 0.05$); mean relative kidney weight in high-dose females was not significantly different from that of controls. There were no indications of DEP treatment-related gross or histopathologic lesions in any group. This study served as a dose range-finding study for a 2-year chronic toxicity and carcinogenicity study of F344/N rats.

In the corresponding mouse study, groups of B6C3F1 mice (10/sex/group) were administered DEP dermally 5 days/week for 4 weeks at 0, 12.5, 25, 50, or 100 µL neat (0, 15, 31, 62, or 123 µg/animal using a density of 1.23 g/mL for DEP as reported by NTP) to shaved interscapular skin (NTP, 1995). Based on reported body weight data, approximate DEP doses were 0, 630, 1,314, 2,594, and 5,212 mg/kg-day for males and 0, 785, 1,590, 3,196, and 6,340 mg/kg-day for females. Animals were observed twice daily; clinical findings and body weights were recorded weekly. At necropsy, kidney, liver, testis, and thymus weights were measured. Comprehensive gross and histopathologic examinations were performed on all animals. No clinical signs of toxicity were observed. Food consumption was similar among control and DEP-treated males and females. There were no significant differences in body weights between DEP-treated male or female rats and their respective controls. Evidence of DEP treatment-related effects on organ weights was limited to female mice of the 25 and 100 µL DEP dose groups that exhibited significantly increased mean absolute liver weight (14% higher than controls $p \leq 0.01$) and relative liver weight (10% higher than controls $p \leq 0.05$). Mean and relative liver weights of females from the 12.5 and 50 µL DEP dose groups were not significantly different from those of controls. There were no indications of DEP treatment-related gross or histopathologic lesions in any group. This study served as a dose range-finding study for a two-year chronic toxicity and carcinogenicity study of B6C3F1 mice.

Reproductive toxicity studies

Fujii et al. (2005)

In a two-generation reproductive toxicity study, groups of male and female Sprague-Dawley rats (24/sex/group) were administered DEP in the diet at 0, 600, 3,000, or 15,000 ppm (Fujii et al., 2005). DEP treatment of the F0 generation (5 weeks of age at the beginning of treatment) commenced 10 weeks prior to mating and continued through mating (1:1 basis), gestation, and lactation. At PND 4, litters were culled as evenly as possible to four males and four females each and continued on study through weaning at PND 21. Those F1 weanlings not selected to serve as F1 parental rats were sacrificed on PND 26. F1 parental rats were continued on the same DEP treatment schedule as that of the corresponding F0 parental rats until weaning of the F2 pups at PND 21. The total DEP treatment periods for both F0 and F1 parental animals were approximately 15 and 17 weeks for the males and females, respectively. Animals were examined daily for clinical signs and mortality. Body weights and food consumption were recorded weekly for both sexes of both parental generations prior to mating. Body weights of F0 and F1 parental females were also recorded on selected gestation and lactation days. For each litter of both generations, sex was determined, body weights were recorded on PNDs 0, 4, 7, 14, and 21, AGD was measured on PNDs 0 and 4, survival was determined on PNDs 0, 4, and 21, and viability indices was calculated. Other parameters assessed in pups included day of preputial separation and vaginal opening and selected indices of physical development and reflex ontogeny.

At sacrifice, weights of brain, liver, kidneys, spleen, pituitary gland, adrenal glands, testes, epididymides, prostate, ovaries, and uterus were recorded for F0 and F1 parental rats and those F1 and all F2 pups sacrificed on PND 26 (Fujii et al., 2005). For paired organs (e.g., kidneys), the average weight of the paired organs was determined and recorded. In addition, thymus and spleen weights were determined for control and high-dose F1 and F2 pups sacrificed at weaning. Histopathological examinations were performed on reproductive organs, mammary glands, pituitary, thyroid, and liver of all control and high-dose F0 and F1 parental animals, those low-dose parental males and females that exhibited abnormal estrous cyclicity or sperm abnormalities, and pairs that failed to mate or produce offspring. Kidneys from F1 parental females in control and high-dose groups were examined histopathologically because the high-dose group exhibited significantly higher kidney weight than controls. Thymus and spleen of selected control and high-dose F1 and F2 weanlings were examined histopathologically because the high-dose groups exhibited significantly lower thymus and spleen weights than controls.

Sperm parameters were evaluated in all surviving F0 and F1 parental males. Six F0 males from each group were assessed for liver CYP450 content and levels of serum testosterone and progesterone to investigate the effects of metabolism on these steroid hormones.

There were no DEP-related mortalities or clinical signs in either parental generation (Fujii et al., 2005). The study authors reported significantly increased body weight and/or body weight gain in mid-dose F0 parental female rats during the premating period, high-dose F1 males during the first treatment week, and high-dose F1 females during the lactation period. Significantly decreased food consumption (magnitude not reported) was observed in mid-dose F0 females during mating and gestation and increased food consumption was observed in high-dose F1 parental males and females during the first treatment week. There were no other significant body weight changes. The reported changes in parental body weight and food consumption were not considered to represent DEP toxicity. Based on body weight and food consumption data for the 600, 3,000, and 15,000 ppm DEP treatment groups, the study authors estimated mean DEP intakes of 40, 197, and 1,016 mg/kg-day, respectively, for the F0 males, 51, 255, and 1,297 mg/kg-day for the F0 females, 46, 222, and 1,150 mg/kg-day for the F1 parental males, and 56, 267, and 1,375 mg/kg-day for the F1 parental females.

Selected organ weights of F0 and F1 parental rats are summarized in Table B.1. Absolute and/or relative liver weights were significantly increased by up to 14% in high-dose F0 and F1 parental males and females (Fujii et al., 2005). Other observed changes were decreased absolute but not relative adrenal weight in high-dose F0 males (-12%), decreased relative but not absolute adrenal weight in high-dose F1 males (-8%), decreased absolute but not relative epididymal weight in high-dose F0 males (-5%), increased absolute and relative thyroid weight (+17–18%) in mid- but not high-dose F1 males, and increased absolute and relative kidney weight in high-dose F1 females (+7–9%). Gross and histopathologic examinations of reproductive organs, endocrine organs, and liver revealed no signs of DEP treatment-related effects in high-dose F0 and F1 parental males or females.

Table B.1. Mean Terminal Body Weights and Selected Organ Weights for Parental Male and Female Sprague-Dawley Rats Administered DEP by Gavage for Approximately 15–17 Weeks Including 10 Weeks Prior to Mating

DEP Dietary Level (ppm)		0	600	3,000	15,000
F0 males examined		22	22	22	22
Final body weight (g)		586 ± 65[a]	575 ± 59	587 ± 34	563 ± 55
Liver	Absolute (g) Relative (%)	18.97 ± 3.05 3.23 ± 0.24	18.04 ± 2.43 3.13 ± 0.29	18.82 ± 1.96 3.21 ± 0.28	19.37 ± 2.51 3.44 ± 0.23[b]
Adrenal	Absolute (mg) Relative ($\times 10^{-3}$)	57 ± 9 9.7 ± 1.4	54 ± 7 9.5 ± 1.4	53 ± 8 8.9 ± 1.2	50 ± 8[b] 8.9 ± 1.3
Epididymides	Absolute (mg) Relative ($\times 10^{-3}$)	1.30 ± 0.13 0.22 ± 0.03	1.23 ± 0.18 0.22 ± 0.04	1.29 ± 0.08 0.22 ± 0.02	1.23 ± 0.11[b] 0.22 ± 0.03
F1 males examined		24	24	24	24
Final body weight (g)		605 ± 48	604 ± 61	617 ± 78	619 ± 67
Liver	Absolute (g) Relative (%)	19.28 ± 2.41 3.19 ± 0.32	19.60 ± 2.88 3.24 ± 0.28	20.15 ± 3.31 3.26 ± 0.29	21.94 ± 4.05[b] 3.53 ± 0.35[c]
Adrenal	Absolute (mg) Relative ($\times 10^{-3}$)	61 ± 6 10.0 ± 0.9	60 ± 9 10.0 ± 1.3	57 ± 8 9.3 ± 1.4	57 ± 6 9.2 ± 0.9[b]
Thyroid	Absolute (mg) Relative ($\times 10^{-3}$)	25.3 ± 5.2 4.2 ± 0.8	27.0 ± 5.0 4.5 ± 0.9	29.8 ± 5.4[c] 4.9 ± 1.0[c]	26.9 ± 5.1 4.4 ± 0.9
F0 females examined		22	22	24	21
Final body weight (g)		313 ± 23	316 ± 20	307 ± 18	317 ± 24
Liver	Absolute (g) Relative (%)	12.96 ± 2.09 4.14 ± 0.57	12.95 ± 1.49 4.11 ± 0.54	13.00 ± 1.44 4.23 ± 0.44	14.44 ± 1.76[b] 4.57 ± 0.52[b]
F1 females examined		23	23	22	23
Final body weight (g)		326 ± 22	330 ± 28	334 ± 30	329 ± 21
Liver	Absolute (g) Relative (%)	13.43 ± 1.33 4.12 ± 0.27	14.14 ± 2.21 4.28 ± 0.54	14.03 ± 1.75 4.21 ± 0.39	14.89 ± 1.62[b] 4.52 ± 0.39[c]
Kidney	Absolute (mg) Relative ($\times 10^{-3}$)	2.26 ± 0.22 0.70 ± 0.06	2.28 ± 0.19 0.69 ± 0.06	2.32 ± 0.24 0.70 ± 0.06	2.47 ± 0.22[c] 0.75 ± 0.06[c]

[a]Mean ± SD.
[b]Significantly different from control by Dunnett's test ($p \leq 0.05$).
[c]Significantly different from control by Dunnett's test ($p \leq 0.01$).

Source: Fujii et al. (2005).

There were no significant effects on sperm counts or motility among F0 or F1 parental male rats, although increased rates of abnormal, and specifically tailless, sperm were noted in the F0 mid-dose (1.26 ± 0.96 and 1.11 ± 0.90%, respectively) group compared to 0.73 ± 0.61 and 0.60 ± 0.53%, respectively, in controls ($p \leq 0.05$) and in F1 mid- (1.31 ± 0.84 and 1.25 ± 0.78%, respectively) and high-dose (1.52 ± 1.18 and 1.40 ± 1.06%, respectively) groups compared to 0.60 ± 0.53% and 0.58 ± 0.48%, respectively, in controls ($p \leq 0.01$). No significant DEP-related changes were observed regarding estrous cyclicity, copulation, fertility, number of implants,

number of pups born, sex ratio, viability before weaning, or AGD at PND 0 or 4 (Fujii et al., 2005). In the high-dose group of F1 parental females, gestation length was significantly shortened (22.1 ± 0.3 versus 22.4 ± 0.5 days; $p \leq 0.05$), but was still within the normal range for this strain. Among the F1 and F2 offspring evaluated for growth during lactation (PNDs 0–21), no significant effects were seen regarding mean body weights of low- or mid-dose F1 and F2 males or females. Effects at the high dose included significantly ($p \leq 0.05$) lower mean body weight in F0 females at PNDs 4, 7, and 14 (11–13% lower than controls) and significantly ($p \leq 0.01$) lower mean body weights in all groups of high-dose F1 (18–19% lower than controls) and F2 (12% lower than controls) males and females at PND 21. Assessments of indices of physical development revealed significantly increased age at pinna detachment (3.0 ± 0.6 versus 2. 0 ± 0.6 days for controls; n=22) and decreased age at incisor eruption (11.2 ± 0.9 versus 11.9 ± 0.7 days for controls; n=22) in high-dose F0 males and no significant change in these parameters in other high-dose groups or any of the low- or mid-dose groups. Age at eye opening was similar among all groups of DEP-treated and control F1 and F2 male and female pups. Among the F1 female pups (n=24) used to produce F2 pups, age at vaginal opening was increased (31.7 ± 2.1 versus 30.0 ± 1.5 days of age for controls; $p \leq 0.05$).

Body weight and selected organ and glandular tissue weight data for F1 and F2 male weanlings at PND 26 sacrifice are summarized in Table B.2. Mean body weights for F1 and F2 male weanlings were 13 and 7% lower, respectively, than corresponding controls (Fujii et al., 2005). Significantly decreased relative liver weight in low-dose F1 male weanlings was considered incidental because there was no significant effect on liver weight at the mid-dose level. There were no statistically significant changes in mean weights of other organs or glands assessed in the low- or mid-dose males. At the high-dose level, mean weights of several organs and glands from F1 and F2 male weanlings were significantly different from those of controls. F1 male weanlings exhibited increased relative (but not absolute) weights of brain (14% higher than controls), liver (11% higher than controls), seminal vesicles (17% higher than controls), and pituitary gland (15% higher than controls); decreased absolute (but not relative) weights of kidneys (10% lower than controls), spleen (11% lower than controls), adrenals (12% lower than controls), and prostate (20% lower than controls); and decreased absolute and relative thymus weight (23 and 11% lower, respectively, than controls). F2 male weanlings exhibited increased mean relative (but not absolute) liver weight (16% higher than controls), decreased mean relative (but not absolute) adrenal gland weight (12% lower than controls), and decreased mean absolute and relative weights of spleen (14 and 12% lower, respectively, than controls) and thymus (20 and 15% lower, respectively, than controls).

Table B.2. Mean Terminal Body Weights and Selected Organ Weights for 26-Day-Old F0 and F1 Male Weanlings of Male and Female Sprague-Dawley Rats Administered DEP by Gavage Prior to Mating, and During Mating, Gestation, and Lactation

DEP Dietary Level (ppm)		0	600	3,000	15,000
F1 male weanlings examined		22	22	23	21
Body weight (g)		84 ± 8[a]	84 ± 8	83 ± 13	73 ± 9[b]
Brain	Absolute (g) Relative (%)	1.62 ± 0.05 1.94 ± 0.17	1.63 ± 0.07 1.96 ± 0.15	1.63 ± 0.09 1.99 ± 0.26	1.59 ± 0.08 2.21 ± 0.22[b]
Liver	Absolute (g) Relative (%)	3.90 ± 0.47 4.63 ± 0.24	3.71 ± 0.42 4.40 ± 0.25[b]	3.83 ± 0.68 4.57 ± 0.22	3.75 ± 0.51 5.15 ± 0.21[b]
Kidney	Absolute (g) Relative (%)	0.99 ± 0.10 1.18 ± 0.07	1.02 ± 0.12 1.21 ± 0.11	0.99 ± 0.16 1.19 ± 0.06	0.89 ± 0.08[b] 1.23 ± 0.09
Spleen	Absolute (g) Relative (%)	0.36 ± 0.05 0.43 ± 0.05	0.34 ± 0.05 0.41 ± 0.05	0.36 ± 0.07 0.43 ± 0.06	0.32 ± 0.04[b] 0.44 ± 0.04
Prostate	Absolute (mg) Relative ($\times 10^{-3}$)	40 ± 10 47 ± 10	40 ± 9 48 ± 9	40 ± 9 48 ± 9	32 ± 9[c] 44 ± 11
Seminal vesicles	Absolute (mg) Relative ($\times 10^{-3}$)	20 ± 3 23 ± 4	20 ± 4 24 ± 5	20 ± 5 24 ± 5	20 ± 4 27 ± 5[c]
Adrenal	Absolute (mg) Relative (%)	26 ± 3 31 ± 4	26 ± 3 31 ± 3	24 ± 4 29 ± 4	23 ± 4[c] 31 ± 5
Pituitary	Absolute (mg) Relative ($\times 10^{-3}$)	3.4 ± 0.4 4.0 ± 0.6	3.4 ± 0.5 4.1 ± 0.4	3.5 ± 0.6 4.2 ± 0.5	3.3 ± 0.6 4.6 ± 0.7[c]
Thymus	Absolute (mg) Relative ($\times 10^{-3}$)	352 ± 48 420 ± 53	340 ± 71 405 ± 78	355 ± 88 422 ± 62	270 ± 52[b] 372 ± 58[c]
F2 male weanlings examined		23	23	22	23
Final body weight (g)		88 ± 14	88 ± 9	88 ± 6	82 ± 9[c]
Liver	Absolute (g) Relative (%)	3.89 ± 0.69 4.42 ± 0.27	3.89 ± 0.54 4.41 ± 0.24	4.01 ± 0.44 4.56 ± 0.32	4.22 ± 0.53 5.14 ± 0.29[b]
Spleen	Absolute (g) Relative (%)	0.35 ± 0.06 0.41 ± 0.07	0.32 ± 0.06 0.37 ± 0.05	0.35 ± 0.06 0.40 ± 0.05	0.30 ± 0.06[c] 0.36 ± 0.05[c]
Adrenal	Absolute (mg) Relative ($\times 10^{-3}$)	25 ± 5 29 ± 4	25 ± 3 28 ± 3	25 ± 3 28 ± 4	22 ± 4[b] 27 ± 4
Thymus	Absolute (mg) Relative ($\times 10^{-3}$)	367 ± 64 420 ± 43	375 ± 61 426 ± 52	358 ± 54 406 ± 45	292 ± 54[b] 356 ± 54[b]

[a]Mean ± SD.
[b]Significantly different from control by Dunnett's test ($p \leq 0.01$).
[c]Significantly different from control by Dunnett's test ($p \leq 0.05$).

Source: Fujii et al. (2005).

Body weight and selected organ and glandular tissue weight data for F1 and F2 female weanlings are summarized in Table B.3. Mean body weights of high-dose F1 and F2 female weanlings were 20 and 7% lower, respectively, than corresponding controls (Fujii et al., 2005).

High-dose F1 female weanlings exhibited decreased mean absolute and relative weights of brain (5 and 18% lower, respectively, than controls) and thymus (30 and 14% lower, respectively, than controls); decreased absolute and increased relative mean liver weight (12% lower and 9% higher, respectively, than controls); and decreased mean absolute (but not relative) weights of kidneys (16% lower than controls), thyroid (14% lower than controls), adrenal glands (19% lower than controls), and uterus (22% lower than controls). High-dose F2 female weanlings exhibited increased mean relative (but not absolute) weights of brain (6% higher than controls) and liver (16% higher than controls); decreased mean absolute (but not relative) weights of kidneys (9% lower than controls) and adrenal glands (17% lower than controls); and decreased mean absolute and relative weights of thymus (19 and 13% lower, respectively, than controls) and uterus (27 and 20% lower, respectively, than controls). Mid-dose F1 female weanlings exhibited decreased absolute (but not relative) adrenal weight (12% lower than controls) and mid-dose F2 female weanlings exhibited decreased mean relative (but not absolute) uterus weight (17% lower than controls).

Table B.3. Mean Terminal Body Weights and Selected Organ Weights for 26-Day-Old F0 and F1 Female Weanlings of Male and Female Sprague-Dawley Rats Administered DEP by Gavage Prior to Mating, and During Mating, Gestation, and Lactation

DEP Dietary Level (ppm)		0	600	3,000	15,000
F1 female weanlings examined		21	22	23	21
Body weight (g)		81 ± 9[a]	78 ± 8	78 ± 11	65 ± 9[b]
Brain	Absolute (g) Relative (%)	1.60 ± 0.07 2.00 ± 0.17	1.59 ± 0.08 2.05 ± 0.18	1.60 ± 0.08 2.08 ± 0.24	1.52 ± 0.11[c] 2.35 ± 0.22[b]
Liver	Absolute (g) Relative (%)	3.41 ± 0.54 4.22 ± 0.26	3.15 ± 0.43 4.03 ± 0.34	3.20 ± 0.63 4.09 ± 0.37	3.00 ± 0.39[c] 4.60 ± 0.23[b]
Kidney	Absolute (g) Relative (%)	0.94 ± 0.10 1.18 ± 0.05	0.92 ± 0.11 1.18 ± 0.09	0.93 ± 0.14 1.20 ± 0.08	0.79 ± 0.09[b] 1.21 ± 0.09
Uterus	Absolute (mg) Relative ($\times 10^{-3}$)	59 ± 11 74 ± 18	61 ± 15 78 ± 19	63 ± 16 81 ± 18	46 ± 11[b] 70 ± 14
Adrenal	Absolute (mg) Relative (%)	26 ± 5 32 ± 5	26 ± 4 33 ± 5	23 ± 3[c] 30 ± 4	21 ± 3[b] 32 ± 4
Thyroid	Absolute (mg) Relative ($\times 10^{-3}$)	7.8 ± 1.5 9.7 ± 2.1	7.4 ± 1.1 9.6 ± 1.7	7.4 ± 1.0 9.6 ± 1.5	6.7 ± 1.0[c] 10.3 ± 1.8
Thymus	Absolute (mg) Relative ($\times 10^{-3}$)	362 ± 50 451 ± 48	353 ± 54 455 ± 70	362 ± 59 467 ± 61	255 ± 45[b] 389 ± 47[b]

Table B.3. Mean Terminal Body Weights and Selected Organ Weights for 26-Day-Old F0 and F1 Female Weanlings of Male and Female Sprague-Dawley Rats Administered DEP by Gavage Prior to Mating, and During Mating, Gestation, and Lactation

DEP Dietary Level (ppm)		0	600	3,000	15,000
F2 female weanlings examined		23	23	21	22
Final body weight (g)		82 ± 11	83 ± 8	83 ± 7	76 ± 4[b]
Brain	Absolute (g) Relative (%)	1.61 ± 0.08 1.99 ± 0.26	1.61 ± 0.06 1.96 ± 0.18	1.60 ± 0.07 1.94 ± 0.14	1.60 ± 0.06 2.10 ± 0.12[b]
Liver	Absolute (g) Relative (%)	3.41 ± 0.49 4.15 ± 0.29	3.46 ± 0.43 4.17 ± 0.32	3.53 ± 0.43 4.23 ± 0.34	3.67 ± 0.27 4.81 ± 0.26[b]
Kidney	Absolute (g) Relative (%)	0.92 ± 0.10 1.12 ± 0.07	0.92 ± 0.10 1.12 ± 0.08	0.91 ± 0.07 1.09 ± 0.05	0.84 ± 0.06[b] 1.10 ± 0.06
Uterus	Absolute (mg) Relative ($\times 10^{-3}$)	63 ± 22 76 ± 23	56 ± 14 67 ± 13	52 ± 10 63 ± 10[c]	46 ± 11[b] 61 ± 14[b]
Adrenal	Absolute (mg) Relative (%)	24 ± 4 29 ± 4	23 ± 3 28 ± 3	23 ± 3 28 ± 4	20 ± 3[b] 27 ± 4
Thymus	Absolute (mg) Relative ($\times 10^{-3}$)	370 ± 63 451 ± 47	372 ± 59 448 ± 50	348 ± 62 418 ± 61	300 ± 49[b] 391 ± 54[b]

[a]Mean ± SD.
[b]Significantly different from control by Dunnett's test ($p \leq 0.01$).
[c]Significantly different from control by Dunnett's test ($p \leq 0.05$).

Source: Fujii et al. (2005).

Among the F0 male rats assessed for liver CYP450 and serum testosterone and progesterone levels, significantly increased mean levels of liver CYP3A2 (1.7-fold higher than controls; $p \leq 0.01$) and CYP4A1 (4.6-fold higher than controls; $p \leq 0.05$) were observed in the high-dose group (Fujii et al., 2005). Significantly lower mean serum testosterone levels were noted in mid- and high-dose groups, although the change from control was larger in the mid-dose group than the high-dose group (0.50 ± 0.26 and 1.26 ± 0.66 ng/mL, respectively, versus 2.53 ± 1.23 ng/mL for controls).

The two-generation reproductive toxicity study of male and female Sprague-Dawley rats administered DEP in the diet (Fujii et al., 2005) identified a NOAEL of 15,000 ppm (1,016–1,375 mg/kg-day) for reproductive effects. Although decreased serum testosterone levels in F0 males and increased frequency of abnormal (tailless) sperm in F1 parental males were observed in 3,000 and 15,000 ppm groups, the researchers considered the changes to be toxicologically insignificant due to lack of consistent dose-response, slight magnitude, and/or absence of associated effects on copulation, fertility indices, sperm counts and motility, or histopathology of testis and epididimides. For developmental effects, the study identified a NOAEL of 3,000 ppm

(197–267 mg/kg-day) and a LOAEL of 15,000 ppm (1,016–1,375 mg/kg-day) for decreased pup weight at weaning in both generations, delayed pinna detachment in F1 male pups, and delayed onset of vaginal opening in F1 female pups. The effects on organ weights of high-dose F1 and F2 weanlings were considered to be secondary to the body weight effects. For systemic effects, a LOAEL of 15,000 ppm (1,016–1,375 mg/kg-day) and NOAEL of 3,000 ppm (197–267 mg/kg-day) are identified based on increased absolute and relative liver weight (up to 14%) in F0 and F1 adult males and females.

Lamb et al. (1987); NTP (1984)

In a continuous breeding study (Lamb et al., 1987; NTP, 1984), groups of male and female Swiss (CD-1) mice were administered control diet (40/sex) or diets containing DEP at 0, 0.25, 1.25, or 2.5% (20/sex/group) for 7 days prior to being grouped as cohabitating pairs for 98 days during which dietary treatment continued and during a 21-day period of segregation following cohabitation. Estimated DEP doses to the low-, mid-, and high-dose groups were 451, 2,255, and 4,509 mg/kg-day, respectively, for the males and 488, 2,439, and 4,878 mg/kg-day, respectively, for the females (based on U.S. EPA [1988] subchronic reference values for body weight and food intake for male and female mice; calculations performed for this review). After the continuous breeding period, the parental mice were separated from their mates and continued on respective treatment for 21 days to allow delivery of any remaining litters. Parental mice were assessed for survival, clinical signs, body weight, and food intake. Reproductive parameters evaluated during the continuous breeding phase of F0 parental mice included numbers of litters/pair, number of pups/litter, pup weight, and number of live pups within 12 hours of birth.

One mid-dose male and two high-dose males and one high-dose female died during the treatment period; cause of death was not specified in the study report (Lamb et al., 1987; NTP, 1984). Food intakes were similar among control and DEP-treated groups. The study authors reported 6% lower average body weight in the high-dose males compared to controls at week 13 (35.6 versus 38.0 g for controls; statistically significant although *p*-value not specified); there were no significant effects on body weight of female mice. There were no significant treatment-related adverse effects on any of the reproductive parameters evaluated. At weaning, the mean body weight (± SE) of the high-dose F1 males was 25% lower than that of controls (8.22 ± 0.37 versus 10.96 ± 0.64 g for controls; *p*-value not provided; n=20). Body weights were not provided in the study reports for other DEP-treated groups of F1 males at weaning or any group of F1 females at weaning.

Because fertility and reproductive performance were not affected by DEP treatment of parental mice, these parameters were assessed in F1 offspring once they reached sexual maturity (Lamb et al., 1987; NTP, 1984). For this phase of the study, the final litters from the control and high-dose groups (2.5% DEP in the diet) of the continuous breeding phase were kept with their mothers during continued treatment, weaned at 21 days of age, and continued on the diet of their mothers. At approximately 10 weeks of age, the F1 animals were cohabitated for an unspecified period of time with mice of their respective treatment groups to produce F2 pups. F1 parental animals were then sacrificed and assessed for body weight and selected organ and tissue weights (liver, brain, pituitary, left testis and epididymis, right testis, right epididymis, prostate, seminal vesicles, ovary and oviduct, uterus). Sperm samples from F1 parental males were assessed for motility, concentration, and abnormalities.

At weaning, mean (± SE) body weight of the DEP-treated F1 males was 25% lower than that of controls (8.22 ± 0.37 versus 10.96 ± 0.64 g for controls; *p*-value not provided; n=20) (Lamb et al., 1987; NTP, 1984). At the start of cohabitation, mean body weight of the DEP-treated F1 males was 11% lower than that of controls (29.13 ± 0.74 versus 32.91 ± 0.81 g for controls; *p*-value not provided). Body weight data for F1 females at weaning and at the beginning of cohabitation were not provided in the study reports.

Table B.4 presents results of terminal body weights and selected organ weights for F1 parental male and female mice (Lamb et al., 1987; NTP, 1984). Mean final body weights of the DEP-treated F1 parental male and female mice were 12 and 8% lower than those of respective controls. DEP-treated F1 parental males exhibited 18% increased mean liver weight (adjusted for body weight) and 32% increased mean prostate weight (absolute and adjusted for body weight) compared to controls. DEP-treated F1 parental females exhibited 15% increased mean absolute liver weight (28% increased mean liver weight adjusted for body weight) and 17% decreased mean absolute pituitary weight (12% decreased mean pituitary weight adjusted for body weight). There were no significant DEP-related effects on absolute or relative weights of brain or pituitary of F1 parental males or reproductive organs of F1 parental males or females. DEP treatment did not affect the percentages of motile or abnormal sperm; however, sperm concentration was decreased by 30% in the high-dose males compared to controls ($p < 0.01$). There were no treatment-related effects on fertility, proportion of pups born alive, live pup birth weight, or sex distribution. The total number of live pups per litter (combined male and female) from the F1 parental mice was significantly ($p < 0.05$) lower than that of controls (9.95 ± 0.67 versus 11.53 ± 0.54 for controls; n=19).

Table B.4. Mean Terminal Body Weights and Selected Organ Weights for F1 Parental Male and Female Mice[a] Administered DEP in the Diet from Weaning at 21 Days for 7 Weeks and During Subsequent Cohabitation to produce F2 Offspring

DEP Dietary Level (%)		0	2.5
F1 parental males (n=20)			
Terminal body weight (g)		34.16 ± 0.81[b]	30.20 ± 0.61[c]
Liver	Absolute (g) Adjusted for body weight (g)	1.83 ± 0.06 1.71 ± 0.04	1.89 ± 0.05 2.01 ± 0.04[c]
Prostate	Absolute (mg) Adjusted for body weight (mg)[d]	25 ± 1.3 25 ± 2.1	33 ± 2.3 33 ± 2.1[e]
F1 parental females (n=20)			
Terminal body weight (g)		30.57 ± 0.61	28.21 ± 0.51[c]
Liver	Absolute (g) Adjusted for body weight (g)	1.84 ± 0.06[f] 1.74 ± 0.04[f]	2.12 ± 0.07[c] 2.22 ± 0.04[c]
Pituitary	Absolute (mg) Adjusted for body weight (mg)	3.5 ± 0.1 3.4 ± 0.1	2.9 ± 0.1[c] 3.0 ± 0.1[e]

[a]The F1 parental mice had been exposed to DEP via the F0 parental mice administered DEP in the diet during cohabitation to produce offspring and via their mothers throughout gestation and lactation.
[b]Mean ± SE.
[c]Significantly different from control ($p \leq 0.01$; specific statistical test method not stated for this endpoint).
[d]Organ weights adjusted for body weight by analysis of covariance.
[e]Significantly different from control ($p \leq 0.05$; specific statistical test method not stated for this endpoint).
[f]n=19.

Sources: Lamb et al. (1987); NTP (1984).

The continuous breeding study (Lamb et al., 1987; NTP, 1984) found no evidence of DEP-induced systemic or reproductive effects in the first generation phase of the study. However, because mean body weight of the F1 males at weaning was 25% lower than that of controls, the high dose (4,509–4,878 mg DEP/kg-day) may be considered a LOAEL for developmental effects. DEP-treated F1 parental males (4,509 mg DEP/kg-day) exhibited significantly depressed mean final body weight, increased mean prostate weight, and decreased sperm concentration. DEP-treated F1 parental females (4,878 mg DEP/kg-day) exhibited significantly increased liver weight and decreased mean pituitary weight. The DEP-treated F1 parental mice produced significantly lower total number of live pups per litter. The DEP-treated group of F1 parental male and female mice (4,509–4,878 mg/kg-day) exhibited adverse systemic and reproductive effects; a NOAEL was not identified.

Developmental toxicity studies

Field et al. (1993)

Groups of time-mated female Sprague-Dawley rats (31 controls and 32/DEP dose group) were administered DEP in the diet during GDs 6–15 at concentrations of 0, 0.25, 2.5, or 5.0%, providing author-estimated doses of 0, 200, 1,910, and 3,210 mg DEP/kg-day, respectively, based on measurements of body weight and food consumption (Field et al., 1993). Dams were observed daily for clinical signs and weighed on GDs 0, 3, 6, 9, 12, 15, 18, and 20. At terminal sacrifice (GD 20), liver, kidneys, and intact uterus were weighed. Live fetuses were removed from gravid uteri, weighed, sexed, and examined for external and visceral abnormalities. The heads from half of the fetuses were prepared for microscopic evaluation and all fetal carcasses were examined for skeletal malformations.

None of the dams died during the study, although one low-dose dam was removed from the study due to a feeding error (Field et al., 1993). The study authors stated that maternal body weight was reduced in mid- and high-dose dams on GD 9 and that high-dose dams weighed less than controls on GDs 12, 15, and 18 (data not shown in the study report). Mean gestational weight gain in the low-dose dams during the DEP treatment period (GDs 6–15) was 16% greater than that of controls; mean gestational weight gain in the high-dose dams during the same period was 42% less than that of controls ($p < 0.05$). For the entire gestational period (corrected for gravid uterine weight), low-dose dams exhibited 18% increased mean gestational weight gain and high-dose dams exhibited 14% decreased mean gestational weight gain ($p < 0.05$). There were no significant effects on gravid uterine weight. Food consumption was significantly reduced in mid- and high-dose groups during GDs 6–9 (20 and 53%, respectively, less than that of controls) and in the high-dose group during GDs 9–12 (13% less than that of controls). However, food consumption increased in mid- and high-dose groups during the remainder of the gestational period and was not significantly different from that of controls when averaged over the entire gestational period. Water consumption in mid- and high-dose dams was significantly lower than that of controls during GDs 6–9 (15–16% less than that of controls). However, water consumption in high-dose dams was significantly greater than that of controls during GDs 15–18 and 18–20; there were no significant effects on water consumption averaged over the entire gestation period. Weights of uterus, liver, and kidney of DEP-treated dams were not significantly different from those of controls.

There were no DEP treatment-related effects on resorption incidence, live litter size, sex distribution, mean fetal body weight per litter, or percentages of fetuses or litters with gross malformations (Field et al., 1993). Fetuses from the high-dose group exhibited significantly increased percentage of extra (rudimentary) rib/litter (21.0 versus 8.8% for controls; $p < 0.05$) and percentage of litters with extra rib (74.2 versus 44.4% for controls; ($p < 0.05$). A significant linear trend was noted for percentage of fetuses with extra rib/litter ($p < 0.05$). This study identified a NOAEL of 1,910 mg DEP/kg-day (2.5% DEP in the diet) for maternal and developmental toxicity. The 3,210 mg DEP/kg-day dose level (5% DEP in the diet) represents a LOAEL for maternal toxicity (depressed body weight gain during DEP treatment) and developmental toxicity (increased incidence of extra rib).

Hardin et al. (1987)

Hardin et al. (1987) administered DEP to groups of time-mated female CD-1 mice (50/group) by gavage at 0 or 4,500 mg/kg-day (in corn oil) during GDs 6–13. Maternal mice were assessed for survival, body weight change, and number of viable litters produced as indices of maternal toxicity. Litter size, birth weight, and neonatal growth and survival to PND 3 served as indices of developmental toxicity. There were no DEP treatment-related effects on any of the assessed indices of maternal or developmental toxicity.

Gray et al. (2000)

DEP was administered by gavage to five time-mated female Sprague-Dawley rats from GD 14 to PND 3 at 750 mg/kg-day (in corn oil vehicle); a vehicle control group of nine time-mated dams was included (Gray et al., 2000). Dams were assessed for survival, clinical signs, and body and weight gain. Number of live pups, litter mean pup weights at birth, weaning, and puberty were recorded. Pup body weights and AGD were determined on PND 2, at which time one male pup from each litter was sacrificed for assessment of paired testes weight and histopathology. At 9–10 days of age, each male pup was examined for sign of hemorrhagic testes. At 13 days of age, males were examined for the presence of areolas/nipples. After weaning at PND 28, male pups were examined daily for onset of puberty. At sacrifice at 3–5 months of age, blood was collected for determination of serum testosterone level and the ventral surface was examined for abnormalities (retained nipples, cleft phallus, vaginal pouch, hypospadias). Internal examinations were performed to identify undescended testes, atrophic testes, epididymal agenesis, prostatic and vesicular agenesis, and abnormalities of the gubernacular cord. Recorded weights included body, pituitary, adrenal, kidney, liver, and the

various components of the reproductive system. For some of the males, spermatid head count was determined in one testis and sperm reserves were assessed in one cauda epididymis. Due to the dosing error and death of two DEP-treated females, offspring were assessed from only three litters. There were no DEP treatment-related effects on any of the above-specified parameters assessed in dams or pups.

Liu et al. (2005)

Liu et al. (2005) administered DEP (in corn oil vehicle) by gavage to groups of pregnant Sprague-Dawley rats on GDs 12–19 at 0 or 500 mg/kg-day in a study designed to assess global gene expression in the fetal testis following in utero exposure. Dam body weights were recorded on GD 7 and daily during the DEP treatment period. At sacrifice on GD 19, fetuses were weighed, AGD was measured, and sex ratio was determined. The testes were removed from male fetuses for assessment of gene expression. The study report did not include information regarding maternal or fetal body weight measurements or sex ratio results. AGDs for fetuses in the DEP treatment group were not significantly different from those of control fetuses. No significant changes in gene expression were detected.

Tanaka et al. (1987)

The Concise International Chemical Assessment Document 52 for Diethyl Phthalate (WHO, 2003) includes a summary of a study by Tanaka et al. (1987) published in Japanese. In the study, groups of pregnant ICR mice (18–20/group) were administered DEP percutaneously on GDs 0–17 at 0, 500, 1,600, or 5,600 mg/kg-day. There were no significant treatment-related effects on dam body weight. Significant effects in DEP-treated dams relative to controls included decreased thymus weight in all DEP-dosed groups and increased adrenal and kidney weights in the high-dose group. Fetal weight in the high-dose group was significantly lower than that of controls ($p < 0.01$). There were no significant effects on fertility index, number of corpora lutea, number of implantations, number of live fetuses, sex ratio, or number of gross malformations. The number of variations/retardations in the cervical and lumbar rib region was significantly higher in the high-dose group ($p < 0.05$).

Singh et al. (1972)

Singh et al. (1972) administered DEP to pregnant Sprague-Dawley rats (5/group) at 0.506, 1.012, or 1.686 mL/kg via intraperitoneal injection on GDs 5, 10, and 15. The study

included a group of untreated controls and groups administered distilled water, normal saline, or cottonseed oil (the study report did not specify whether a particular vehicle was used for DEP treatment). Dams were sacrificed on GD 20. Assessments were made regarding embryo-fetal toxicity (resorptions and stillbirths), gross and skeletal fetal malformations, and fetal size. Fetal skeletal evaluations were performed on 30–50% of the fetuses. Resorptions totaled 44, 0, and 3.6% in low-, mid-, and high-dose DEP-treated groups compared to 0% in untreated controls and 3–7% in the various vehicle-treated controls. There were no dead fetuses in any group and numbers of corpora lutea in DEP-treated groups were similar to those of untreated and vehicle controls. Number and percent of live fetuses were 35 (56%), 57 (100%), and 54 (96%) for low-, mid-, and high-dose groups, respectively, compared to 59 (100%) for untreated controls and 44–55 (88–94%) for vehicle controls. Average fetal weights (g ± SD) were significantly lower in all DEP-treated groups (2.63 ± 0.24, 2.85 ± 0.19, and 2.85 ± 0.27 for low-, mid-, and high-dose groups, respectively, compared to 4.83 ± 0.01 for untreated controls and 4.10–4.65 for vehicle controls). Unspecified skeletal abnormalities were reported in 26.3, 47.1, and 81.3% of the low-, mid-, and high-dose fetuses examined compared to 0% of the untreated control fetuses and 0–14.3% of the vehicle control fetuses.

Chronic toxicity and carcinogenicity studies

NTP (1995)

The NTP (1995) conducted chronic toxicity and carcinogenicity studies of DEP applied dermally to groups of F344/N rats and B6C3F1 mice (60/sex/dose/species) 5 days/week for 104 weeks (rats) and 104–105 weeks (mice). Interim evaluations were performed at 15 months (10 animals/sex/dose/species). All animals were observed twice daily. Clinical findings were recorded monthly. Animals were weighed at study initiation, weekly for the first 13 weeks, and monthly thereafter. At 15-month interim sacrifice, blood was collected for hematology (rats and mice) and clinical chemistry (rats only); brain, kidney, and liver were weighed. Gross and comprehensive histopathologic examinations were performed on all control and high-dose animals at 15-month interim sacrifice and all animals at terminal sacrifice.

In the rat study (NTP, 1995), DEP was applied neat to the shaved interscapular skin at 0, 100, or 300 µL/animal-day (0, 123, and 369 mg/animal using a density of 1.23 g/mL for DEP as reported by NTP). Based on reported mean body weights for the time periods of 1–13, 14–52, and 53–105 weeks (and adjustment for 5 days of treatment/week), approximate TWA doses of DEP were 230 and 743 mg/kg-day to the low- and high-dose males and 379 and 1,170 mg/kg-

day to the low- and high-dose females. There were no significant differences in survival among control and DEP-treated male or female rats. Survival to 15-month interim sacrifice was ≥95% for all groups. However, survival to terminal sacrifice among the control, low-, and high-dose groups was only 8, 12, and 12%, respectively, for the males and 59, 56, and 47%, respectively, for the females. Body weights of low- and high-dose male rats averaged for treatment weeks 1–13, 14–52, and 53–105, were 3–4 and 7–9%, respectively, lower than controls and were 2 and 7%, respectively, lower than controls among males that survived to terminal sacrifice. Body weights of DEP-treated female rats were generally 1–6% lower than controls through most of the study, but were comparable to controls among female rats that survived to terminal sacrifice. There were no indications of DEP treatment-related clinical signs except for increased incidence of slight crusting of the skin at the application site of DEP-treated rats.

Body and organ weight data from DEP-treated rats at 15-month interim sacrifice are summarized in Table B.5. Mean absolute and relative liver and kidney weights of DEP-treated male and female rats were not significantly different from those of controls (NTP, 1995). High-dose female rats exhibited significantly increased hematocrit, hemoglobin, and red blood cell counts compared to controls at interim sacrifice; the study authors considered the differences minimal and consistent with hemoconcentrations from dehydration. Pathology evaluations revealed significantly increased incidences of acanthosis at the application site of low- and high-dose males at interim and terminal sacrifice and high-dose females at terminal sacrifice; this lesion was considered an adaptive response to application site irritation. There were no statistically significant treatment-related increased incidences of nonneoplastic lesions at any other site or of neoplastic lesions at any site in males or females. The study authors determined that under the conditions of the study, there was no evidence of carcinogenic activity of DEP in the male or female F344/N rats, but noted that the sensitivity of the male rat portion of the study was reduced due to poor survival in all groups. For nonneoplastic effects, this study identified NOAELs of 743 and 1,170 mg/kg-day for male and female F344/N rats, respectively, the highest doses tested.

Table B.5. Mean Body Weights and Liver and Kidney Weights at 15-Month Interim Sacrifice of Male and Female F344/N Rats Exposed to DEP via Dermal Application Once per Day, 5 Days/Week

DEP Dermal Dose (µL/Rat)		0	100	300
Males; number assessed		10	10	9
Body weight (g)		436 ± 11[a]	419 ± 18	406 ± 9
Liver	Absolute (g) Relative (mg/g body weight)	15.139 ± 0.643 34.69 ± 1.14	15.491 ± 0.670 37.72 ± 2.59	15.026 ± 0.450 37.07 ± 1.08
Kidney	Absolute (g) Relative (mg/g body weight)	1.666 ± 0.054 3.83 ± 0.13	1.700 ± 0.061 4.13 ± 0.25	1.687 ± 0.050 4.17 ± 0.15
Females; number assessed		8	10	10
Body weight (g)		268 ± 6	261 ± 8	263 ± 9
Liver	Absolute (g) Relative (mg/g body weight)	9.573 ± 0.175 35.78 ± 0.83	9.699 ± 0.317 37.48 ± 1.53	9.728 ± 0.279 37.20 ± 1.06
Kidney	Absolute (g) Relative (mg/g body weight)	1.074 ± 0.027 4.02 ± 0.12	1.079 ± 0.035 4.17 ± 0.17	1.109 ± 0.028 4.25 ± 0.14

[a]Mean ± SE.

Source: NTP (1995).

In the corresponding mouse study (NTP, 1995), DEP was dissolved in acetone and applied to the shaved interscapular skin at 0, 7.5, 15, or 30 µL/animal-day (0, 9.2, 18.5, and 36.9 mg/animal-day using a density of 1.23 g/mL for DEP as reported by NTP). Based on reported mean body weights for the time periods of 1–13, 14–52, and 53–105 weeks (and adjustment for 5 days of treatment/week), approximate TWA doses of DEP were 191, 387, and 775 mg/kg-day to the low-, mid-, and high-dose males and 209, 415, and 834 mg/kg-day to the low-, mid-, and high-dose females. An initial 2-year study in mice that employed dermal doses of DEP neat at 0, 35, or 100 µL/animal/day was aborted due to marked reductions in body weight gain. There were no statistically significant differences in survival among control and DEP-treated male or female mice. Survival to terminal sacrifice among the control, low-, mid-, and high-dose mice was 86, 86, 92, and 86%, respectively for the males and 82, 75, 76, and 74%, respectively, for the females. There were no significant treatment-related clinical signs except for increased incidence of slight crusting of the skin at the application site of high-dose males and females.

Body and organ weight data from DEP-treated mice at 15-month interim sacrifice are summarized in Table B.6. High-dose females exhibited significantly reduced mean body weight (8% lower than controls); mid- and high-dose females exhibited significantly increased relative kidney weight (8–9% higher than controls) (NTP, 1995). A few minor sporadic hematology differences between DEP-treated mice and controls were not considered treatment related. Pathology evaluations revealed incidences of basophilic foci of 0/50, 1/50, 9/50, and 3/50 in the liver of the control, low-, mid-, and high-dose males, respectively, but the incidence was significantly increased only in the mid-dose group ($p \leq 0.01$). There were no statistically significant treatment-related increased incidences of nonneoplastic lesions at any other site in males or at any site in females.

Table B.6. Mean Body Weights and Liver and Kidney Weights at 15-Month Interim Sacrifice of Male and Female B6C3F1 Mice Exposed to DEP via Dermal Application Once per Day, 5 Days/Week

DEP Dermal Dose (µL/Rat)		0	7.5	15	30
Males; number assessed		10	10	10	10
Body weight (g)		39.9 ± 0.9[a]	37.6 ± 0.9	40.8 ± 0.6	37.8 ± 0.9
Liver	Absolute (g) Relative (mg/g body weight)	1.752 ± 0.070 44.00 ± 1.60	1.709 ± 0.051 45.50 ± 0.97	1.771 ± 0.078 43.40 ± 1.71	1.748 ± 0.142 46.29 ± 3.80
Kidney	Absolute (g) Relative (mg/g body weight)	0.410 ± 0.009 10.30 ± 0.12	0.402 ± 0.008 10.73 ± 0.24	0.390 ± 0.011 9.56 ± 0.22	0.373 ± 0.007[b] 9.89 ± 0.20
Females; number assessed		10	9	10	10
Body weight (g)		39.1 ± 0.05	36.5 ± 1.1	37.5 ± 0.8	36.0 ± 0.9[c]
Liver	Absolute (g) Relative (mg/g body weight)	1.623 ± 0.051 41.49 ± 1.13	1.500 ± 0.060 41.22 ± 1.50	1.551 ± 0.039 41.47 ± 1.25	1.536 ± 0.030[d] 43.31 ± 0.80[d]
Kidney	Absolute (g) Relative (mg/g body weight)	0.273 ± 0.004 7.00 ± 0.16	0.271 ± 0.009 7.44 ± 0.15	0.286 ± 0.005 7.64 ± 0.15[c]	0.272 ± 0.011 7.55 ± 0.22[c]

[a]Mean ± SD.
[b]Significantly different from control by Williams' or Dunnett's test ($p \leq 0.01$).
[c]Significantly different from control by Williams' or Dunnett's test ($p \leq 0.05$).
[d]n=9.

Source: NTP (1995).

In male mice, incidences of hepatocellular adenomas and hepatocellular carcinomas of DEP-treated groups were not significantly different from control incidences; however, combined incidences of adenoma or carcinoma were significantly increased at high dose (18/50 versus 9/50

controls; p=0.034) (NTP, 1995). Incidences of hepatocellular adenomas in control, low-, mid-, and high-dose female mice were 4/50, 12/51 (p=0.017), 14/50 (p=0.006), and 10/50, respectively. Although the incidences were significantly increased in low- and mid-dose groups, a significant dose-related trend was not found. Incidences of hepatocellular carcinomas in DEP-treated female mice were not significantly different from control incidence. Combined incidences of adenoma or carcinoma were significantly increased in low- and mid-dose females and reflected the increases in adenomas. Because the incidence of hepatocellular adenomas in the high-dose male mice was similar to that of historical controls, and in the absence of a dose-response trend for liver neoplasms in the female mice, the study authors indicated that the marginal increases in hepatocellular neoplasms provided only equivocal evidence of carcinogenic activity. For nonneoplastic effects, this study identified NOAELs of 775 and 834 mg/kg-day for male and female B6C3F1 mice, respectively, the highest doses tested.

NTP (1995) also reported the results of an initiation/promotion study of DEP. Groups of male Swiss (CD-1) mice (50/group) were administered various initiation/promotion treatments for 1 year to assess the initiation/promotion potential of DEP (NTP, 1995). Chemicals were applied to the clipped interscapular skin. DEP was tested as an initiator with and without the known skin tumor promoter, 12-O-tetradecanoylphorbol-13-acetate (TPA). DEP was tested as a promoter with and without the known skin tumor initiator, 7,12-dimethylbenzanthracene (DMBA). Comparative control groups included vehicle control (acetone/acetone), initiation/promotion control (DMBA/TPA), initiator control (DMBA/acetone), and promoter control (acetone/TPA). The initiation phase consisted of a single 0.1 mL application of DEP (neat), DMBA (0.5 mg/mL acetone), or acetone during the first week of treatment. The promotion phase generally consisted of 0.1 mL applications of DEP (neat), TPA (0.05 mg/mL in acetone 3 times/week for 8 weeks, then 0.025 mg/mL in acetone 2 times/week for 44 weeks), or acetone 3 or 5 times/week from week 2 until study termination. Due to severe irritation in groups receiving TPA as positive promotion controls or acetone, treatment was suspended from weeks 8 to 10 and resumed at two treatments per week. There was no evidence that DEP acted as a skin tumor initiator or promoter under the conditions of this study. The positive initiation/promotion (DMBA/TPA) control group exhibited high incidences of squamous cell papilloma and squamous cell papilloma or carcinoma as expected.

RIFM (1955)

Api (2001) summarized the results from an unpublished study (RIFM, 1955) in which rats were fed DEP at 0, 0.5, 2.5, or 5% in the diet for 2 years (approximate doses of 0, 250,

1,250, and 2,500 mg/kg-day, respectively). Slightly decreased body weight gain throughout the study and decreased food utilization efficiency in high-dose rats were reported. There were no treatment-related effects on hemocytology, blood sugar, non-protein nitrogen levels, or urinalysis results, and no evidence of treatment-related gross or microscopic lesions. The lack of study details in the available summary of the study precludes the usefulness of the study for quantitative risk assessment.

Additional studies

Pereira et al. (2007, 2006); Pereira and Rao (2007)

Pereira and coworkers performed a series of studies in which male and female Wistar rats were administered DEP in the diet at low concentrations (10–50 mg/kg food) for periods of approximately 5 months. One study employed only male rats (Pereira et al., 2006). Two other studies used male and female rats exposed for periods that included premating periods and exposures throughout mating, gestation, and postpartum phases for one generation (Pereira and Rao, 2007) or two generations (Pereira et al., 2007). All three studies reported adverse effects at oral DEP doses ≤2.85 mg/kg-day, although it is questionable whether DEP was the cause of the observed effects. The effects reported are generally not consistent with other studies of DEP or other phthalates, and the dose levels are orders of magnitude lower than DEP treatment-related effect levels identified in other repeated-dose oral studies. The one study that included multiple dose levels reported no clear dose-response or the reverse of the usual dose-response pattern (changes were seen at the low dose, but not the mid or high doses) for most altered endpoints.

Groups of young adult male Wistar rats (6/group) were administered dietary DEP (in corn oil) at 0, 10, 25, or 50 mg/kg food/day (author-reported DEP doses of 0, 0.57, 1.425, and 2.85 mg/kg-day, respectively) for 5 months (Pereira et al., 2006). Food consumption and body weights were monitored. Liver weights were determined at terminal sacrifice at 5 months, and liver and serum levels of acid phosphatase (ACP), LDH, ALT, AST, total triglycerides, and total cholesterol were determined. Liver glycogen and glutathione levels and amount of liver-lipid peroxidation were determined as well. Representative liver tissues were processed for light and electron microscope histopathologic evaluations. There were no indications of DEP treatment-related effects on behavior or food consumption. The study report did not include results of body weight assessments. The mean relative liver weight of the low-dose group was 20% higher than that of controls ($p \leq 0.05$); mean relative liver weights of the mid- and high-dose groups were not significantly different from that of controls. Low-, mid-, and high-dose groups

exhibited significantly increased serum and liver LDH, ALT, AST, and total triglyceride levels (31% to as much as 17-fold higher than controls, but with a flat or decreasing dose-response for most endpoints). Serum ACP was significantly increased in low-, mid-, and high-dose groups (4.25-, 2.25-, and 1.9-fold, respectively, higher than controls); liver ACP was significantly increased in the low-dose group only (2-fold higher than controls). Low-, mid-, and high-dose groups exhibited significantly increased liver glycogen (21%, 2.2-fold, and 2.9-fold higher than controls). Total cholesterol was significantly increased in livers of mid- and high-dose groups (37% and 2.7-fold higher than controls) and significantly decreased in the serum of mid- and high-dose groups (91% less than controls). Liver glutathione levels of low- and high-dose groups were decreased (62 and 36% lower than controls). The amount of liver-lipid peroxidation was significantly increased in low-, mid-, and high-dose groups (8.1-, 3.3-, and 5.7-fold higher than that of controls). The study authors reported severe vacuolation, fatty degeneration, and loss of hepatic architecture in the livers of the low-dose rats and a lesser degree of histopathologic liver lesions in mid- and high-dose groups, but incidence data were not included in the study report. Electron microscopy revealed dose-related increased proliferation of mitochondria in hepatocytes of DEP-treated rats and increased numbers of peroxisomes in hepatocytes of low-dose rats.

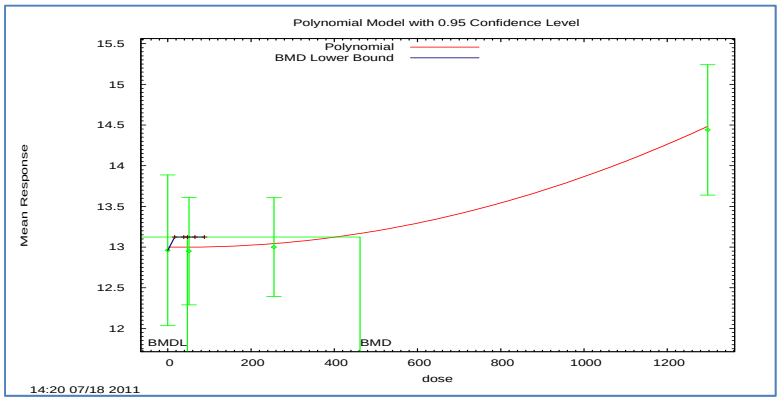
In the one-generation study (Pereira and Rao, 2007), groups of young adult Wistar rats (6/sex/group) were administered DEP in the diet at 0 or 50 mg/kg food/day (estimated as 2.85 mg/kg-day by the authors) for 100 days prior to mating, during 10 days of mating, and throughout gestation and lactation until termination at PND 21. Male and female pups were counted and examined for malformations. Six pups of each sex were assessed for body weight; serum LDH, alkaline phosphatase (ALP), and ACP levels; and liver histopathology. The study authors reported that the DEP-treated group exhibited decreased litter size, but did not include quantitative data to substantiate the finding. The study authors also stated that both male and female DEP-exposed pups exhibited sluggishness, lethargic behavior, and decreased activity compared to control pups. The mean body weights of the 21-day-old DEP-treated male and female pups were 35 and 24% lower than those of sex-matched controls. The DEP-treated male pups exhibited 16% lower mean absolute liver weight, but 31% higher mean relative liver weight than controls. The DEP-treated female pups exhibited 56 and 42% lower mean absolute and relative liver weights than controls. The DEP-treated male pups also exhibited significantly increased mean serum ACP, ALP, and LDH levels (4.9-, 15-, and 3.4-fold higher than controls); increased mean liver ACP and LDH levels (4.5- and 1.8-fold higher than controls); and decreased mean liver ALP level (4-fold lower than controls). The DEP-treated female pups exhibited significantly increased mean serum ACP, ALP, and LDH levels (6.2-, 14-, and 3.9-fold

higher than controls) and increased mean liver ACP and LDH levels (5.2- and 2.4-fold higher than controls). The study authors stated that mild vacuolations were observed in the livers of DEP-exposed male and female pup, but incidence data were not provided.

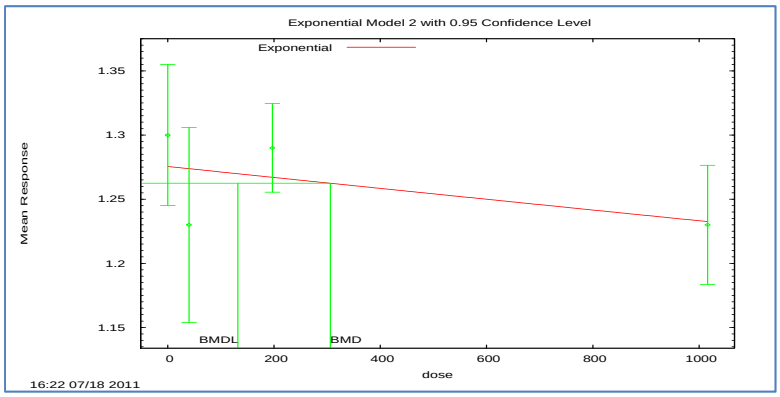
In the two-generation study, groups of young adult Wistar rats (6/sex/group) were administered DEP in the diet at 0 or 50 mg/kg food/day (2.85 mg/kg-day) for 100 days prior to mating, during 10 days of mating, and throughout gestation and lactation. After weaning, six pups of each sex were examined for malformations; the remaining pups were continued on the same treatment as their parents to produce a second generation that was sacrificed at PND 21 (weaning). Body weights and food consumption were monitored. Adrenal and thyroid from parental rats and pups were removed at sacrifice, weighed, and processed for histopathologic evaluation. The study authors stated that adrenal and thyroid weights of the DEP-treated groups were not significantly different from those of controls. Histopathologic evaluation revealed vacuolations and degeneration in the zona fasciculata region of the adrenal cortex of DEP-treated parental and F1 male (but not female) rats. Reported histopathologic lesions of the thyroid included shrinkage of follicles, loss of thyroglobulin, and fibrosis of the interfollicular epithelium of parents and offspring of both sexes and generations. The study report did not include incidence data for the histopathologic lesions.

Appendix C. BMD_{10} and $BMDL_{10}$ Summaries

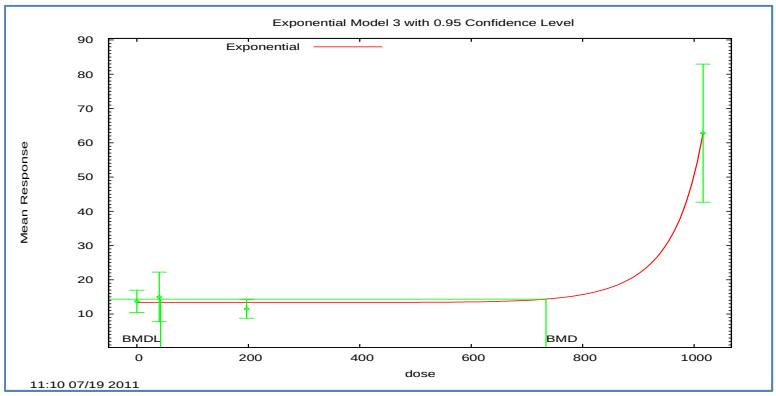
F0 Female SD Rat Absolute Liver Weight, LOAEL = 1297 MKD (Diet; Fujii et al., 2005)				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Exponential 2	147	101	0.87	186.5
Exponential 3	472	103	0.98	188.2
Linear	140	94	0.85	186.5
Polynomial	462	47	0.99	188.2
Power	469	96	0.98	188.2



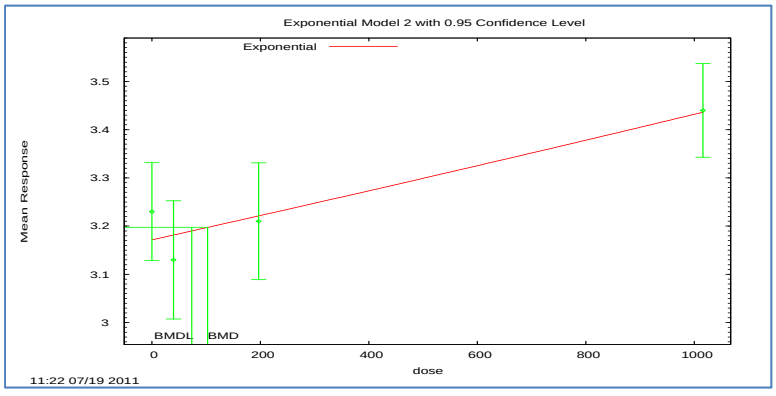
F0 Male Absolute Epididymal Weight, LOAEL = 1016 MKD (Diet; Fujii et al., 2005)				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Exponential 2	306	132	0.11	-285
Exponential 3	904	136	0.04	-284
Linear	309	136	0.11	-285.5
Polynomial	828	46	0.04	-284
Power	909	140	0.04	-283.7



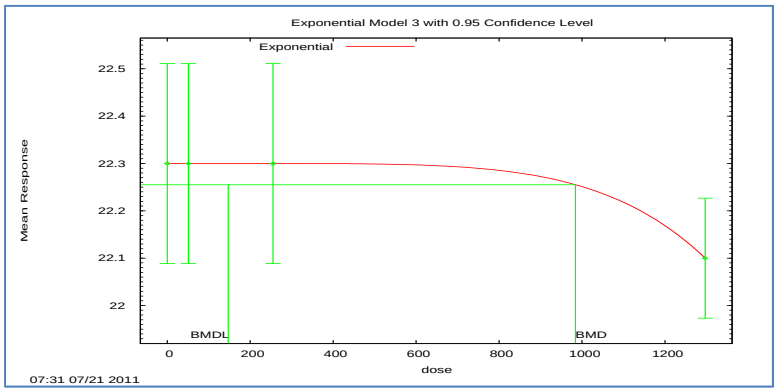
F0 Male CYP4A1 Activity, LOAEL = 1016 MKD (Diet; Fujii et al., 2005)				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Exponential 2	50	39	0.36	140.1
Exponential 3	734	42	0.52	140.4
Linear	31	16	0.06	143.7
Polynomial	421	37	0.66	140.2
Power	756	48	0.52	140.4



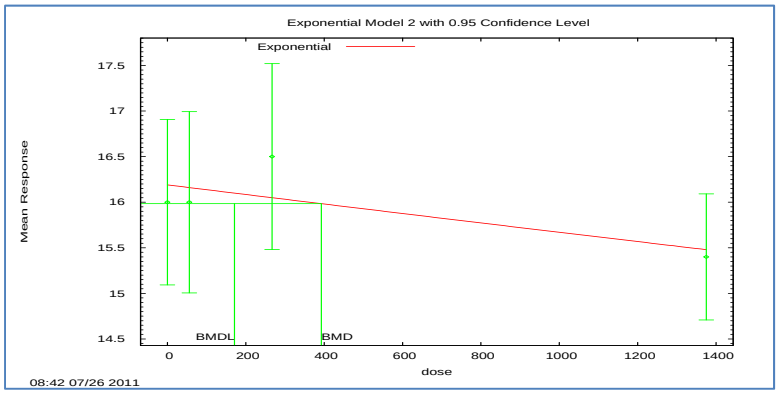
F0 Female Absolute Liver Weight, LOAEL = 1297 MKD (Diet; Fujii et al., 2005)				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Exponential 2	103	74	0.32	-156
Exponential 3	247	75	0.17	-154
Linear	99	70	0.32	-156
Polynomial	327	36	0.16	-154
Power	245	71	0.17	-154.4



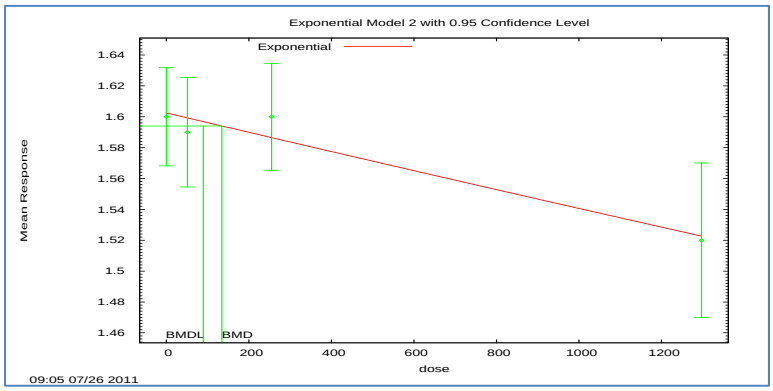
F0 Female Gestation Length, LOAEL = nd (Diet; Fujii et al., 2005)				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Exponential 2	276	145	0.94	-51.8
Exponential 3	984	147	1	-49.9
Linear	277	147	0.94	-51.8
Polynomial	698	49	0.99	-49.9
Power	959	148	1	-49.9



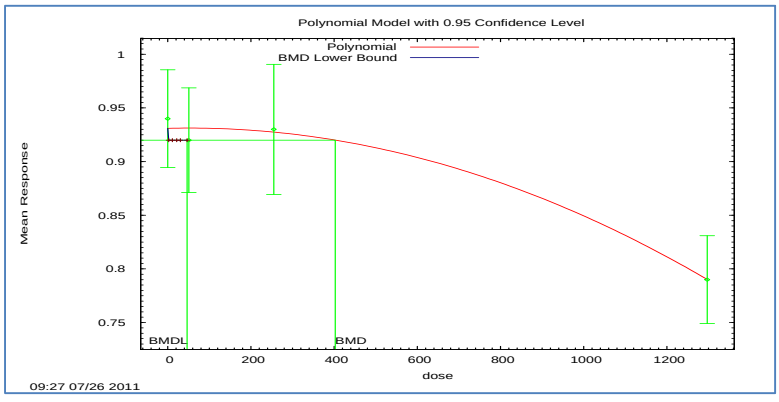
F1 Female Absolute Pituitary Gland Weight, LOAEL = nd (Diet; Fujii et al., 2005)				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Exponential 2	393	171	0.49	228.7
Exponential 3	1209	182	0.35	230.1
Linear	397	178	0.49	228.7
Polynomial	1269	118	0.81	229.3
Power	1198	189	0.35	230.1



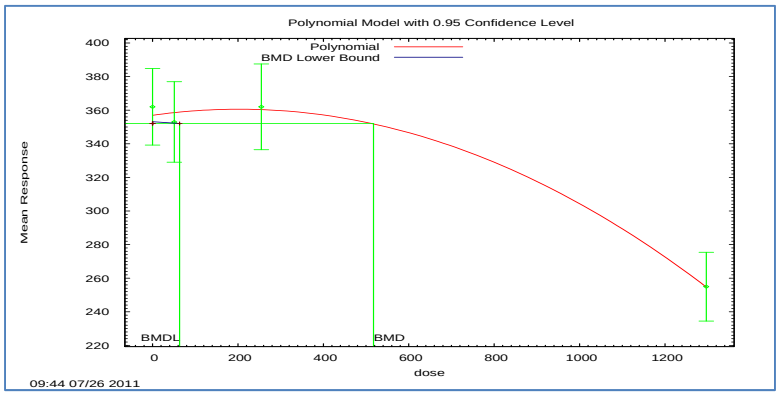
F1 Female Pup Absolute Brain Weight, LOAEL = 1297 MKD (Diet; Fujii et al., 2005)				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Exponential 2	134	89	0.64	-336.9
Exponential 3	1033	94	0.65	-335.6
Linear	137	93	0.65	-336.9
Polynomial	650	54	0.65	-335.6
Power	1011	97	0.65	-335.6



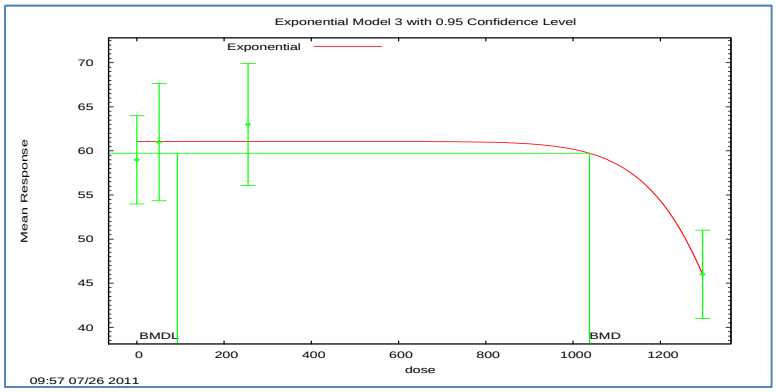
F1 Female Pup Absolute Kidney Weight, LOAEL = 1297 MKD (Diet; Fujii et al., 2005)				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Exponential 2	90	65	0.56	-290.3
Exponential 3	959	68	0.55	-289.2
Linear	97	71	0.59	-290.5
Polynomial	403	47	0.54	-289.1
Power	952	74	0.55	-289.2



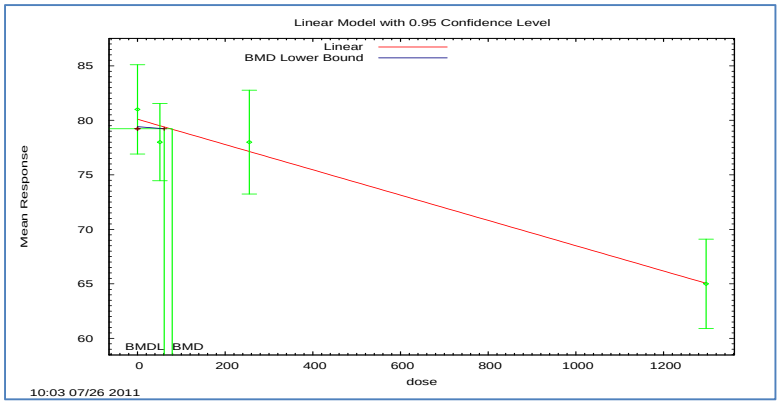
F1 Female Pup Absolute Thymus Weight, LOAEL = 1297 MKD (Diet; Fujii et al., 2005)				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Exponential 2	54	42	0.13	782
Exponential 3	941	75	0.5	780.4
Linear	62	50	0.19	781.3
Polynomial	517	64	0.49	780.4
Power	1016	67	0.5	780.4



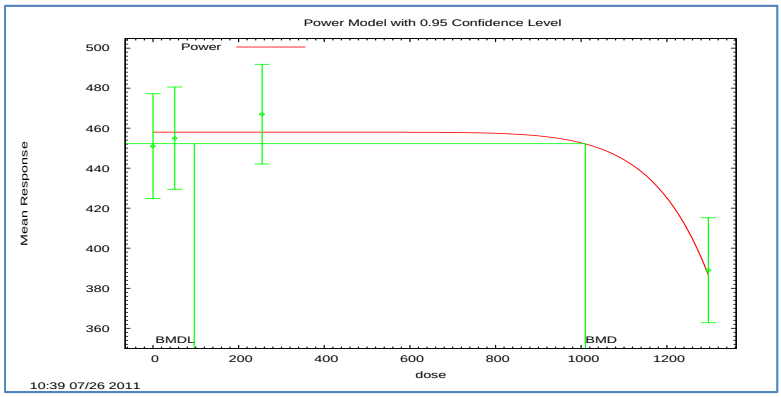
F1 Female Pup Absolute Uterus Weight, LOAEL = 1297 MKD (Diet; Fujii et al., 2005)				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Exponential 2	103	69	0.17	545.7
Exponential 3	1038	93	0.32	545.2
Linear	115	81	0.2	545.4
Polynomial	921	134	0.8	544.2
Power	1052	98	0.32	545.2



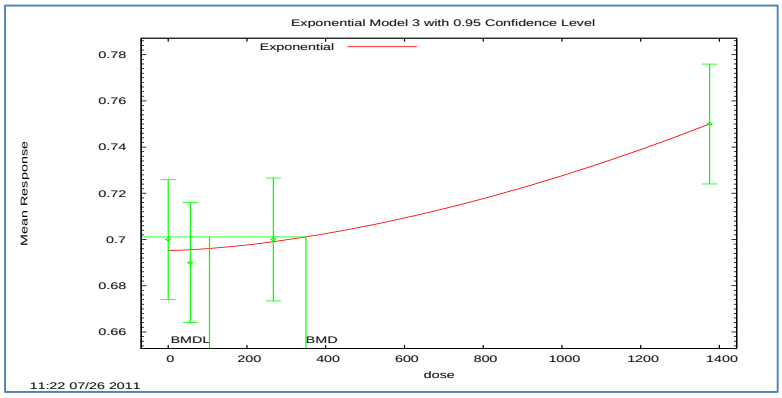
F1 Female Pup Weight, LOAEL = 1297 MKD (Diet; Fujii et al., 2005)				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Exponential 2	72	54	0.58	478.8
Exponential 3	120	54	0.32	480.7
Hill	112	61	na	482.7
Linear	79	61	0.61	478.7
Polynomial	113	33	0.34	480.6
Power	111	61	0.33	480.7



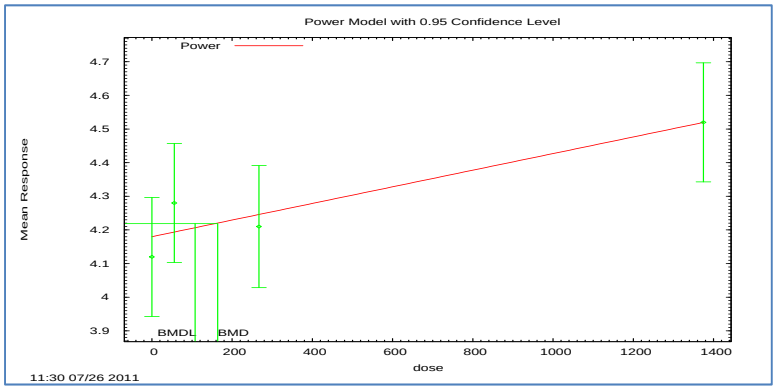
F1 Female Pup Relative Thymus Weight, LOAEL = 1297 MKD (Diet; Fujii et al., 2005)				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Exponential 2	100	70	0.16	798
Exponential 3	1018	98	0.32	797
Linear	107	77	0.18	798
Polynomial	907	143	0.98	796
Power	1010	97	0.32	797



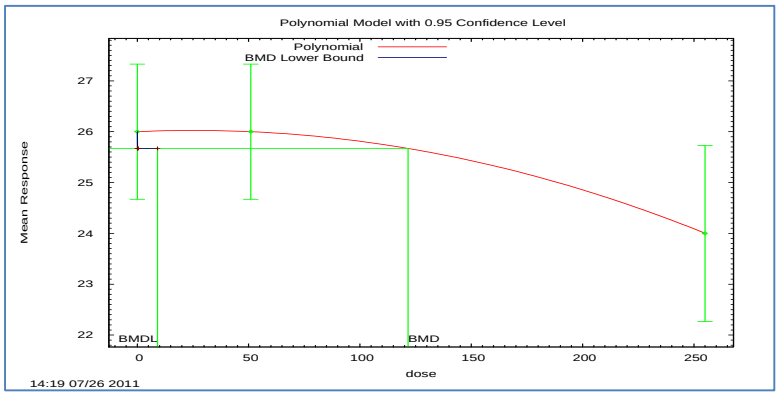
F1 Female Relative Kidney Weight, LOAEL = 1375 MKD (Diet; Fujii et al., 2005)				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Exponential 2	148	103	0.74	-418.5
Exponential 3	350	105	0.55	-416.8
Linear	143	98	0.74	-418.5
Polynomial	405	46	0.54	-416.5
Power	347	100	0.55	-416.8



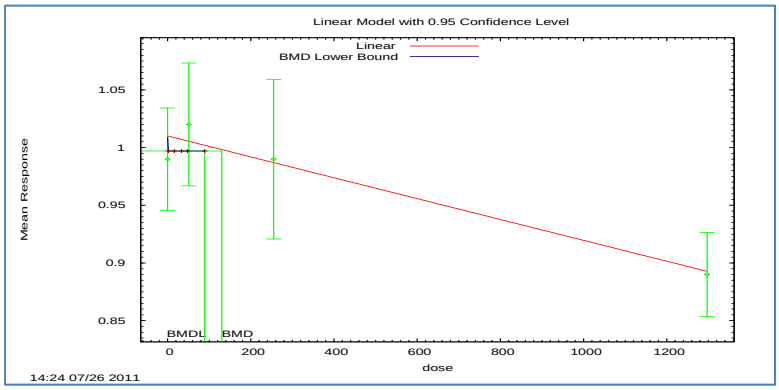
F1 Female Relative Liver Weight, LOAEL = 1375 MKD (Diet; Fujii et al., 2005)				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Exponential 2	170	114	0.42	-68
Exponential 3	170	114	0.42	-68
Linear	164	108	0.42	-68
Polynomial	230	40	0.19	-66
Power	164	108	0.42	-68



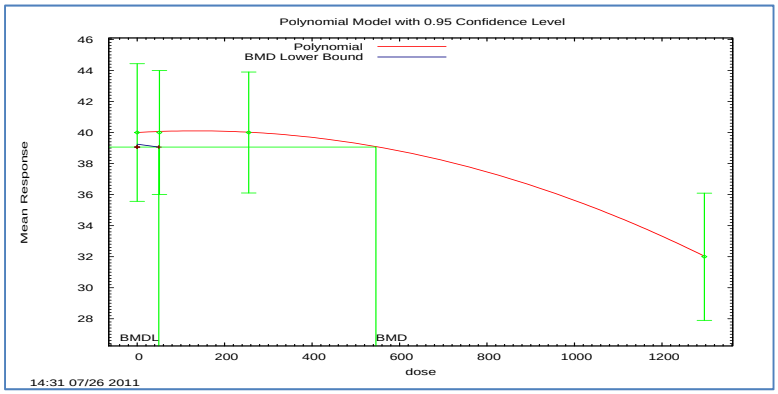
F1 Male Pup Absolute Adrenal Weight, 3 points; LOAEL = 1297 MKD (Diet; Fujii et al., 2005)				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Exponential 2	38	21	0.65	233.2
Exponential 3	186	22	na	235
Linear	39	23	0.66	233.2
Polynomial	122	9.1	na	235
Power	188	23	na	235



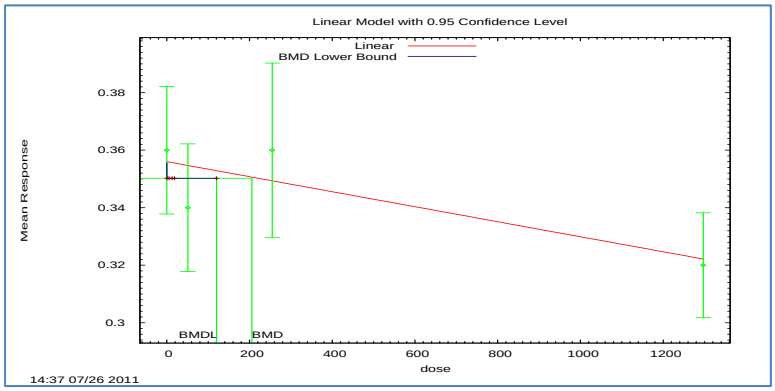
F1 Male Pup Absolute Kidney Weight, LOAEL = 1297 MKD (Diet; Fujii et al., 2005)				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Exponential 2	123	82	0.59	-282.7
Exponential 3	268	83	0.37	-280.9
Linear	130	89	0.61	-282.7
Polynomial	297	41	0.36	-280.9
Power	270	90	0.37	-280.9



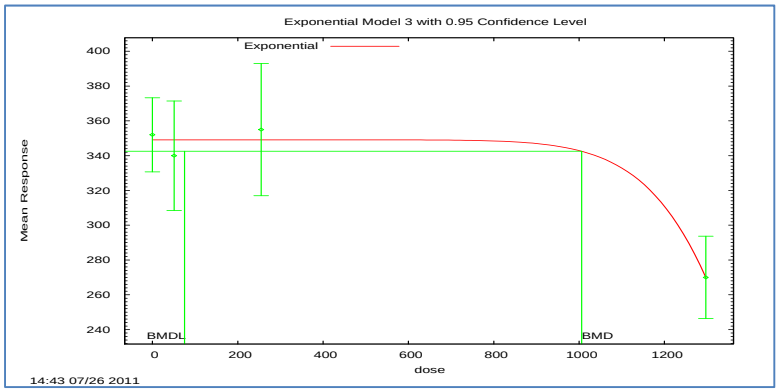
F1 Male Pup Absolute Prostate Weight, LOAEL = 1297 MKD (Diet; Fujii et al., 2005)				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Exponential 2	127	80	0.77	482.2
Exponential 3	832	84	1	483.6
Linear	140	94	0.8	482.1
Polynomial	546	49	0.98	483.6
Power	920	97	1	483.6



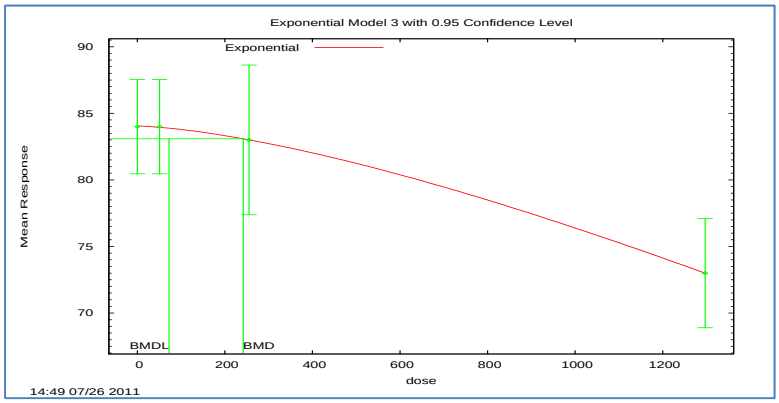
F1 Male Pup Absolute Spleen Weight, LOAEL = 1297 MKD (Diet; Fujii et al., 2005)				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Exponential 2	198	112	0.25	-421
Exponential 3	1064	119	0.15	-419.7
Linear	206	120	0.25	-421.1
Polynomial	925	67	0.16	-419.9
Power	1087	127	0.15	-419.7



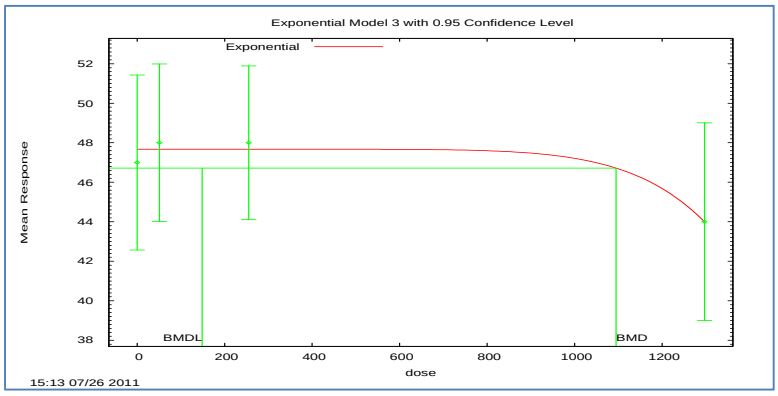
F1 Male Pup Absolute Thymus Weight, LOAEL = 1297 MKD (Diet; Fujii et al., 2005)				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Exponential 2	95	65	0.3	832.7
Exponential 3	1006	75	0.42	833
Linear	105	77	0.34	832.5
Polynomial	711	68	0.46	832.9
Power	1007	84	0.42	833



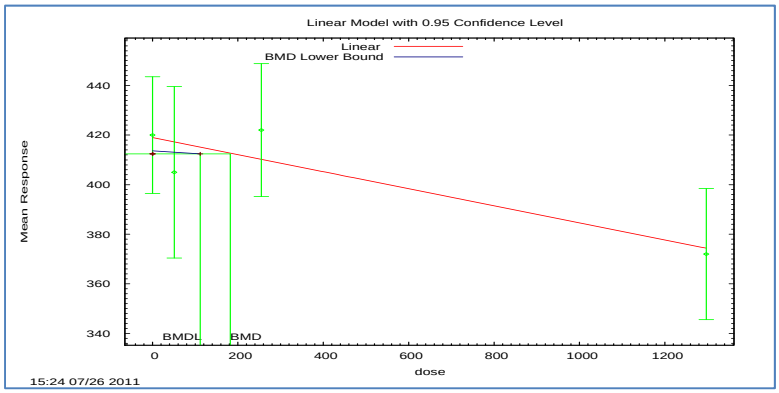
F1 Male Pup Body Weight, LOAEL = 1297 MKD (Diet; Fujii et al., 2005)				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Exponential 2	102	72	0.88	491.4
Exponential 3	242	73	0.97	493.2
Hill	252	32	na	495.2
Linear	109	78	0.9	491.4
Polynomial	236	40	0.95	493.2
Power	241	79	0.97	493.2



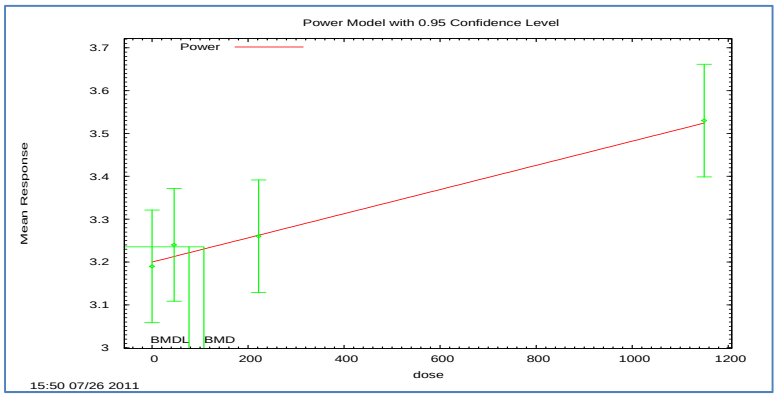
F1 Male Pup Relative Prostate Weight, LOAEL = nd (Diet; Fujii et al., 2005)				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Exponential 2	324	145	0.82	491.3
Exponential 3	1095	148	0.69	493
Linear	333	156	0.82	491.3
Polynomial	993	58	0.78	493
Power	1130	160	0.69	493.1



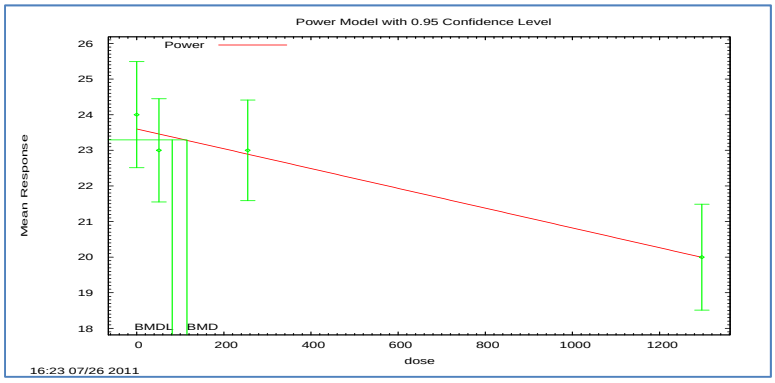
F1 Male Pup Relative Thymus Weight, LOAEL = 1297 MKD (Diet; Fujii et al., 2005)				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Exponential 2	174	103	0.42	822.2
Exponential 3	1070	110	0.32	823.5
Linear	182	112	0.43	822.2
Polynomial	875	66	0.35	823.3
Power	1051	118	0.32	823.5



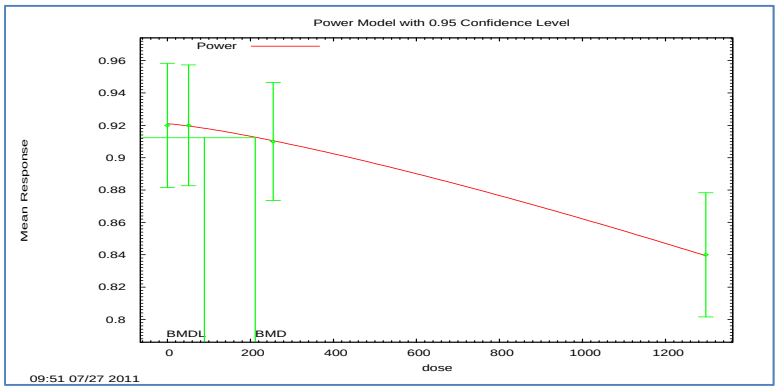
F1 Male Relative Liver Weight, LOAEL = 1150 MKD (Diet; Fujii et al., 2005)				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Exponential 2	113	82	0.91	-126
Exponential 3	113	82	0.91	-126
Linear	108	77	0.91	-126
Polynomial	116	30	0.66	-124
Power	108	77	0.91	-126



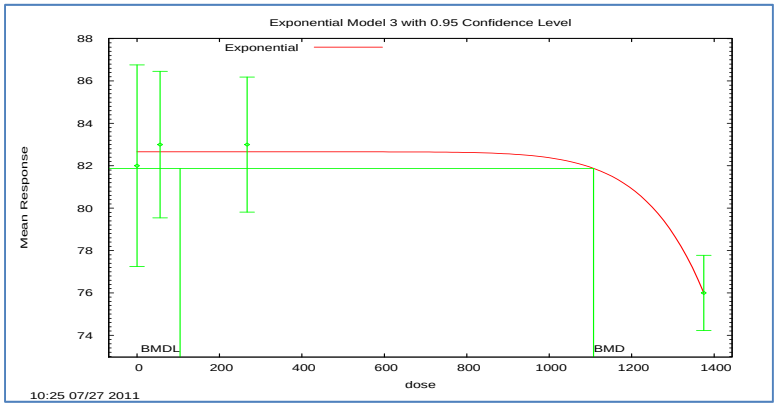
F2 Female Pup Absolute Adrenal Gland Weight, LOAEL = 1375 MKD (Diet; Fujii et al., 2005)				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Exponential 2	107	73	0.67	295.8
Exponential 3	107	73	0.67	295.8
Linear	115	82	0.67	295.8
Polynomial	112	32	0.37	297.8
Power	115	82	0.67	295.8



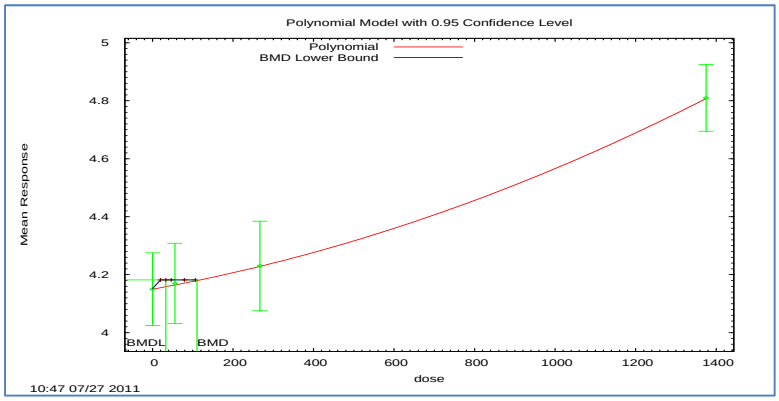
F2 Female Pup Absolute Kidney Weight, LOAEL = 1375 MKD (Diet; Fujii et al., 2005)				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Exponential 2	124	83	0.96	-341.4
Exponential 3	212	84	0.96	-339.5
Linear	130	89	0.97	-341.4
Polynomial	203	38	0.94	-339.5
Power	212	89	0.96	-339.5



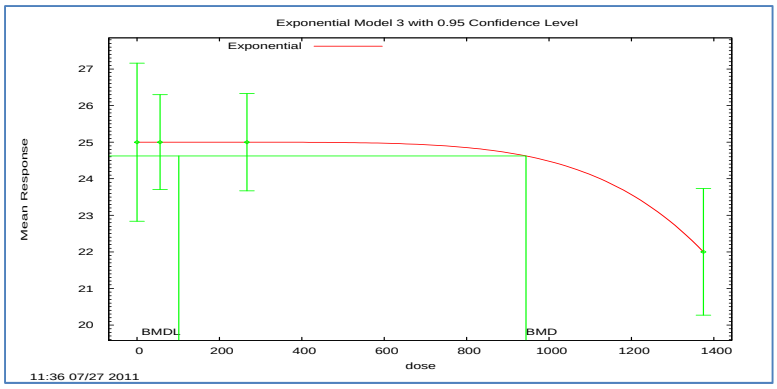
F2 Female Pup Body Weight, LOAEL = 1375 MKD (Diet; Fujii et al., 2005)				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Exponential 2	151	98	0.59	461
Exponential 3	1108	104	0.62	462
Hill	1023	55	na	464
Linear	157	104	0.6	461
Polynomial	837	65	0.74	462
Power	1126	110	0.62	462



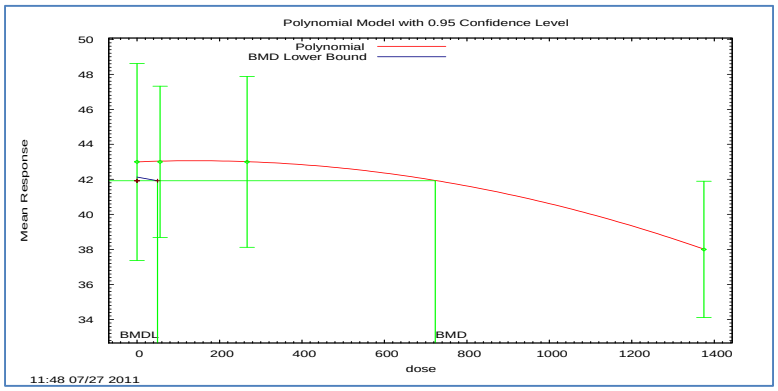
F2 Female Pup Relative Liver Weight, LOAEL = 1375 MKD (Diet; Fujii et al., 2005)				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Exponential 2	66	54	0.88	-121
Exponential 3	125	55	0.91	-119.3
Linear	61	50	0.83	-120.9
Polynomial	111	33	0.95	-119.3
Power	128	50	0.91	-119.3



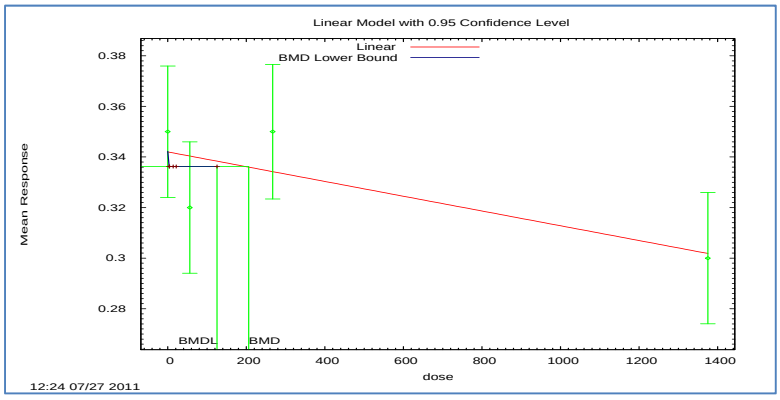
F2 Male Pup Absolute Adrenal Gland Weight, LOAEL = 1375 MKD (Diet; Fujii et al., 2005)				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Exponential 2	156	99	0.83	338.6
Exponential 3	944	102	1	340.2
Linear	165	108	0.85	338.6
Polynomial	597	51	0.98	340.2
Power	1014	111	1	340.2



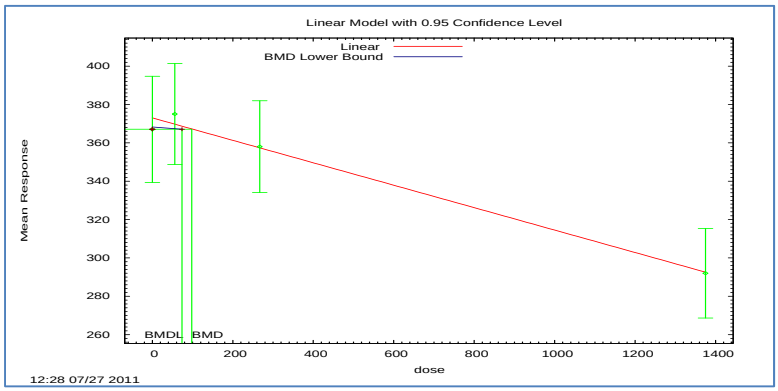
F2 Male Pup Absolute Prostate Weight, LOAEL = nd (Diet; Fujii et al., 2005)				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Exponential 2	265	134	0.94	527
Exponential 3	1003	136	1	528.8
Linear	278	149	0.94	527
Polynomial	723	50	0.99	528.8
Power	1063	151	1	528.8



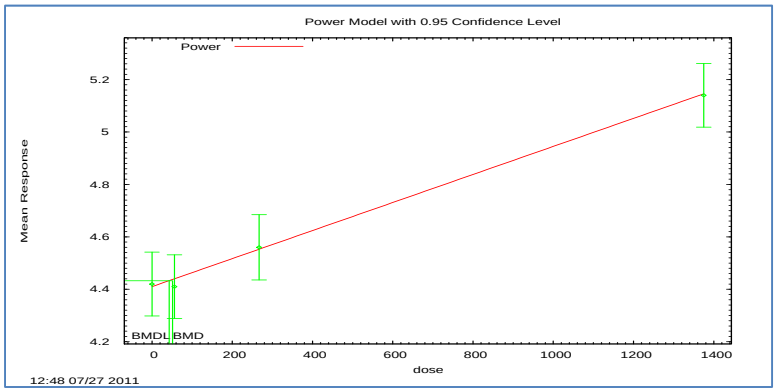
F2 Male Pup Absolute Spleen Weight, LOAEL = 1375 MKD (Diet; Fujii et al., 2005)				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Exponential 2	196	114	0.09	-414.4
Exponential 3	1147	124	0.05	-413.2
Linear	206	125	0.1	-414.4
Polynomial	1007	77	0.05	-413.4
Power	1152	134	0.05	-413.2



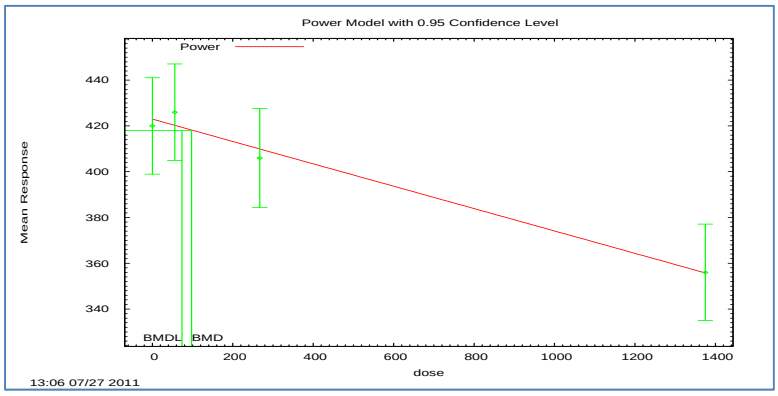
F2 Male Pup Absolute Thymus Weight, LOAEL = 1375 MKD (Diet; Fujii et al., 2005)				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Exponential 2	87	64	0.78	833.9
Exponential 3	152	64	0.55	835.7
Linear	98	74	0.8	833.8
Polynomial	133	35	0.53	835.8
Power	151	74	0.55	835.7



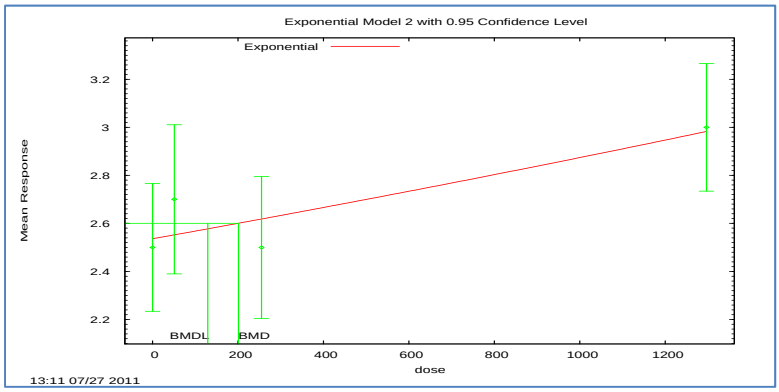
F2 Male Pup Relative Liver Weight, LOAEL = 1375 MKD (Diet; Fujii et al., 2005)				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Exponential 2	56	47	0.84	-137.8
Exponential 3	56	47	0.84	-137.8
Linear	51	43	0.86	-137.8
Polynomial	48	24	0.59	-135.8
Power	51	43	0.86	-137.8



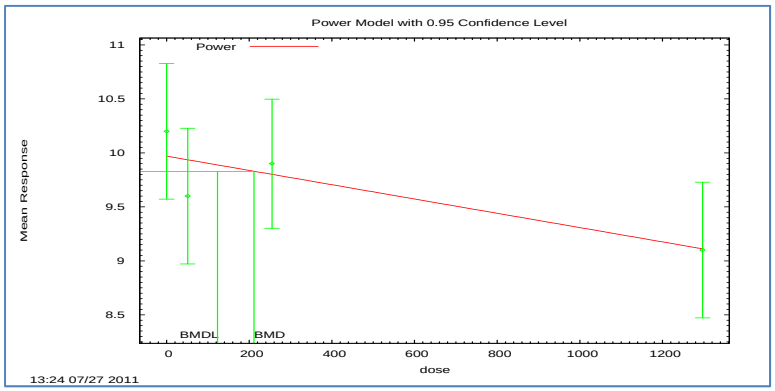
F2 Male Pup Relative Thymus Weight, LOAEL = 1375 MKD (Diet; Fujii et al., 2005)				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Exponential 2	90	66	0.76	800.9
Exponential 3	90	66	0.76	800.9
Linear	98	74	0.75	800.9
Polynomial	74	29	0.48	802.8
Power	98	74	0.75	800.9



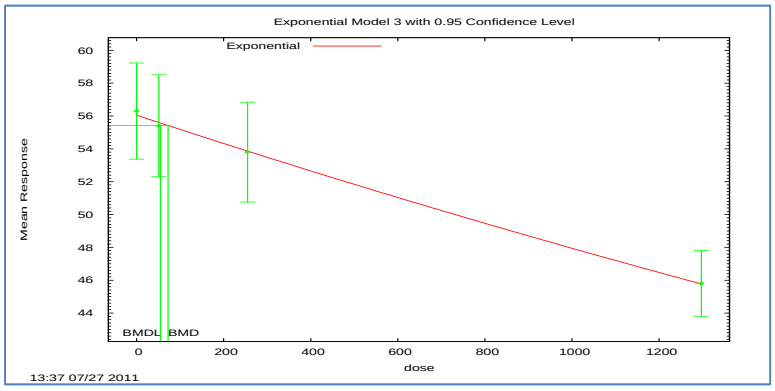
F1 Female Pup Age at Pinna Detachment, Days, LOAEL = nd (Diet; Fujii et al., 2005)				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Exponential 2	201	129	0.36	17.3
Exponential 3	1087	135	0.23	18.7
Linear	188	115	0.35	17.3
Polynomial	870	65	0.24	18.6
Power	1071	121	0.23	18.7



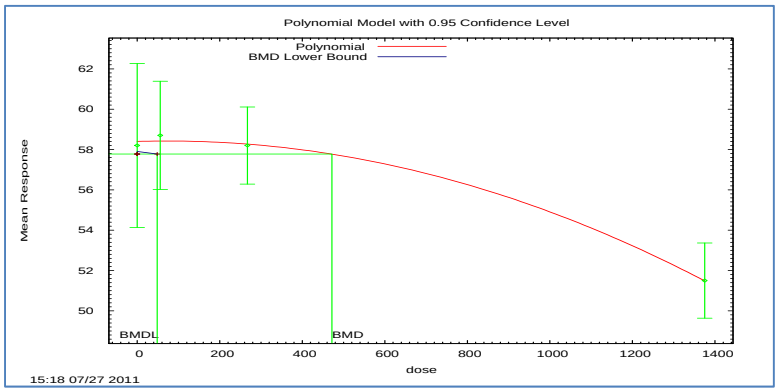
F1 Female Pup Body Weight, Day 4, LOAEL = 1297 MKD (Diet; Fujii et al., 2005)				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Exponential 2	203	115	0.37	156.7
Exponential 3	203	115	0.37	156.7
Linear	211	123	0.37	156.7
Polynomial	292	41	0.16	158.6
Power	211	123	0.37	156.7



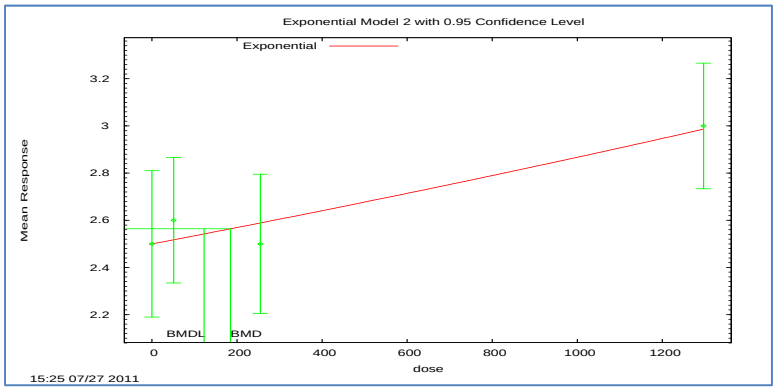
F1 Female Pup Body Weight, Day 21, LOAEL = 1297 MKD (Diet; Fujii et al., 2005)				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Exponential 2	72	55	0.97	427.1
Exponential 3	72	55	0.97	427.1
Linear	80	62	0.95	427.1
Polynomial	66	27	0.82	429.1
Power	80	62	0.95	427.1



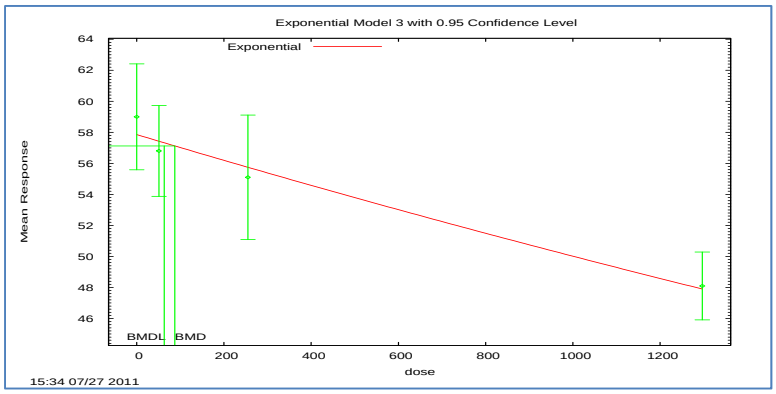
F2 Female Pup Body Weight, Day 21, LOAEL = 1375 MKD (Diet; Fujii et al., 2005)				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Exponential 2	113	79	0.73	422.8
Exponential 3	433	82	0.78	424.2
Linear	120	86	0.75	422.7
Polynomial	472	49	0.79	424.2
Power	437	88	0.78	424.2



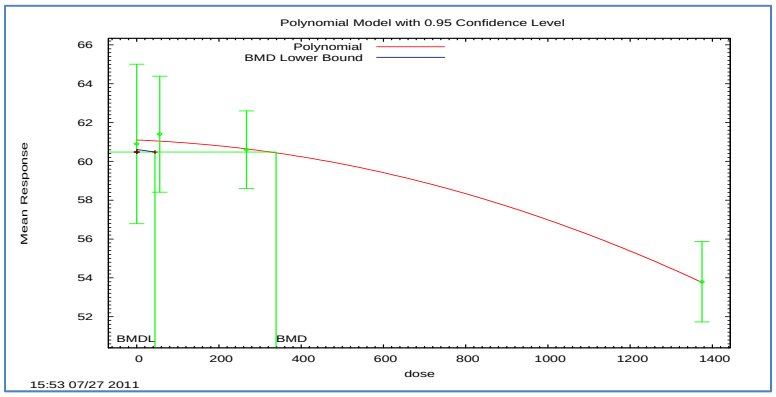
F1 Male Pup Age of Pinna Detachment, LOAEL = 1297 MKD (Diet; Fujii et al., 2005)				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Exponential 2	185	123	0.66	16.1
Exponential 3	1085	126	0.55	17.6
Linear	171	108	0.64	16.1
Polynomial	736	56	0.55	17.6
Power	1075	113	0.55	17.6



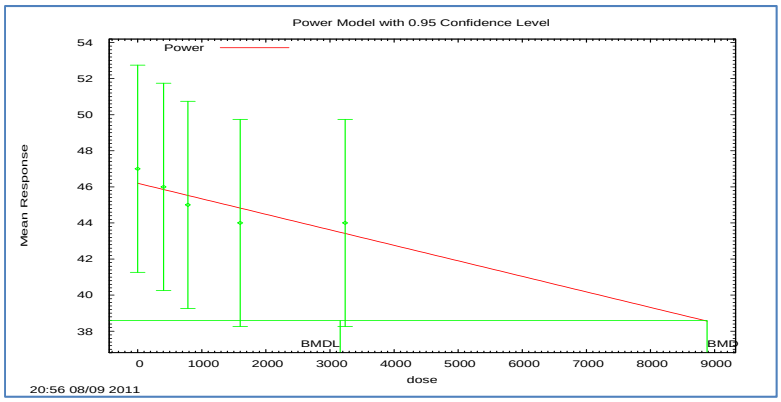
F1 Male Pup Body Weight, Day 21, LOAEL = 1297 MKD (Diet; Fujii et al., 2005)				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Exponential 2	87	63	0.63	448.9
Exponential 3	87	63	0.63	448.9
Linear	96	71	0.6	449
Polynomial	50	24	0.5	450.4
Power	96	71	0.6	449



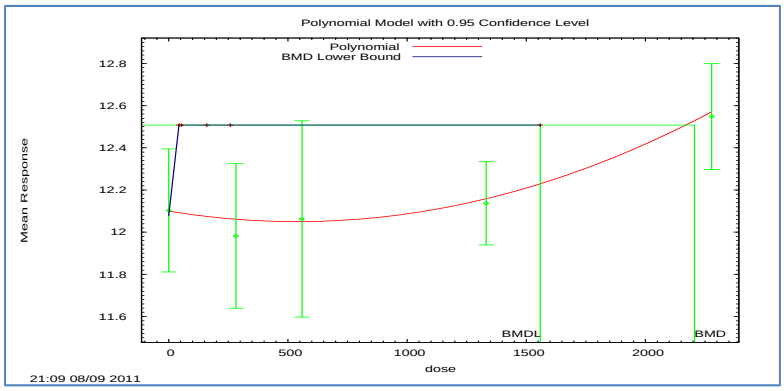
F2 Male Pup Body Weight, Day 21, LOAEL = 1375 MKD (Diet; Fujii et al., 2005)				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Exponential 2	113	79	0.8	440.9
Exponential 3	314	81	0.78	442.5
Linear	120	86	0.83	440.9
Polynomial	339	45	0.77	442.6
Power	316	88	0.78	442.5



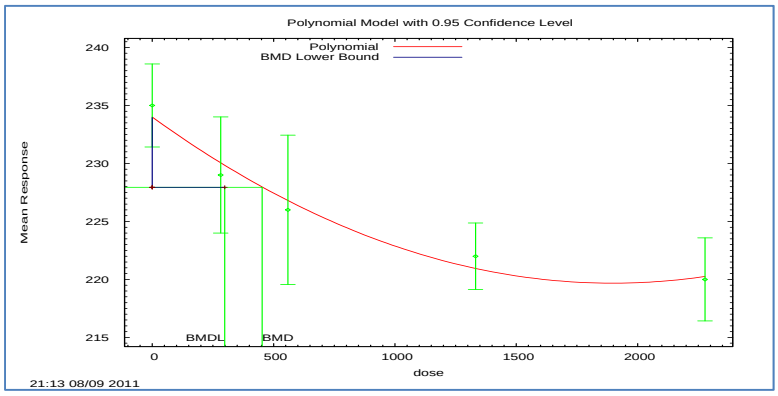
Female Rat Body Weight Gain Final, 28 Days, LOAEL = nd (Dermal; NTP, 1995)				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Exponential 2	9297	3117	0.95	259.3
Exponential 3	9297	3117	0.95	259.3
Linear	8883	3159	0.95	259.3
Polynomial	-9999	3346	1	261
Power	8883	3159	0.95	259.3



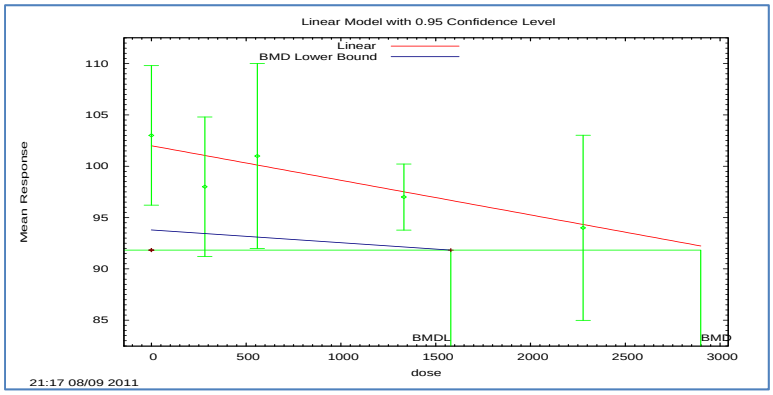
Male Rat Absolute Liver Weight, 28 Days, LOAEL = nd (Dermal; NTP, 1995)				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Exponential 2	2056	1296	0.52	-26.6
Exponential 3	2172	1532	0.81	-26.4
Linear	2063	1285	0.52	-26.5
Polynomial	2206	1558	0.87	-26.5
Power	2171	1531	0.81	-26.4



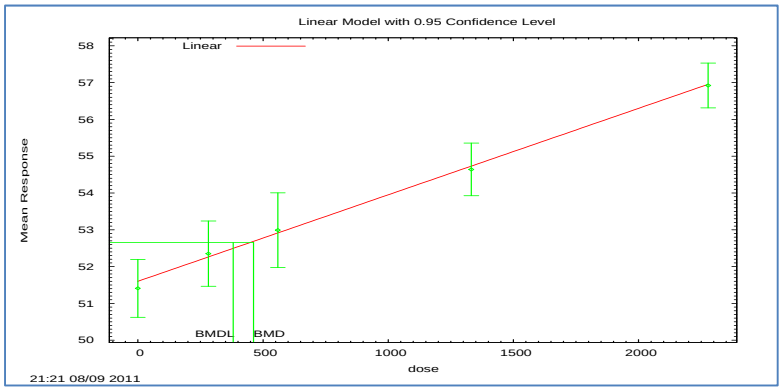
Male Rat Body Weight at Necropsy, 28 Days, LOAEL = nd (Dermal; NTP, 1995)				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Exponential 2	1052	775	0.1	240.4
Exponential 3	1052	775	0.1	240.4
Linear	1078	800	0.1	240.6
Polynomial	453	298	0.58	237.3
Power	1078	800	0.1	240.6



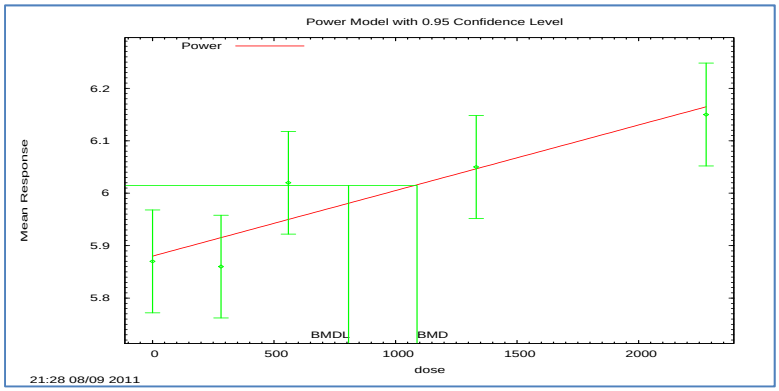
Male Rat Body Weight Gain Final, 28 Days, LOAEL = 1600 MKD				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Exponential 2	2925	1542	0.77	283.9
Exponential 3	2925	1542	0.77	283.9
Linear	2898	1579	0.77	283.9
Polynomial	3139	914	0.57	285.9
Power	2898	1579	0.77	283.9



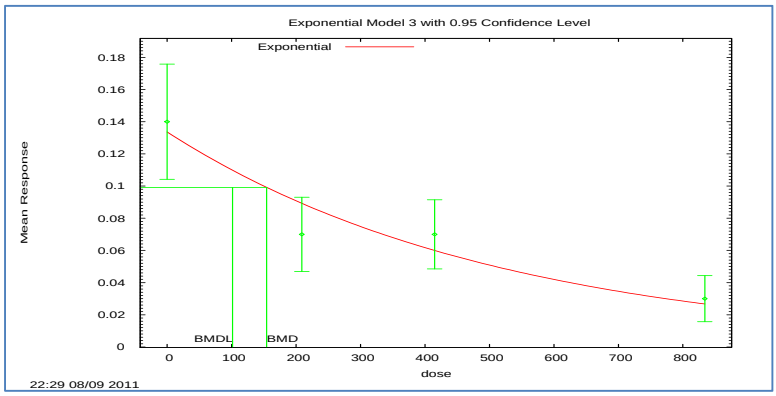
Male Rat Relative Liver Weight, 28 Days, LOAEL = 1600 MKD (Dermal; NTP, 1995)				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Exponential 2	481	399	0.9	64.3
Exponential 3	481	399	0.9	64.3
Linear	462	381	0.93	64.2
Polynomial	436	299	0.82	66.2
Power	462	381	0.93	64.2



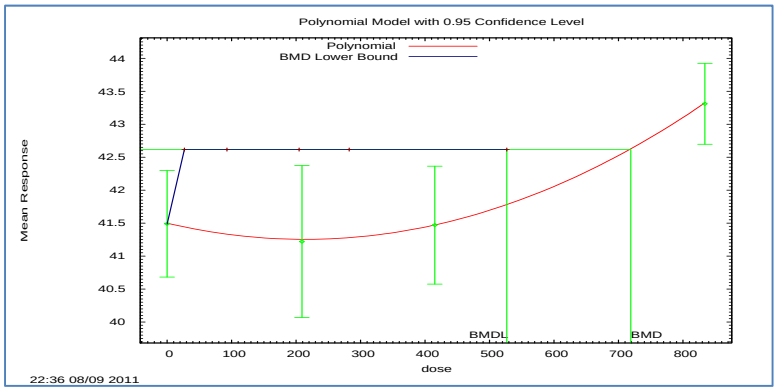
Male Rat Relative Right Testis Weight, 28 Days, LOAEL = nd (Dermal; NTP, 1995)				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Exponential 2	1105	824	0.19	-143.3
Exponential 3	1105	824	0.19	-143.3
Linear	1088	807	0.19	-143.3
Polynomial	754	425	0.15	-142.2
Power	1088	807	0.2	-143.3



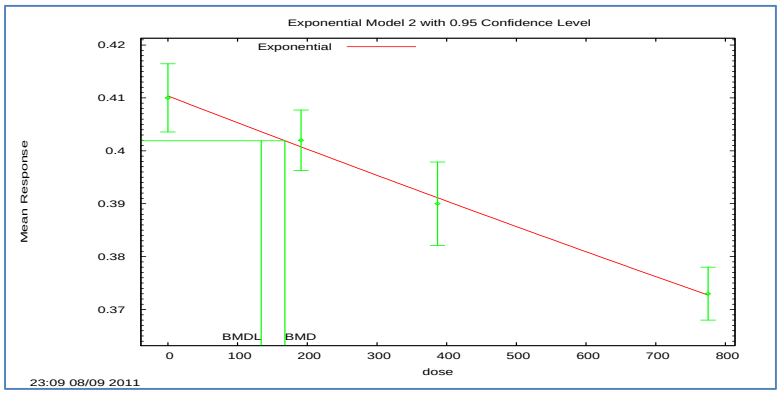
Female Mouse Eosinophil Number, 60 Weeks, LOAEL = 1100 MKD (Dermal; NTP, 1995)				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Exponential 2	154	102	0.11	-217.7
Exponential 3	154	102	0.11	-217.7
Linear	310	234	0.01	-213.3
Polynomial	155	104	0.03	-215.4
Power	310	234	0.01	-213.3



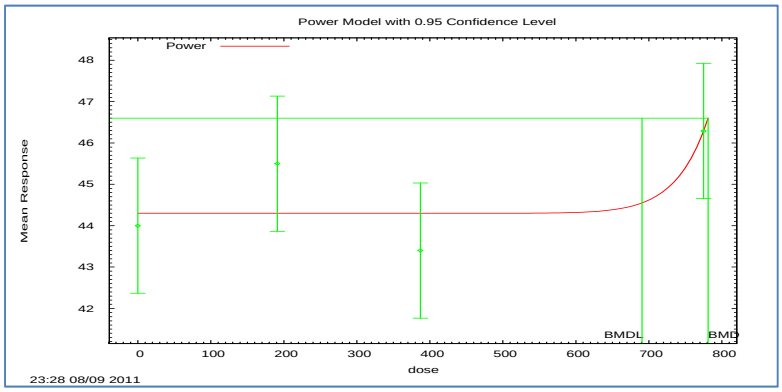
Female Mouse Relative Liver Weight, 60 Weeks, LOAEL = nd (Dermal; NTP, 1995)				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Exponential 2	525	355	0.09	58.2
Exponential 3	739	509	0.6	55.7
Linear	525	351	0.09	58.3
Polynomial	719	527	0.95	55.4
Power	738	508	0.6	55.7



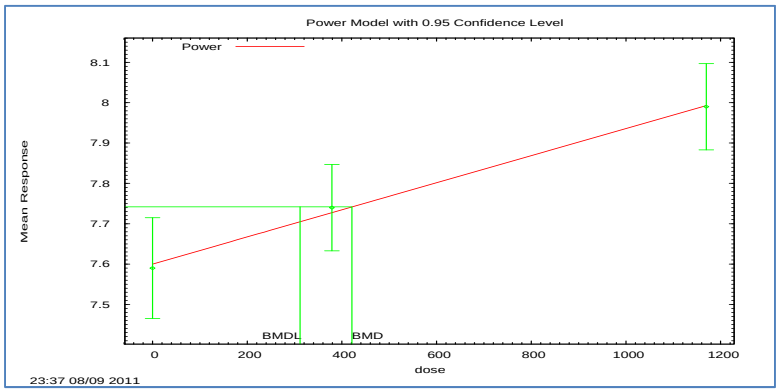
Male Mouse Absolute Kidney Weight, 60 Weeks, LOAEL = 1050 MKD (Dermal; NTP, 1995)				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Exponential 2	168	134	0.81	-335.8
Exponential 3	171	134	0.52	-333.8
Linear	175	140	0.79	-335.7
Polynomial	164	109	0.52	-333.8
Power	175	140	0.79	-335.7



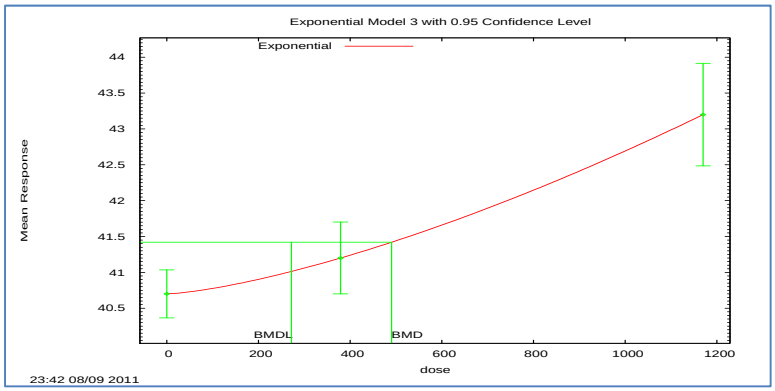
Male Mouse Relative Liver Weight, 60 Weeks, LOAEL = nd (Dermal; NTP, 1995)				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Exponential 2	1024	534	0.03	114.9
Exponential 3	781	691	0.03	114.6
Linear	1038	530	0.03	114.9
Polynomial	867	609	0.02	115.6
Power	781	691	0.1	112.6



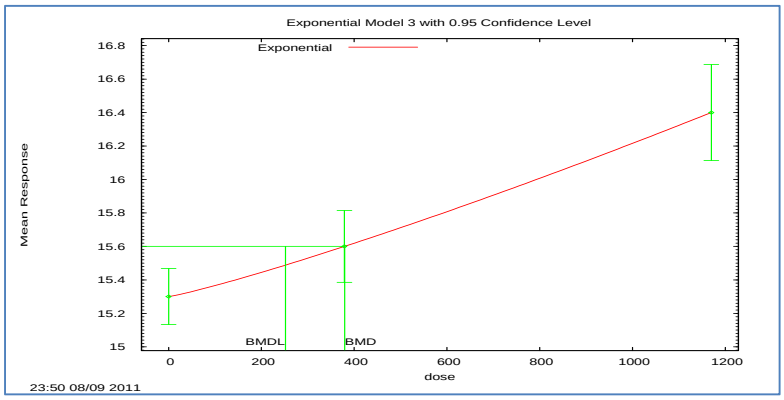
Female Rat Erythrocyte Number, 60 Weeks, LOAEL = 1600 MKD (Dermal; NTP, 1995)				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Exponential 2	429	319	0.7	-75.4
Exponential 3	429	319	0.7	-75.4
Linear	421	312	0.72	-75.4
Polynomial	356	183	na	-73.6
Power	421	311	0.72	-75.4



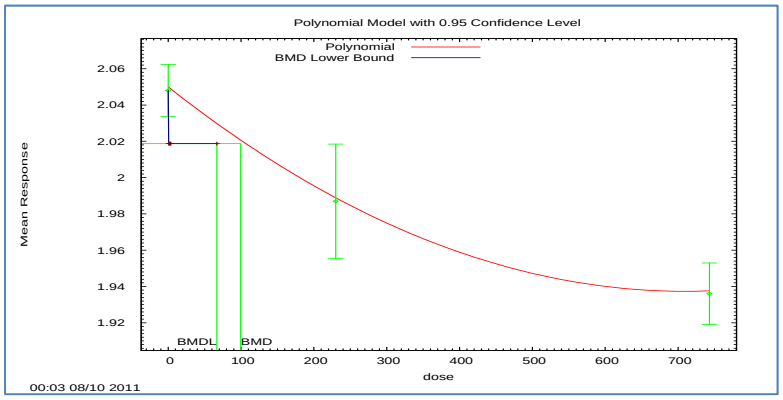
Female Rat Hematocrit, 60 Weeks, LOAEL = 1600 MKD (Dermal; NTP, 1995)				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Exponential 2	338	259	0.33	16.6
Exponential 3	490	272	na	17.6
Linear	331	253	0.3	16.7
Polynomial	499	249	na	17.6
Power	489	267	na	17.6



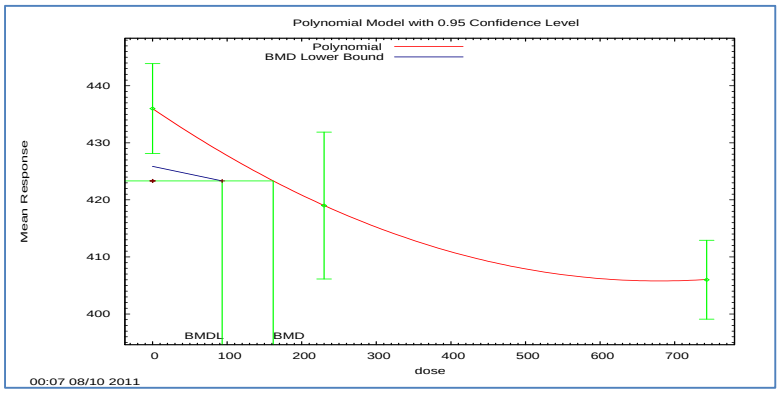
Female Rat Hemoglobin Level, 60 Weeks, LOAEL = 1600 MKD (Dermal; NTP, 1995)				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Exponential 2	324	250	0.7	-33.2
Exponential 3	380	252	na	-31.3
Linear	316	242	0.65	-33.1
Polynomial	380	199	na	-31.3
Power	380	245	na	-31.3



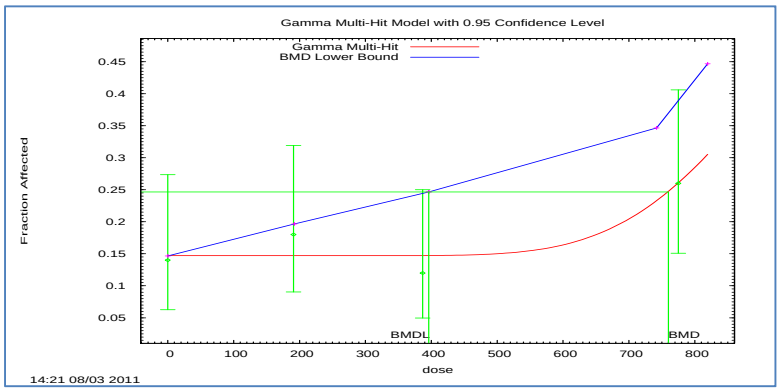
Male Rat Absolute Brain Weight, 60 Weeks, LOAEL = 1015 MKD (Dermal; NTP, 1995)				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Exponential 2	216	164	0.03	-165.3
Exponential 3	216	164	0.03	-165.3
Linear	222	169	0.03	-165.1
Polynomial	100	67	na	-167.7
Power	222	169	0.03	-165.1



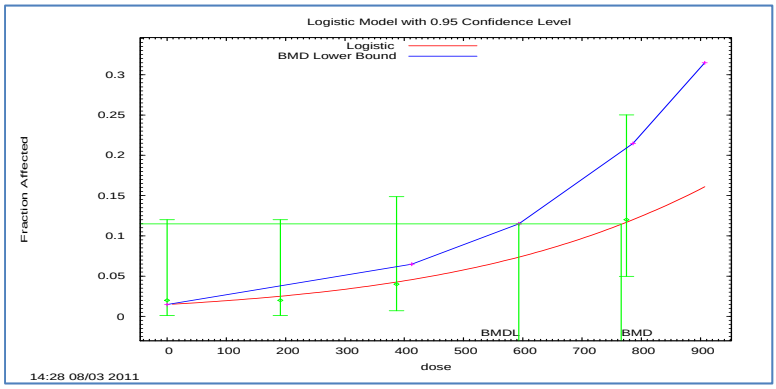
Male Rat Body Weight at Necropsy, 60 Weeks, LOAEL = nd (Dermal; NTP, 1995)				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Exponential 2	336	236	0.14	184.4
Exponential 3	336	236	0.14	184.4
Linear	346	245	0.13	184.5
Polynomial	162	93	na	184.3
Power	346	245	0.13	184.5



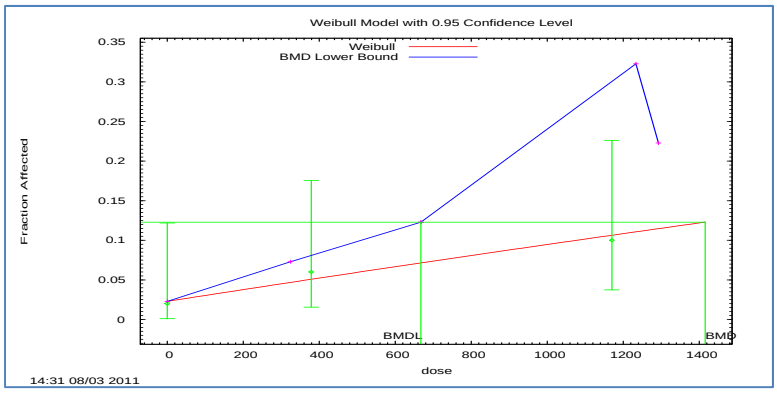
Male Mouse % Follicular Cell Hyperplasia of Thyroid, 103 Weeks, LOAEL = nd (Dermal; NTP, 1995)				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Gamma	760	396	0.69	186.4
Logistic	737	420	0.45	187.4
Probit	744	407	0.44	187.4
Weibull	769	396	0.69	186.4



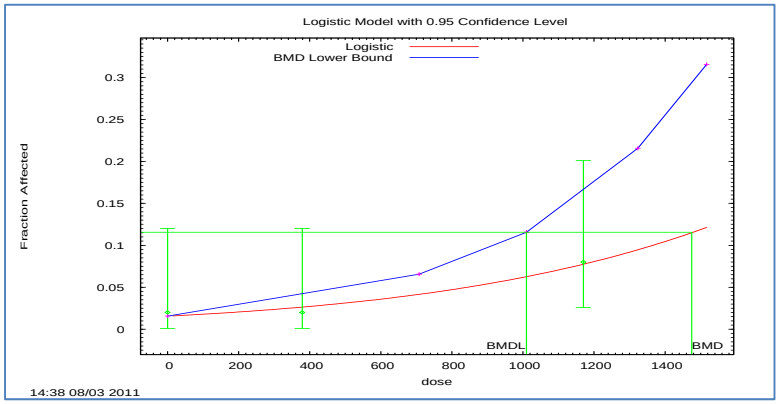
Male Mouse % Incidence of Lung Congestion, 103 Weeks, LOAEL = nd (Dermal; NTP, 1995)				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Gamma	1042	725	0.9	79.1
Logistic	1038	803	0.92	77.2
Multistage	1281	688	0.6	78.2
Probit	1042	775	0.9	77.3
Weibull	1042	729	0.88	79.1



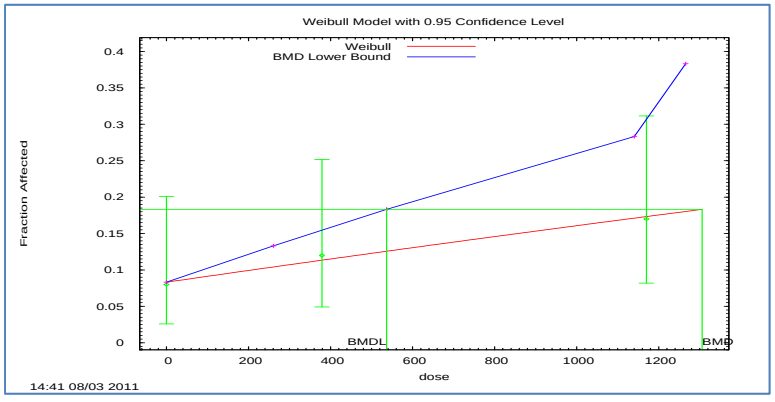
Female Rat % Incidence of Adrenal Medulla Gland Focal Hyperplasia, 103 Weeks, LOAEL = nd (Dermal; NTP, 1995)				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Gamma	1416	668	0.72	68.9
Logistic	1386	912	0.51	69.2
Probit	1392	878	0.53	69.2
Weibull	1416	668	0.72	68.9



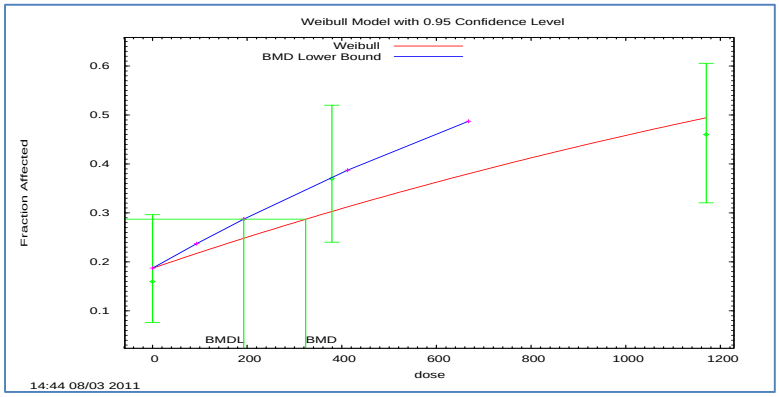
Female Rat % Incidence of Cystic Ovary, 103 Weeks, LOAEL = nd (Dermal; NTP, 1995)				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Gamma	1310	951	na	53.5
Logistic	1475	1010	0.7	51.6
Probit	1529	988	0.67	51.7
Weibull	1262	955	na	53.5



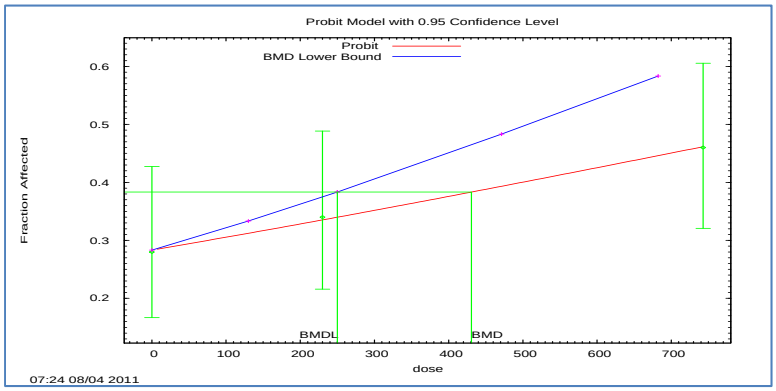
Female Rat % Incidence of Focal Hyperplasia of the Pars Distalis Pituitary Gland, 103 Weeks, LOAEL = nd (Dermal; NTP, 1995)				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Gamma	1306	537	0.86	111.6
Logistic	1305	735	0.76	111.7
Probit	1306	706	0.78	111.7
Weibull	1306	537	0.86	111.6



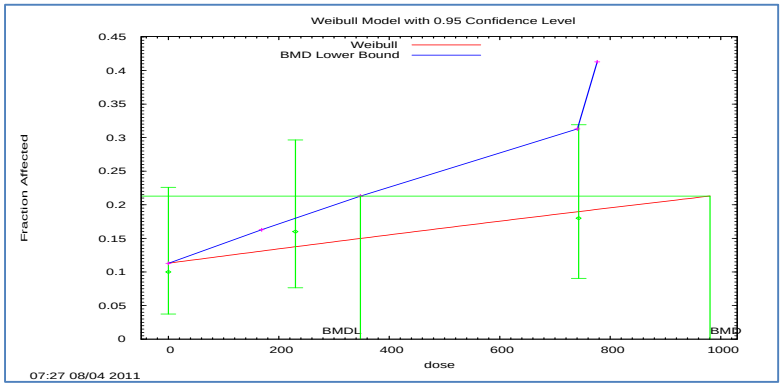
Female Rat % Incidence of Skin Acanthosis, 103 Weeks, LOAEL = 520 MKD (Dermal; NTP, 1995)				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Gamma	323	193	0.22	183
Logistic	488	352	0.11	184.1
Probit	471	336	0.11	184
Weibull	323	193	0.22	183



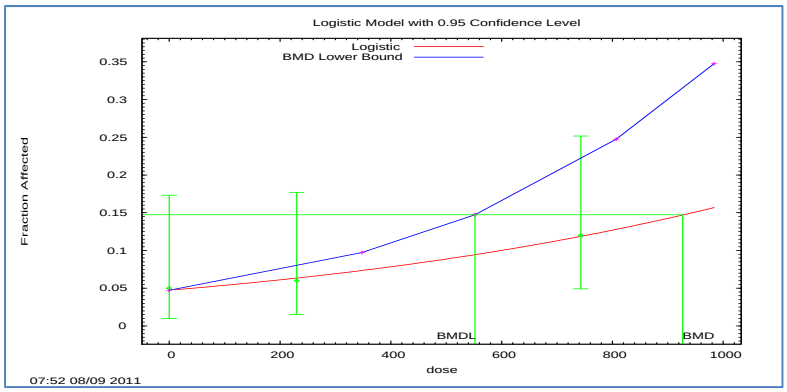
Male Rat % Incidence of Atrophy of the Pancreatic Acinus, 103 Weeks, LOAEL = nd (Dermal; NTP, 1995)				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Gamma	391	184	na	198.4
Logistic	435	256	0.92	196.4
Probit	431	250	0.93	196.4
Weibull	391	184	na	198.4



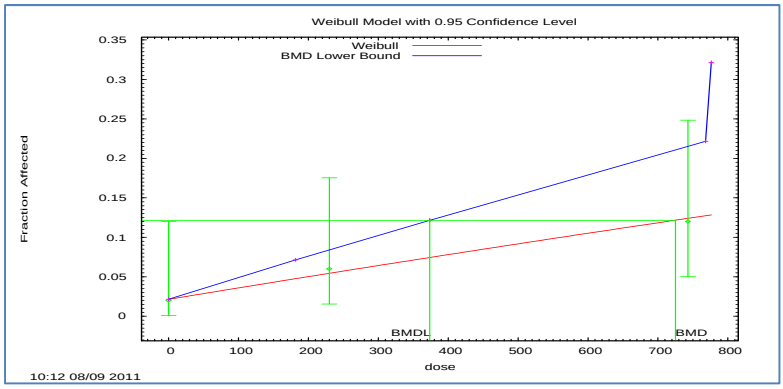
Male Rat % Incidence of Brain Compression, 103 Weeks, LOAEL = nd (Dermal; NTP, 1995)				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Gamma	981	348	0.57	127.9
Logistic	985	469	0.52	128
Probit	986	452	0.53	128
Weibull	981	348	0.57	127.9



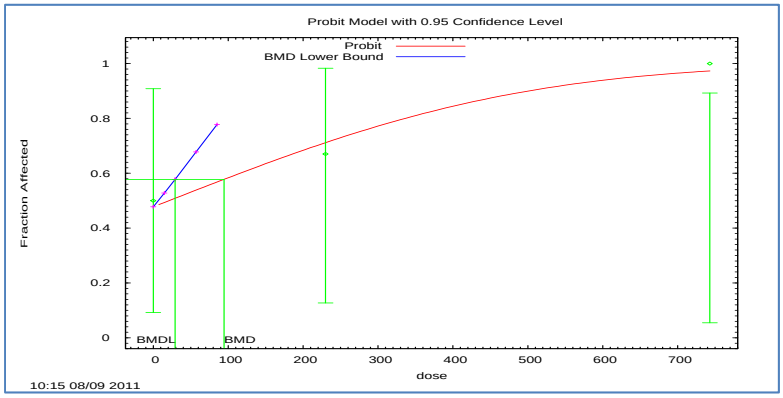
Male Rat % Incidence of Focal Hyperplasia of the Pituitary Pars Distalis, 103 Weeks, LOAEL = nd (Dermal; NTP, 1995)				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Gamma	936	443	na	81.7
Logistic	927	552	0.9	79.7
Probit	943	534	0.88	79.7
Weibull	927	443	na	81.7



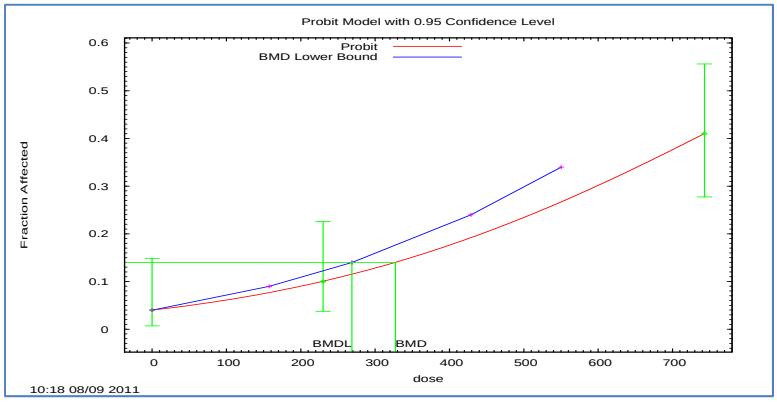
Male Rat % Incidence of Liver Necrosis, 103 Weeks, LOAEL = nd (Dermal; NTP, 1995)				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Gamma	725	373	0.84	74
Logistic	766	542	0.54	74.2
Probit	761	518	0.57	74.2
Weibull	725	373	0.84	74



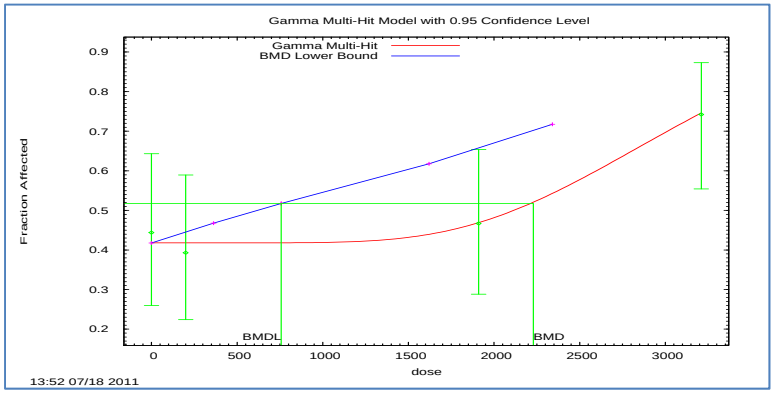
Male Rat % Incidence of Mesentery Fat Granuloma, 103 Weeks, LOAEL = nd (Dermal; NTP, 1995)				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Gamma	205	14	na	15.3
Logistic	92	26	0.78	13.4
Probit	94	29	0.81	13.4
Weibull	188	14	na	15.4



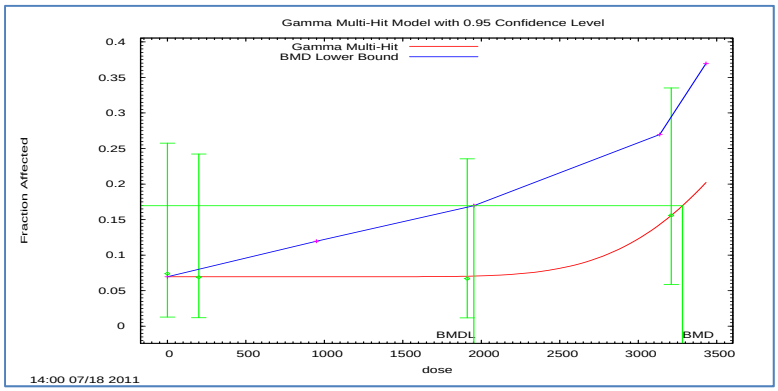
Male Rat % Incidence of Skin Acanthosis, 103 Weeks, LOAEL = 1015 MKD (Dermal; NTP, 1995)				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Gamma	309	149	na	124.3
Logistic	355	293	0.87	122.4
Probit	327	269	0.99	122.3
Weibull	313	149	na	124.3



Percent of Litters with Extra Ribs, LOAEL = 3210 MKD (Dietary, Gd 6-15; Field et al., 1993)				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Gamma	2229	757	0.7	160.1
Logistic	1058	683	0.34	160.1
Multistage	908	485	0.25	160.3
Probit	1056	682	0.35	160.1
Weibull	2279	757	0.7	160.1



Percent of Litters with Malformed Fetuses, LOAEL = 3210 MKD (Dietary, Gd 6-15; Field et al., 1993)				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Gamma	3282	1953	0.99	75.3
Logistic	3928	2137	0.77	75.8
Multistage	4913	1763	0.56	65.7
Probit	4052	2076	0.76	75.9
Weibull	3238	1953	0.99	75.3



Percent of Litters with Variations, LOAEL = 3210 MKD (Dietary, Gd 6-15; Field et al., 1993)				
Model	**BMD_{10}**	**$BMDL_{10}$**	**P-value**	**AIC**
Gamma	1378	382	0.59	149.5
Logistic	765	509	0.67	148
Multistage	539	311	0.52	144.8
Probit	784	530	0.69	147.9
Weibull	1337	382	0.58	149.5