Proposition 65 Maximum Allowable Dose Level (MADL) for Reproductive Toxicity for Di-isodecyl Phthalate (DIDP)

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Reproductive and Cancer Hazard Assessment Branch

SUMMARY

The maximum allowable dose level (MADL) for di-isodecyl phthalate (DIDP) is **2200 micrograms/day (µg/day).** This value is based on the developmental effects of DIDP as observed in the two-generation reproductive toxicity study in rats by Exxon Biomedical Sciences Incorporated (EBSI, 2000). The MADL is calculated based on a body weight of 58 kg for a pregnant woman (Title 27, California Code of Regulations, section 25803(b))[1].

BACKGROUND

This report describes the derivation of a maximum allowable dose level (MADL) for DIDP (CAS No. 68515-49-1 and 26761-40-0). DIDP is a complex substance with two different CAS Numbers.

DIDP is mainly (95%) used as a plasticizer in polyvinyl chloride plastics. DIDP is also used in rubbers, anti-corrosion paints, anti-fouling paints, sealing compounds and textile inks. End products that may contain DIDP include automobile undercoating, building materials, wires and cables, shoes, carpet backing, pool liners, and gloves. In addition to direct contact and inhalation of DIDP-containing air, human exposure may also occur through food as a result of uptake by food animals, certain vegetables, and migration of DIDP from food packaging.

DIDP 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 toxicity), effective April 20, 2007. This listing was based on formal identification of DIDP as causing developmental toxicity by the National Toxicology Program (NTP) in its final report titled "NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Di-Isodecyl Phthalate (DIDP)" ("NTP-CERHR Monograph on DIDP"; NTP-CERHR, 2003). The NTP, solely as to final reports of the NTP's Center for the Evaluation of Risks to Human Reproduction (NTP-CERHR), is a body

[1] All further references to regulations are to Title 27 of the California Code of Regulations, unless otherwise noted

recognized as authoritative for the listing of chemicals as known to cause reproductive toxicity under Proposition 65 (Section 25306(1)).

Procedures for the development of Proposition 65 MADLs are provided in Sections 25801 and 25803. 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 No Observable Effect Level (NOEL) based on the most sensitive study deemed to be of sufficient quality. The NOEL shall be the highest dose level which results in no observable reproductive effect expressed in milligrams of chemical per kilogram of bodyweight per day.

STUDY SELECTION

Relevant studies or reports that provide information on the developmental toxicity of DIDP have been identified through literature searches and reviewed.

Human Studies

No relevant human data on the developmental effects of DIDP were identified in the literature search by OEHHA.

Studies in Laboratory Animals

The NTP-CERHR Monograph on DIDP (NTP-CERHR, 2003) identified five animal studies that provided relevant data on the developmental effects of DIDP. The literature search conducted by OEHHA found no additional studies.

OEHHA has reviewed all five studies. The study reports of Hardin et al. (1987) and Hellwig et al. (1997) do not include detailed information on the study design or data analysis and thus it is not possible to determine if they are of sufficient quality to serve as the basis for a MADL. The developmental toxicity study reported by Waterman et al. (1999) and the two-generation reproductive toxicity studies by Exxon Biomedical Sciences Incorporated (EBSI) (1997 and 2000) followed generally accepted experimental protocols. Sufficient information is provided in the study reports to determine that these studies are of sufficient quality to serve as the basis for a MADL. Data from the studies were reviewed to determine which of the studies is the most sensitive.

Among the three studies, the study in rats by Waterman et al. (1999) found increased incidence of skeletal variations, rudimentary lumbar ribs, and supernumerary cervical ribs in the fetuses from dams treated by gavage with 500 mg/kg-d of DIDP from gestational day (GD) 6 to 16. The NTP-CERHR (2003) identified this dose as a Lowest

Observable Effect Level (LOEL) and the lower dose used in the study, 100 mg/kg-d, as a NOEL.

EBSI reported two two-generation reproductive toxicity studies (1997 and 2000, respectively). The full final reports of these studies were provided to OEHHA by the ExxonMobil Chemical Company and were reviewed by OEHHA.

In the first two-generation reproductive toxicity study in rats (EBSI, 1997), the authors observed significantly reduced pup survival index on PND 1 and 4 in the F2 generation among all DIDP-treated groups (0.2, 0.4, and 0.8% in feed). The live birth indices for F1 and F2 pups were also lower in all DIDP-treated groups, but were only statistically significant in F1 pups of the 0.8% dose group and in F2 pups of the 0.2% dose group. Pups in the F1 and F2 generations from the 0.8%-dose group also had reduced birth weights. DIDP at 0.2% in feed was thus considered a LOEL by the NTP-CERHR (NTP-CERHR, 2003). The study authors estimated that 0.2% in feed during the gestational period for the dams of F1 and F2 pups was equivalent to 131-149 mg/kg-d and 135-152 mg/kg-d, respectively (EBSI, 1997).

In the second two-generation reproductive toxicity study in rats exposed to 0.06, 0.2 or 0.4% DIDP in feed (EBSI, 2000), the authors found no developmental effects in F1 pups. There were statistically significant reductions in the survival index on PND 1 and 4 among F2 pups from dams exposed to DIDP at concentrations of 0.2% and 0.4% in feed, respectively. The authors reported no other developmental effects resulting from prenatal exposure to DIDP at doses lower than 0.2% in feed. Therefore, 0.2% and 0.06% in feed are considered to be the LOEL and NOEL, respectively. The estimated doses for these two concentrations of DIDP for the dams of F2 pups during gestation were 134-151 (0.2%) and 38-44 mg/kg-d (0.06%), respectively (EBSI, 2000).

The two two-generation reproductive toxicity studies conducted by EBSI (1997 and 2000) thus observed a LOEL in the range of 131 -152 mg/kg-d on reduced offspring survival index on PND 1 and 4. This LOEL is the lowest among all three studies of sufficient quality, and thus this study is identified as the most sensitive study. The NOEL of 38 mg/kg-d from the second two-generation reproductive toxicity study (EBSI, 2000) is the appropriate basis for calculation of the MADL.

MADL CALCULATION

The NOEL is the highest dose level that results in no observable reproductive effect, expressed in milligrams of chemical per kilogram of bodyweight per day. The NOEL is converted to a milligram per day dose level by multiplying the assumed human body weight by the NOEL (Section 25803(b)). When the applicable reproductive effect is upon the pregnant woman, the MADL is calculated based on a human body weight of

58 kg.

The following calculations were performed to derive the MADL for DIDP via the oral route of exposure, based on a NOEL of 38 mg/kg-day for developmental effects observed in rats by EBSI (2000).

Calculation of the NOEL for a 58 kg woman:
38 mg/kg-day × 58 kg = 2204 mg/day

The MADL is derived by dividing the NOEL by one thousand (Section 25801(b)(1)).

MADL = 2204 mg/day ÷ 1000 = **2204 µg/day or 2200 µg/day after rounding.**

For the purpose of Proposition 65, exposure by dermal contact or inhalation or via multiple routes that leads to absorbed doses equivalent to the MADL proposed above should be the maximum allowable dose level.

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