CHEMICAL MEETING THE CRITERIA FOR LISTING AS CAUSING REPRODUCTIVE TOXICITY VIA THE AUTHORITATIVE BODIES MECHANISM

DI(2-ETHYLHEXYL) PHTHALATE IDENTIFIED BY NIOSH AND FDA

PACKAGE 6d

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Reproductive and Cancer Hazard Assessment Section
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

Di(2-ethylhexyl) phthalate (CAS No. 117-81-7) meets the criteria for listing under Proposition 65 via the authoritative bodies listing mechanism. The regulatory guidance for listing by this mechanism is set forth in Title 22, California Code of Regulations (CCR), Section 12306. For example, the regulations include provisions covering the criteria for evaluating the documentation and scientific findings by the authoritative body to determine whether listing under Proposition 65 is required.

The National Institute for Occupational Safety and Health (NIOSH) and the U.S. Food and Drug Administration (U.S. FDA) have been identified as authoritative bodies for purposes of Proposition 65 (22 CCR Section 12306(l)) and both organizations have recognized di(2-ethylhexyl) phthalate (DEHP) as a chemical causing developmental and reproductive toxicity (DART).

OEHHA has found that DEHP has been "formally identified" by an authoritative body (NIOSH) as causing reproductive toxicity according to the regulations covering this issue (22 CCR 12306(d)). The chemical is the subject of a report which is published by the authoritative body and which concludes that the chemical causes reproductive toxicity (NIOSH, 1990) (22 CCR 12306(d)(1)), and the document specifically and accurately identifies the chemical and has been "published by the authoritative body in a publication, such as, but not limited to, the federal register for an authoritative body which is a federal agency" (22 CCR 12306(d)(2)(C)).

Similarly, DEHP has been "formally identified" by an authoritative body (U.S. FDA) as causing reproductive toxicity according to the regulations covering this issue (22 CCR 12306(d)). The chemical is the subject of a report which is published by the authoritative body and which concludes that the chemical causes reproductive toxicity (U.S. FDA, 2001) (22 CCR 12306(d)(1)), and the document specifically and accurately identifies the chemical and has been "published by the authoritative body in a publication, such as, but not limited to, the federal register for an authoritative body which is a federal agency" (22 CCR 12306(d)(2)(C)).

Male Reproductive Toxicity

NIOSH (1990): DEHP can cause testicular damage in rats.

Relying upon numerous studies in experimental animals, NIOSH (1990) made the conclusion presented above. The studies cited by NIOSH had been conducted in different species (mice, rats, and hamsters), via different routes of exposure (gavage, in diet, subcutaneous or intraperitoneal injection), and were treated for different periods of time (from a single dose to repeated doses for more than 100 days). Examples of the cited studies include: Melnick et al. (1987); Oishi (1984); Oishi and Hiraga (1983); Saxena et al. (1985); Agarwal et al. (1985); Seth et al. (1976); Curto and Thomas (1982); Gray et al. (1982); and Gray and Butterworth (1980). Decreased testicular weight, marked testicular atrophy, or reduced fertility had been observed in one or several of the studies listed above, except one study in which no effect on testicular weights was observed in male Swiss mice following daily intraperitoneal injection of 50 or 100 mg/kg DEHP for five days or alternate daily for 20 days (Curto and Thomas, 1982). In addition to studies on DEHP, several studies regarding the male reproductive effects of mono-(2-ethylhexyl) phthalate, a metabolite of DEHP, were also reviewed by NIOSH (Oishi and Hiraga, 1980a; 1980b; Curto and Thomas, 1982). Taking into account the criteria specified in 22 CCR 12306(g)(2), OEHHA has evaluated all of the studies cited by NIOSH in support of their findings with regard to the reproductive toxicity of DEHP, and has found that the criteria for "as causing reproductive toxicity" specified in regulations (22 CCR 12306(g)) have been satisfied for DEHP. In making this finding, OEHHA relied upon only the documents and reports cited by NIOSH. OEHHA did not review additional studies not relied on by NIOSH, nor did OEHHA consider information contained in sources outside of the administrative records. A brief discussion of representative studies cited by the authoritative body that provide evidence on the reproductive toxicity of DEHP and which were available to the public and OEHHA is presented below.

Agarwal et al. 1985. This is a fertility study in mice cited by NIOSH. In this study, adult male ICR mice, eight per group, was administrated by subcutaneous injection of 1, 2, 5, and 10 ml/kg of DEHP on day 1, 5, and 10, and was then mated one to one with untreated adult virgin females. The authors stated that all animals appeared healthy and active throughout the study period. The authors found that a single mating at day 21 resulted in a reduction in the incidence of pregnancies in the DEHP-treated groups. Examination of pregnant females on gestational day 13 also revealed an increase in the incidence of preimplantation losses and early fetal deaths in the DEHP-treated groups.

Gray and Butterworth 1980. This is a male reproductive toxicity study cited by NIOSH. In this study, groups (four-five per group) of male Wistar rats of different ages (four-week-old, 10-week-old, and 15-week-old) were treated daily by gavage with 2.8 g/kg DEHP for 10 days. The body weights of DEHP-treated rats were approximately 80-90 of the corresponding controls in all three age groups. The authors did not report any other general toxicity data. Relative

testicular weight was reduced in four-week-old rats treated with DEHP, but not in other two age groups. Testicular atrophy, comprising a loss of spermatids and spermatocytes was observed in four- and ten-week-old rats. No testicular damage was produced in 15 week-old rats. The weights of the seminal vesicles and ventral prostate were also reduced in the four- and 10-week, but not in the 15-week-old rats.

Gray et al. 1982. In this study cited by NIOSH, the testicular effects of DEHP and several other phthalate esters were investigated. Six 4-6 weeks old Sprague-Dawley rats and seven Syrian hamsters of the same age were treated orally for nine days with 2.8 g/kg/day and 4.2 g/kg/day, respectively. The authors observed tubular atrophy in the testes of both species but the effect was more severe in rats than in hamsters.

Melnick et al. 1987. This paper cited by NIOSH is a summary report about several reproductive and developmental toxicity studies of DEHP conducted by the National Toxicology Program (NTP). The paper provided relatively detailed information about the NTP findings from a Fertility Assessment by Continuous Breeding (FACB) in mice and from developmental toxicity studies in rats and mice. However, only findings from the FACB study were included in the NIOSH document and thus were reviewed by OEHHA. In the FACB study cited by NIOSH, male and female CD-1 mice were fed diets containing 0, 0.01, 0.1, or 0.3% DEHP during a seven day pre-mating period and a subsequent 98-day cohabitation period. After the cohabitation period, the animals were continued individually on treatment for 20 more days. Following the continuous breeding, male mice from the high-dose (0.3%) group were randomly paired with control females (cross-over trial) to determine which sex was affected. The authors provided no information about the number of animals per group, or the time the animals were sacrificed and were subject to histological evaluation, or the general toxicity of DEHP. The authors reported that exposure to DEHP resulted in complete suppression of fertility in the 0.3% dose group and significant reduction in the 0.1% group compared to the control group. Fertility was also significantly reduced for male mice in the 0.3% dose group paired with control females. In addition, the authors found significant decrease in weights of testes and epididymides, epididymal sperm concentration, and percentage of motile sperm in mice from the 0.3% dose group. Extensive destruction of seminiferous tubules was also observed in mice of the high-dose group.

Saxena et al. 1985. This is a male reproductive study cited by NIOSH. The study was conducted in 13-week-old male Wistar albino rats, six animals per group. The animals treated orally with 2.0g/kg DEHP daily for seven days. The authors found no gross toxicity symptoms in treated animals. Morphological degeneration of germ cells and marked changes in biochemical activities were observed in the testes of DEHP-treated animals by the authors.

Seth et al. 1976. This is a reproductive study cited by NIOSH. In this study, male (ten per group) and female (20 per group) albino rats were given three intraperitoneal injections of 5ml/kg DEHP or saline (control) on day 1, 5, and 10 and the animals were sacrificed for examination. The strain of the animals was not reported by the authors. The authors found no mortality or gross abnormality in treated animals but reported focal degeneration of seminiferous tubules and edema of interstitium in the testes of treated rats.

U.S. FDA (2001): The adverse testicular effects seen in DEHP-exposed rodents could theoretically occur in DEHP-exposed humans, since there is no mechanistic reason to assume that the adverse testicular effects are species specific.

Similar to the conclusion drawn by NIOSH, U.S. FDA also stated that the critical toxicity studies for derivation of Tolerable Intake (TI) values for DEHP (i.e., doses of a compound that are not expected to result in adverse effects following exposure for a defined period) were studies conducted in experimental animals and were based on adverse effects produced by DEHP on the testes, an organ that appears to be particularly sensitive to DEHP. The U.S. FDA conclusions and statements regarding the testicular effect of DEHP were based on numerous studies in laboratory animals. Some aspects of the DEHP-caused testicular damage, characterized as decreased testicular weights, germ cell degeneration in the testis or testicular atrophy, decreased epididymal sperm count, etc., were observed in all of the cited oral studies in rats and in several studies in which the animals were exposed to DEHP by intravenous or intraperitoneal injects (e.g., Seth et al., 1976; Douglas et al., 1986; or AdvaMed, 2001 as reported in the FDA document). OEHHA also noticed that obvious testicular effects of DEHP were not observed in several non-oral studies (i.e., treatment via subcutaneous, intravenous, or intraperitoneal injection) in rats or mice (e.g., Douglas et al., 1986; Nair et al., 1998) or in many studies performed in primates (Rhodes et al., 1986; Pugh et al., 2000). Taking into account the criteria specified in 22 CCR 12306(g)(2), OEHHA has evaluated the studies cited by U.S. FDA in support of their findings with regard to the reproductive toxicity of DEHP, and has found that the criteria for "as causing reproductive toxicity" specified in regulations (22 CCR 12306(g)) have been satisfied for DEHP. In making this finding, OEHHA relied upon only the documents and reports cited by U.S. FDA. OEHHA did not review additional studies not relied on by U.S. FDA, nor did OEHHA consider information contained in sources outside of the administrative records. A brief discussion of representative studies cited by the authoritative body that provide evidence on the reproductive toxicity of DEHP and which were available to the public and OEHHA is presented below.

Agarwal et al. 1989. This is a male reproductive toxicity study cited by U.S. FDA. In this study, sexually mature male and female ICR mice 8-10 weeks of age were treated by subcutaneous injection with 1-100 ml/kg undiluted DEHP on Day 1, 5, and 10 of the experiment. On Day 21 of the experiment, ten to 16 mice from each group were mated with untreated mice of the opposite sex for seven consecutive days to evaluate fertility; the other animals (number of animals per group not reported, likely 4-10 animals per group) were sacrificed on Day 21

for biochemical and histological evaluation. The authors found that the incidence of pregnancy of untreated females mated to DEHP-treated males was markedly reduced. Decreased testicular weights, altered biochemical changes (e.g., decreased ATPase activity), and severe atrophic changes in the seminiferous tubules were found in male animals treated with DEHP.

David et al. 2000. This is a chronic toxicity study cited by U.S. FDA as a critical study for derivation of an oral TI value for DEHP. In this study, groups (55-80 animals per sex per group) of Fischer 344 rats were treated with 0, 100, 500, 2500, or 12,500 ppm of DEHP in diet for 104 weeks. A set of 10 animals per sex from groups treated with 0, 2500, or 12,500 ppm DEHP were sacrificed after Week 78 for histopathology. Testicular weights of male rats treated with 12,500 ppm DEHP were significantly decreased at the end of experiment. The authors also reported that incidence of bilateral aspermatogenesis was significantly increased in male rats treated with 12,500 ppm DEHP at Week 78 and in animals treated with ≥500 ppm DEHP at termination (Week 105).

Poon et al. 1997. This is a subchronic oral toxicity study cited by U.S. FDA. U.S. FDA also used the NOAEL and LOAEL values (No Observed Adverse Effect Level and Lowest Observed Adverse Effect Level, respectively) observed in this study as the basis for derivation of an oral TI for DEHP. In this study, groups of 10 male and 10 female Sprague-Dawley rats were administered DEHP in diet at 0, 5, 50, 500, or 5,000 ppm for 13 weeks. Mild vacuolizations in Sertoli cells were observed in male rats exposed to 500 ppm DEHP. Mild to moderate seminiferous tubule atrophy and Sertoli cell vacuolization were observed in male animals exposed to 5,000 ppm DEHP. The authors reported that the NOAEL was 50 ppm in diet or 3.7 mg/kg/day.

Sjoberg et al. 1985. This is one of the studies that U.S. FDA relied upon for derivation of parental TI values. In this study, groups of male Sprague-Dawley rats (5-6 animals per group) were treated by intravenous injections with 0, 5, 50, or 500 mg/kg/day DEHP on alternate days for 12 days. The authors found that treatment did not cause any significant change in the testis weight or morphological alteration at the light microscopic level. However, the authors reported that Sertoli cell vacuolization and degeneration in association with degenerated germ cells were found in three of the five animals exposed to 500 mg/kg DEHP when the tissues were examined at the electron microscopic level.

Developmental Toxicity

NIOSH (1990): DEHP and its metabolite MEHP are teratogenic and embryolethal to rodents. Based on animal data it can be concluded that DEHP is teratogenic. Due to a lack of human data the degree of risk to humans can not be evaluated, but DEHP should be considered as potentially teratogenic in humans.

NIOSH (1990) reviewed numerous developmental studies reported in peer-reviewed toxicological journals and drew the conclusions presented above. A majority of the studies were conducted in mice via the oral route of exposure (Thomas et al., 1979; Tomita et al., 1982; Yagi et al., 1980; Shiota and Mima, 1985; Shiota and Nishimura, 1982; Shiota et al., 1980). Several studies were conducted in rats via oral treatment (Nikonorow et al., 1973) or by intravenous (Lewandowski et al., 1980) or intraperitoneal injection (Shiota and Mima, 1985; Singh et al., 1972). Following oral exposure to DEHP at a variety of dose levels for one or several days during gestation, reduced fetal body weights and/or increased incidence of malformations had been observed in rats (Nikonorow et al., 1973) or mice (Tomita et al., 1982; Yagi et al., 1980; Shiota and Mima, 1985; Shiota and Nishimura, 1982; Shiota et al., 1980). Similar effects were also observed in rats (Ruddick et al., 1981) or mice (Tomita et al., 1982; Yagi et al., 1980) following oral treatment with mono-(2-ethylhexyl) phthalate (MEHP), a metabolite of DEHP. No obvious teratogenicity was found in one study in mice following oral treatment or intraperitoneal injection of MEHP (Shiota and Mima, 1985); similarly, no obvious developmental toxicity was found in rats (Lewandowski et al., 1980) or mice (Shiota and Mima, 1985) following intravenous or intraperitoneal injection, respectively. Severe teratogenicity of DEHP was reported in a rat study following three intraperitoneal injections of DEHP each on gestational day 5, 10 and 15 (Singh et al., 1972). Taking into account the criteria specified in 22 CCR 12306(g)(2), OEHHA has evaluated the studies cited by NIOSH in support of their findings with regard to the developmental toxicity of DEHP, and has found that the criteria for "as causing reproductive toxicity" specified in regulations (22 CCR 12306(g)) have been satisfied for DEHP. In making this finding, OEHHA relied upon only the documents and reports cited by NIOSH. OEHHA did not review additional studies not relied on by NIOSH, nor did OEHHA consider information contained in sources outside of the administrative records. A brief discussion of representative studies cited by the authoritative body that provide evidence on the developmental toxicity of DEHP and which were available to the public and OEHHA is presented below.

Shiota and Nishimura 1982. This is a developmental toxicity study cited by NIOSH. The study was conducted in ICR-JCL mice at 8-16 weeks of age, with 7-24 pregnant animals per group. The animals were treated with DEHP in diet at levels of 0, 0.05, 0.1, 0.2, 0.4, and 1.0% (by weight) from Gestation Day (GD) 1 through GD 18 when the dams were sacrificed and examined. No mortality or behavioral abnormalities were observed in the dams, but the maternal weight was significantly depressed during the later gestation period in the groups given ≥0.2% DEHP. The authors reported increased resorptions, decreased fetal weight, delayed ossification, neural tube defects, and tail anomalies. The lowest observed effective level (LOEL) appears to be 0.1%, indicated by malformations and altered skeletal development.

Nikonorow et al. 1973. This is a developmental toxicity study cited by NIOSH. The study was conducted in Wistar rats, with 10 pregnant animals per group. The animals were treated by gavage with 0, 0.34, or 1.7 g/kg of DEHP from GD 1 through GD 21 when the dams were sacrificed and examined. No data on

maternal toxicity were reported by the authors. Average body weights of fetuses from dams of both DEHP-treated groups were significantly lower than that of the control group. No detectable differences in the number of live and dead fetuses, number of fetal resorptions, or in skeletal development between the DEHP-treated and the control groups were observed.

Yagi et al. 1980. This is a developmental toxicity study cited by NIOSH. The study was conducted in ddY-Slc (SPF) mice 7-8 weeks of age, 3-8 pregnant animals per group. The animals were given a single oral dose of DEHP at levels of 30, 10, 7.5, 5, 2.5, or 1.0 ml/kg on GD 6, 7, 8, 9, or 10. A group of four mice which received 10 ml/kg olive oil was included as controls. In addition, three groups of mice, 2-8 animals per group, were treated with a single dose of 0.1, 0.5, or 1ml/kg MEHP (a metabolite of DEHP) on GD 7, 8 or 9. Decreased maternal body weights were observed in dams treated with 10 ml/kg DEHP on GD 7 or 8, but not in dams treated on GD 9 or 10. The average body weights of fetuses from all DEHP-treated groups were significantly lower than that of the controls. No live fetuses were found in dams treated with 5 or 10 ml/kg DEHP on gestational day 7. Gross and skeletal abnormalities in the live fetuses occurred with 2.5 or 7.5 ml/kg of DEHP given orally on days 7 or 8 of gestation respectively. Similar toxic effects were observed with the administration of MEHP. The gross abnormalities included exencephaly, open eyelid, and club foot. Skeletal abnormalities occurred in the skull, cervical and/or thoracic bones. The authors concluded that both DEHP and MEHP exert similar effects on the mouse fetus and the lethal and/or teratogenic effects of DEHP are probably due to its metabolite, MEHP.

U.S. FDA (2001): Exposure to DEHP during gestation, followed by postnatal exposure, resulted in the development of adverse testicular effects in the offspring at doses approximately an order of magnitude lower than those that produced adverse effects in rodents exposed only in the postnatal period.

U.S. FDA (2001): [There is] increased sensitivity to DEHP-induced testicular effects during pre- and postnatal exposure.

The statements presented above in bold and others similar to these made by U.S. FDA were based on numerous studies in which the animals were exposed to DEHP either prenatally or perinatally. In addition, comparing the TI values established by U.S. FDA to other health-based exposure limits for DEHP, U.S. FDA listed some studies that demonstrated the fetal effects or teratogenicity of DEHP (e.g., Tyl et al., 1988). The majority of the studies cited by FDA regarding the adverse effects of DEHP following prenatal or perinatal exposure were performed in rats or mice. Taking into account the criteria specified in 22 CCR 12306(g)(2), OEHHA has evaluated the studies cited by U.S. FDA in support of their findings with regard to the developmental toxicity of DEHP, and has found that the criteria for "as causing reproductive toxicity" specified in regulations (22 CCR 12306(g)) have been satisfied for DEHP. In making this finding, OEHHA relied upon only the documents and reports cited by U.S. FDA. OEHHA did

not review additional studies not relied on by U.S. FDA, nor did OEHHA consider information contained in sources outside of the administrative records. A brief discussion of representative studies cited by the authoritative body that provide evidence on the developmental toxicity of DEHP and which were available to the public and OEHHA is presented below.

Arcadi et al. 1998. This is a developmental study cited by U.S. FDA. In this study, adult female Long-Evans rats, 12 rats/group, were exposed to DEHP in drinking water at concentrations of 0, 32.5, or 325 µl/L from gestational day 1 to Day 21 after delivery of offsprings. At different times after delivery (21, 28, 35, 42, and 56 days), eight litters per group were selected and one pup from each was sacrificed for examination. Treatment with DEHP did not cause any significant effect on body weight gains of dams or pups. The authors found no difference in the mean number of live pups per dam between the DEHP-treated groups and the control. Increased liver weights, decreased kidney and testis weights were observed in pups in DEHP-treated groups. A spectrum of histopathological alterations was observed in the kidneys, livers, and testes of rats perinatally exposed to DEHP. The authors reported that both concentrations of DEHP caused a gross disorganization of the seminiferous tubule structure, detachment of spermatogonial cells from basal membranes, and thickening of boundary tissues in the testes of male pups.

Gray et al. 1999. This study cited by U.S. FDA investigated the developmental toxicity of DEHP in a transgenerational study in rats. Two groups (eight and ten animals per group, respectively) pregnant Sprague-Dawley rats were treated by gavage with DEHP (750 mg/kg/day) or vehicle only (corn oil), respectively, from gestational day 14 to day 3 of lactation. The authors did not report any data on the maternal effects due to exposure to DEHP. The authors found that DEHP treatment caused a significant decrease in average pup weight and average anogenital distance of all pups on postnatal day 2 and high levels of testicular and epididymal abnormalities, including atrophy and agenesis, when the male pups were examined at about five months of age.

Parks et al. 2000. This is a developmental study cited by U.S. FDA. In this study, pregnant Sprague-Dawley rats were dosed daily by gavage from GD 14 through the day of necropsy (GD 17, 18, 20, or postnatal day 2) with vehicle only (corn oil) or 750 mg/kg/day DEHP. A total of four dams per group per time point were used. Maternal body weight gain of treated dams was significantly reduced on GD 17, 18, 20, and postnatal 2. Treatment from GD14 to up to GD 20 did not affect the body weights of fetuses. Testicular weights of fetuses were significantly reduced in groups treated with DEHP from GD14 to GD20. Testosterone levels in fetal testes were significantly lower in all groups exposed to DEHP. Histopathological examination of testicular tissues performed in groups treated from GD 14- PND 2 had found abnormal, multinucleated gonocytes in male pups examined.

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