Five Proposition 65 Maximum Allowable Dose Level (MADL) for Reproductive Toxicity for Di(2-ethylhexyl)phthalate (DEHP) by Intravenous Injection

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SUMMARY

The maximum allowable dose levels (MADL) for di(2-ethylhexyl)phthalate (DEHP) for exposure by intravenous injection (i.v.) are **4200 micrograms/day (*μg*/day)** for adults, 600 *μg*/day for infant boys (29 days to 24 months of age) and 210 *μg*/day for neonatal infant boys (birth to 28 days of age). These values are based on the male reproductive effects observed in rats by Cammack et al. (2003). As specified in regulation, when the applicable reproductive effect is upon the male, the MADL is calculated based on a human body weight of 70 kg (Title 22, California Code of Regulations, Section 12803(b)) [1]. In the case of DEHP, however, developing animals are sensitive to the testicular effects of DEHP (e.g., Sjoberg et al., 1985a; 1986; Li et al., 2000; CERHR, 2000; U.S. FDA, 2001; Borch et al., 2004). Bodyweights of infants and neonatal infants are markedly lower than that of an adult. Accordingly, age-specific MADLs have been calculated for infant and neonatal infant boys based on bodyweights of 10 (Section 12703(a)(8)) and 3.5 kg, respectively (Sections 12801(a) and 12803(a)(6)). Children and adolescents also differ in bodyweight from adults. Age-specific MADLs for males in those age groups can be calculated by application of the default bodyweights specified in Section 12703(a)(8).

In the study by Cammack et al. (2003), decreased testicular weights and histopathological changes were found in male rats (3-5 days of age at the beginning of treatment) treated intraveneously for 21 days with DEHP at 300 and 600 mg/kg-day. Testicular effects were not seen in rats treated at 60 mg/kg-day; this dose was therefore identified as the No Observable Effect Level (NOEL) in this study. The testicular effects of DEHP observed in rats are considered relevant to humans, based on mechanistic and other relevant data.

BACKGROUND

This report describes the derivation of ~~a~~ maximum allowable dose levels (MADL<u>s</u>) for DEHP (CAS No. 117-81-7) via the i.v. route.

[1] All further references to regulations are to Title 22, California Code of Regulations unless otherwise noted

DEHP is mainly used as a plasticizer of polyvinyl chloride (PVC) in the manufacture of a wide variety of consumer products, including i.v. tubing and blood bags (OEHHA, 1997; CERHR, 2000). DEHP was listed under the Safe Drinking Water and Toxic Enforcement Act of 1986 (commonly known as Proposition 65, codified at Health and Safety Code Section 25249.5 et seq.) as known to the State to cause reproductive toxicity (developmental and male reproductive toxicity), effective October 24, 2003. This listing was based on formal identification of DEHP as causing developmental and male reproductive toxicity by the National Institute for Occupational Safety and Health (NIOSH, 1990) and by the U.S. Food and Drug Administration (U.S. FDA, 2001). NIOSH and U.S. FDA are authoritative bodies under Proposition 65 for identification of chemicals as causing reproductive toxicity (Section 12306(l)).

Procedures for the development of Proposition 65 MADLs are provided in Section 12801 and 12803. Exposure at a level 1,000 times greater than the MADL is expected to have no observable effect. As defined in regulation, a MADL is derived from a NOEL based on the most sensitive study deemed to be of sufficient quality (Section 12803). This document addresses the i.v. route of exposure for DEHP to assist in the implementation of Proposition 65 relative to the widespread human exposures by this route.

STUDY SELECTION

Relevant studies or reports that provide information on the developmental or male reproductive toxicity of DEHP have been identified through literature searches and through reviewing documents produced by authoritative bodies or other expert groups. These documents included the two reports by the authoritative bodies that provided the primary support for the Proposition 65 listing of DEHP as a chemical known to cause reproductive toxicity – the U.S. FDA (2001) document *Safety Assessment of Di (2-ethylhexyl)phthalate (DEHP) Released from PVC Medical Devices,* and the NIOSH (1990) document *NIOH and NIOSH basis for an Occupational Health Standard: Di (2-ethylhexyl) phthalate (DEHP).* In addition, the detailed review by an expert panel convened by the National Toxicology Program's Center for the Evaluation of Risks to Human Reproduction (2000) entitled *NTP-CERHR Expert Panel Report on Di (2-ethylhexyl) Phthalate* was consulted. There is only one human study regarding the developmental or male reproductive effects of DEHP following i.v. exposure (Rais-Bahrami et al., 2004). In this study testicular volume, phallic length, and the serum levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone were examined in 13 adolescent males (14-16 years of age) exposed to DEHP as neonates on extracorporeal membrane oxygenation (ECMO) support. Mean values for these parameters were within the appropriate range for the degree of pubertal development. Detailed information (e.g., time and duration on ECMO, range of the values for sexual hormones or testicular volumes) was not reported, and no control group was included in the study. Therefore, OEHHA has determined that there is no human study that is "of sufficient quality" for MADL development for the purposes of Proposition 65, and the MADL is necessarily based on animal studies.

Male Reproductive Toxicity in Animals

Four studies provide relevant information on testicular effects of DEHP following i.v. administration (Petersen et al. 1975; Sjoberg et al. 1985b; Baxter Healthcare Corporation 2000; Cammack et al. 2003).

The study by Petersen et al. (1975) was briefly reported in U.S. FDA (2001), but more detailed reporting was not available to OEHHA. With regard to this study, the U.S. FDA stated, "Although Petersen et al. (1975) reported reduced fertility in mice following IV injection of DEHP, some uncertainty exists about the actual doses that were used in the study. For example, Petersen et al. (1975) state: 'three levels 5 mg, 25 mg, and 50 mg per 100 cc of serum were used.' If this concentration was correct, it would require administration of approximately 30 ml of serum to a rat to achieve the stated doses. This is obviously a physical impossibility." In the absence of details on the design, dosage, conduct and outcome for this study, OEHHA could not conclude that this study was "of sufficient quality" for MADL development, as that term is used in Section 12803.

The study by Baxter Healthcare Corporation (2000) was cited in the documents by the U.S. FDA (2001) and CERHR (2000). The study report is not available to OEHHA. With regard to this study, the CERHR stated that "Baxter Healthcare Corporation (*213*) submitted a summary describing testicular histology in neonatal rats and rabbits following IV exposure to 62/mg/kg bw/day DEHP in 4% Bovine Serum Albumin. Control rats were dosed with saline. Rats (n= 7 treated and 8 controls) were dosed on pnd 3-21 and rabbits (n=5 treated and 7 controls) were dosed on pnd 14-42. The animals were sacrificed on the day of or the day after the last treatment and testes were preserved in formalin. No histopathological effects were observed in the testes." The U.S. FDA (2001) reported that "The Baxter Healthcare Corporation (Baxter, 2000) recently made public the results of an unpublished study in which neonatal male rats or rabbits were injected either with DEHP or 4% bovine serum albumin during postnatal days 3-21 (rats) or 14-42 (rabbits). Histopathological examination of the testes and other organs of DEHP-exposed animals revealed no histologic alterations that could be attributed to the test material administered at a dose of 62 mg/kg/day." The limited information about this study reported by the U.S. FDA (2001) or CERHR (2000) is not sufficient to support a conclusion that the study by Baxter Health Care study is "of sufficient quality" to serve as a basis for MADL development.

The studies by Sjoberg et al. (1985b) and Cammack et al. (2003) found that DEHP causes obvious testicular damage in young or neonatal rats. Major findings from these two studies, including NOELs and Lowest Observed Effect Levels (LOELs), are summarized in Table 1.

Table 1. Testicular effects of DEHP via i.v. exposure

Study	Animals	Treatment	General	Male reproductive	NOEL

Reference			Toxicity	effects & LOEL	
Sjoberg et al., 1985b	Male Sprague Dawley rats 40-day-old, 5-6 rats per group and one group of five 25-day-old.	**IV infusion** of DEHP emulsion. 0, 5, 50, or 500 mg/kg, six injections on alternative days for 40 day-old rats. 25-day-old rats treated at 500 mg/kg-day. Examined on day 12.	Increased relative weights of liver and liver peroxisome counts at 500 mg/kg.	No effect on testicular weights. No histopathological changes in paraffin-embedded testicular tissues. Cytoplasmic vacuolation in Sertoli cells of both ages treated with 500 mg/kg DEHP. LOEL: 500 mg/kg (average 250 mg/kg-day)	50 mg/kg or 25 (mg/kg-day)
Cammack et al., 2003	Male Sprague Dawley rats, 3-5 days old, 16 animals per group	**IV infusion** of DEHP emulsion in Intralipid. 0, 60, 300, 600 mg/kg-day for 21 days. Examined on day 22 or 90 days after treatment.	Decreased body weights at 600 mg/kg-day.	Decreased testicular weights, partial depletion of the germinal epithelium, or decreased diameter of the seminiferous tubules at 300 & 600 mg/kg-day. LOEL: 300 mg/kg-day	60 mg/kg-day

Sjoberg et al. (1985b) injected groups of five to six 40 day-old male Sprague Dawley rats with 0, 5, 50 or 500 mg/kg DEHP emulsified with egg yolk phosphatides in a glycerol solution. Treatments were administered six times on alternate days over a 12 day period. One group of 25 day old rats were similarly treated with 500 mg/kg. Cytoplasmic vacuolation in Sertoli cells and degeneration in spermatocytes were observed in both 25 and 40 day old animals given 500 mg/kg, when the tissues were fixed and processed for examination by electron microscopy, but not in tissues processed for regular paraffin sections. No other obvious effects were found. Cytoplasmic vacuolation in Sertoli cells is a subtle but common morphological changes in the testis following treatment with testicular toxicants (Creasy, 2001; 2003). CERHR noted that testicular development during the perinatal period was not evaluated, but because the testicular effects observed were subtle, they suspected that, for this study, the true no observable adverse effect level (NOAEL) was closer to lowest observed adverse effect level of 500 mg/kg (250 mg/kg-day average) than that observed in the study (25 mg/kg-day average). Finally, CERHR (2000) comments that "The endpoints were histological, and are thus sensitive. However, the limited exposure duration and lack of functional evaluation severely limit the utility of these data, and they are not valuable for setting a NOAEL or LOAEL." With regard to non-oral studies in general CERHR (2000) notes "No other reviewed studies were found to be useful in this regard…" The perinatal period, potentially a time of greater susceptibility for DEHP's reproductive effects, was not tested in this study.

After the publication of the CERHR, U.S. FDA and NIOSH evaluations, Cammack et al. (2003) published a study in neonatal rats on the male reproductive effects of DEHP following i.v. injection or oral administration. In this study commissioned by the Advanced Medical Technology Association, male Sprague Dawley rats, 3-5 days old, 16 animals per group, were treated with DEHP either by i.v. injection (i.v. groups; 0, 60, 300, or 600 mg/kg-day) or by gavage (oral groups; 0, 300, 600 mg/kg-day). All animals

except the oral group receiving 600 mg/kg-day were treated for 21 days. The oral group receiving 600 mg/kg-day only received treatment for 19 days. This group was a replacement for another group initially treated by gavage with 1000 mg/kg-day DEHP. Because of high mortality in the 1000 mg/kg-day group, this group was terminated and replaced with a new group receiving 600 mg/kg-day DEHP. At the end of the 21-day treatment period, seven animals from each group were necropsied and nine animals from each group were allowed to recover until 90 days of age. All the animals at the end of the experiment were necropsied, and sperm samples obtained from the vas deferens were assessed for motility and morphology. Total sperm counts (expressed as million sperm per gram frozen tissues) in the caudal section of frozen epididymis or frozen testis were determined. At the end of the 21-day treatment period in animals treated with DEHP by i.v. injection, body weights in the 600-mg/-kg-day group were significantly reduced and the mean liver weights (absolute and relative to body weight) in the 300 and 600 mg/kg-day group were significantly increased. Absolute testis weights in the 300 and 600 mg/kg-day i.v. groups were significantly decreased by approximately 33% and 48%, respectively (0.326±0.013g and 0.253±0.011g in the 300 and 600 mg/kg-day groups, respectively, compared to 0.486±0.016g in the vehicle-only control group). Histopathological changes, consisting of partial depletion of the germinal epithelium and/or decreased diameter of the seminiferous tubules, were present in all animals of the 300 and 600 mg/kg-day i.v. groups. The authors stated that the Sertoli cells of the treated animals were normal in appearance when compared to those of the control animals. At the end of recovery (90 days of age; approximately 64-66 days of recovery), absolute testis weights in rats treated with 300 or 600 mg/kg-day were still significantly lower than those of the control animals. No treatment-related histopathological changes were observed in the testis, epididymis, or prostate. No effect on sperm motility or morphology or testicular sperm count was observed, but epididymal sperm counts were significantly increased in rats treated with 300 or 600 mg/kg-day. In animals treated with 60 mg/kg-day by i.v. injection, the authors reported no treatment-related effects on testis weights or morphology or sperm parameters. Therefore, the NOEL for the testicular effects of DEHP following i.v. injection as observed in this study is 60 mg/kg-day.

Although the LOEL of 250 mg/kg-day observed in the study by Sjoberg et al. (1985b) is lower than that (300 mg/kg-day) in the study by Cammack et al., the NOEL (60 mg/kg-day) in the study by Cammack et al. (2003) is still below 250 mg/kg-day. Therefore, for the purpose of Proposition 65, the study by Cammack et al. (2003) is identified as "the most sensitive study deemed to be of sufficient quality" for the male reproductive effects of DEHP following i.v. injection.

Developmental Effects in Animals

There is only one i.v. study, by Lewandowski et al. (1980), in the literature that reported potential developmental effects of DEHP following i.v. injection. In this study, pregnant Sprague-Dawley rats (25 per group) were treated by i.v. injection of plasma-soluble extracts from PL-146 and PL-130 strips from gestational day (GD) 6 to 15. PL-130 and PL-146 are plastics used in the manufacture of blood storage bags and extracts contained

approximately 185 μg/ml DEHP. Other chemicals possibly extracted were not reported. Reported DEHP doses of PL-130 extracts were 1.3 and 4.7 mg/kg-day, while those for PL-146 extracts were 1.4 and 5.3 mg/kg-day. The control group was treated with plasma only. The animals were examined on GD 20. No obvious maternal toxicity was observed. The authors reported that there was no effect on fetal viability, total number of implantations, resorptions, or fetal weights. There was no increase in skeletal and visceral anomalies. Since this study did not produce a developmental effect, it is not utilized for the determination of the NOEL (Section 12803(a)(1)). Effects of DEHP on male reproductive organs were not assessed in this study. As noted by CERHR (2000), exposure levels in this study were low relative to doses administered in feeding studies precluding a comparison of developmental toxicity by oral and i.v. routes.

The developing reproductive system is believed to be the most sensitive target for DEHP toxicity (CERHR, 2000). Animals in the study by Cammack et al. (2003) were treated early in the postnatal developmental period, and examined for several aspects of potential effects on the testicular structure and function. Thus, the findings from this study provide information on the effects of i.v.-injected DEHP on testicular development during a postnatal period critical for establishment of testicular structure and function. Effects on developing reproductive systems from prenatal i.v. exposure to DEHP have not been studied experimentally.

Relevance of Rodent Studies to Humans

In selecting the most sensitive study for the male reproductive effects of DEHP following i.v. injection, OEHHA has considered carefully the relevance to humans of testicular effects in rats. It is generally accepted in the scientific community that "an agent that produces an adverse reproductive effect in experimental animal studies is assumed to pose a potential reproductive threat to humans" (U.S. EPA, 1996). In the case of DEHP, however, studies in non-human primates, particularly common marmosets (Rhodes et al., 1986; Kurata et al., 1998; MCSI, 2003), have failed to demonstrate male reproductive effects. Accordingly, OEHHA considered whether the NOEL in rats should be adjusted based on the assumption that the common marmoset is a better model for human testicular function than is the rat. After reviewing all available primate studies, OEHHA notes that the testis of the common marmoset has some unique characteristics that are different from other mammals including rats, cynomolgus macaques, and humans. For example, sperm production and androgen synthesis in humans, macaque monkeys, and rodents are under regulation by hormones produced in the pituitary, such as follicle-stimulating hormone (FSH) and luteinizing hormone (LH). However, the pituitary of common marmoset does not produce LH. Instead, it produces chorionic gonadotropin (CG), which is only produced in the placenta of humans or rodents (Muller et al., 2004). Both CG and LH in mammals use the same receptor, the LH receptor. The gene for this receptor in common marmoset is lacking one segment called exon 10. Lack of exon 10 in the LH receptor causes androgen deficiency and hypogonadism in humans (Zhang et al., 1998; Gromoll et al., 2000). Indeed, because of fundamental differences in the testis between common marmosets and humans, it has been suggested that "the use of this

animal model cannot be recommended for reproductive toxicology assessment" (Zuhkle & Weinbauer, 2003). Based on the facts discussed above, OEHHA has determined that the data from studies in common marmosets cannot not be used as basis for MADL development for DEHP, nor can they be used as a basis for adjusting the rat NOEL. Lack of adverse testicular effects in common marmosets following DEHP treatment does not affect the relevance to humans of experimental data obtained from studies in rats.

OEHHA has also considered carefully the relevance to humans of testicular effects in rats according to modes of actions that have been generally recognized by academic researchers (e.g., Boekelheide, 2004) and in the expert reviews (e.g., U.S. FDA, 2003; CERHR, 2000). In particular, OEHHA has reviewed information relevant to potential involvement of peroxisome proliferator-activated receptor (PPAR) in the testicular effects of DEHP. As stated in the CERHR document (CERHR, 2000), "In contrast to hepatic toxicity, testicular toxicity is noted in PPAR-alpha knockout mice exposed to DEHP, albeit that appearance of the testicular effects was delayed compared to wild-type mice. In addition, the guinea pig, a non-responding species to the peroxisomal-proliferation effects of DEHP, is susceptible to the testicular effects of this agent." The Phthalates Expert Panel of CERHR concluded that, "the reproductive toxicity of DEHP appears independent of PPAR-alpha." Relevant findings that OEHHA has reviewed support the statements by the CERHR cited above. Therefore, the weight of the evidence supports a finding that the testicular effects of DEHP observed in rats are relevant to humans, based on mechanistic data including those on involvement of PPAR.

MADL Calculation

The controlling regulation specifies that, "where multiple reproductive effects provide the basis for the determination that a chemical is known to the state to cause reproductive toxicity, the reproductive effect for which studies produce the lowest NOEL shall be utilized for the determination of the NOEL" (Section 12803(a)(1)). In this case, there is no prenatal developmental study of DEHP by i.v. injection that produced a developmental effect. Thus, the most sensitive study for the male reproductive effects of DEHP following i.v. injection, i.e., the study by Cammack et al. (2003), is selected as the basis for developing the MADL for DEHP by i.v. injection.

The NOEL is the highest dose level which results in no observable reproductive effect, expressed in milligrams of chemical per kilogram of bodyweight per day (Section 12803(a)(1)). The NOEL is converted to a milligram per day dose level by multiplying the assumed human body weight by the NOEL (Section 12803(b)). When the applicable reproductive effect is upon the male, the MADL is generally calculated based on a human body weight of 70 kg (Section 12803(b)). As noted earlier, developing animals are sensitive to the testicular effects of DEHP (e.g., Sjoberg et al., 1985a; 1986; Li et al., 2000; CERHR, 2000; U.S. FDA, 2001; Borch et al., 2004). The bodyweights of infants and neonatal infants are approximately 7-20 fold lower than that of an adult (National Center for Health Statistics, 2005). Thus, exposure of an infant to DEHP at a MADL calculated on the basis of an adult body

weight of 70 kg would result in a dose up to 20-fold higher than the corresponding dose in adults. Accordingly, age-specific MADLs have been calculated for infant boys of age 29 days to 24 months and for infant boys during the neonatal period (0-28 days of age) (as also allowed by regulation (Sections 12801(a) and 12803(a)(6)). The neonatal period is "the period immediately succeeding birth and continuing through the first 28 days of extrauterine life," as defined by Stedman's Medical Dictionary (27th Edition). For neonatal infants, the 50th percentile birthweight for boys of 3.5 kg is used (National Center for Health Statistics, 2005). For purposes of this regulation the body weight of 10 kg for infants aged 0-2 years of age specified in Section 12703(a)(8) is applied to infants to 29 days-24 months of age. Boy children and adolescents also have lower body weights than do the adult. If males in those age groups are exposed to DEHP via the i.v. route, age-specific MADLs can be calculated by application of the corresponding default bodyweights specified in Section 12703(a)(8).

The following calculations were performed to derive the MADLs for DEHP via the i.v. route of exposure, based on a NOEL 60 mg/kg-day for the male reproductive effects as observed in the study by Cammack et al. (2003).

For Adults:

When the applicable reproductive effect is upon the male, human body weight of 70 kilograms shall be assumed (Section 12803(b)).

Calculation of the NOEL for a 70 kg man:

60 mg/kg-day × 70 kg = 4200 mg/day

The MADL is derived by dividing the NOEL by one thousand (Section 12801(b)(1)). Thus, the adjusted NOEL was divided by 1,000 to obtain the MADL.

$MADL_{adult\ i.v}$ = 4200 mg/day ÷ 1000 = 4.2 mg/day or **4200 µg/day**

For Infants and Neonatal Infants Boys:

Assuming a body weight of 10 kg for a one-year-old infant (National Center for Health Statistics, 2005), an exposure of an infant to DEHP at the level of the $MADL_{adult}$ (4200 µg/day) is equivalent to 420 µg/kg-day. In order to derive a MADL for infants of 4200 µg/day, it would require a NOEL of 420 mg/kg-day (4200 µg/day ÷ 10 kg × 1000 = 420 mg/kg-day). This estimated infant NOEL would be seven-fold higher than the NOEL for the adult (60 mg/kg-day), indicating that application of the adult-derived MADL would result in a 7-fold higher dose in infants and a higher dose in neonatal infants. It is even higher than the LOEL (300 mg/kg-day) observed by Cammack et al. (2003) in rats treated from PND 3-5 until weaning on PND 21. Therefore, a MADL based on the body

weight of an adult human may not be protective against male reproductive effects in a neonatal or infant boy, or to a lesser extent in boys during childhood or adolescence.

Section 12801(a) specifies that "nothing in this article shall preclude a person from using evidence, standards, assessment methodologies, principles, assumptions or levels not described in this article to establish that a level of exposure has no observable effect at one thousand (1,000) time the level in question," while Section 12803(a)(6) specifies that "when available data are of such quality that anatomic, physiologic, pharmacokinetic and metabolic considerations can be taken into account with confidence, they may be used in the assessment." In this case, the anatomic and physiologic differences between an infant boy and an adult man can be taken into account with much confidence. Therefore, MADLs specific to infants and neonatal infant boys are developed as follows:
The infant period extends from birth to age 24 months and an average body weight of 10 kg over this developmental period is assumed (Section 12703(a)(8); OEHHA, 2000; National Center for Health Statistics, 2005). For purposes of this regulation this same average body weight of 10 kg is used to apply to those infants ages 29 days-24 months of age.

Calculation of the NOEL for a 10 kg infant:

60 mg/kg-day × 10 kg = 600 mg/day

$MADL_{infant\ i.v.}$ = 600 mg/day ÷ 1000 = **600 µg/day**.

The neonatal period consists of the first 28 days of the infant period (Stedman's Medical Dictionary (27th Edition)). For infants ages 0-28 days (i.e., neonatal infants), the 50^{th} percentile birthweight for boys of 3.5 kg is used (National Center for Health Statistics, 2005).

Calculation of the NOEL for a 3.5 kg neonatal infant:

60 mg/kg-day × 3.5 kg = 210 mg/day

$MADL_{neonatal\ infant\ i.v.}$ = 210 mg/day ÷ 1000 = **210 µg/day**.

All the MADLs derived above (4200 µg/day for adults, 600 µg/day for infant boys and 210 µg/day for neonatal infant boys) apply to exposure to DEHP by the i.v. route.

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