MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for Diethyl Phthalate (CAS # 84-66-2)

FROM: Robert Sills, AQD Toxics Unit Supervisor

SUBJECT: Diethyl Phthalate ITSL change in the averaging time from 24 hrs to annual

DATE: December 27, 2016

The current ITSL for diethyl phthalate is 2800 ug/m^3, with annual averaging time (AT).

Previously, the ITSL was established on November 23, 2015 at 2800 ug/m^3 with 24 hr averaging time (see attached justification memo dated February 11, 2003, which was mistakenly not implemented until November 23, 2015 due to an oversight). The averaging time (AT) assigned to the ITSL previously (see attached 2/11/03 memo) was 24 hours, as per the default methodology at that time (Rule 232(2)(b)). The ITSL was based on an EPA (1987) Reference Dose (RfD) of 0.8 mg/kg-d, which EPA derived from a subchronic (16 week) rat oral feeding bioassay. The critical effects were decreased growth rate, decreased food consumption, and altered organ weights. EPA (1987) applied a total uncertainty factor (UF) = 1000, which consisted of a UF = 10 for each interspecies extrapolation, intraspecies variability, and subchronic-to-chronic conversion. The current file review concludes that the AT for the ITSL may appropriately be set at annual, based on the nature and duration of the key study and the ITSL value derivation, as allowed under Rule 229(2)(b).

References:

EPA. 1987. Integrated Risk Information System (IRIS database). Chemical file for Diethyl Phthalate. Oral RfD assessment last revised 9/30/87. Retrieved on 12/27/16.

MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

February 11, 2003

To: File for Diethyl Phthalate (CAS# 84-66-2)

From: Michael Depa, Toxics Unit

Subject: ITSL for Diethyl Phthalate

The initial threshold screening level (ITSL) for diethyl phthalate (DEP) is 2800 µg/m³ (24-hour averaging time).

The following references or databases were searched to identify data to determine the screening level: Environmental Protection Agency's (EPA's) Integrated Risk Information System (IRIS), the Registry of Toxic Effects of Chemical Substances (RTECS), the American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values (TLV), National Institute of Occupational Safety and Health (NIOSH) Pocket Guide to Hazardous Chemicals, Environmental Protection Bureau Library, International Agency for Research on Cancer (IARC) Monographs, Chemical Abstract Service (CAS) Online (1967- September 2000), National Library of Medicine (NLM), Health Effects Assessment Summary Tables (HEAST), and National Toxicology Program (NTP) Status Report. The EPA has not established a reference concentration (RfC) for DEP. The RfD for DEP is 0.8 mg/kg/day. The ACGIH TLV and the NIOSH REL are 5 mg/m³. The NTP performed dermal studies on DEP. The NTP did not perform oral or inhalation studies. There was no data meeting the minimum criteria for establishing an RfC. The Agency for Toxic Substances and Disease Registry (ATSDR) published oral Minimum Risk Levels (MRLs). The ATSDR acute oral MRL is 7 mg/kg/day and the intermediate MRL is 6 mg/kg/day.

The molecular weight for DEP is 222.23g, and the water solubility and vapor pressure @20°C are 1080 mg/L and 3.45 x 10^{-4} mmHg, respectively (ATSDR, 1995). The chemical structure is shown in Figure 1.

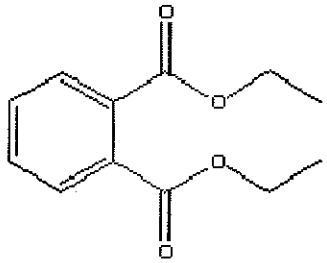

Figure 1. Chemical Structure of Diethyl Phthalate

Animal Studies

In a reproduction study, groups of 8 breeding pairs of male and female mice CD-1 mice were dosed in the feed with 0, 0.46, 2.44, or 4.4 g/kg/day of DEP for 14 weeks (Morrissey et al.,

1989). There was no adverse effect at any dose level on the following parameters: fertility index, mean number of litter per pair, mean number of lives pups per pair, mean number of live male pups per pair, mean number of live female pups per pair, proportion of pups born alive, sex of pups born alive, mean live pup weight per litter, mean live male and mean live female pup weight per litter. A reproductive NOAEL of 4.4 g/kg/day was identified from this study.

Groups of 31 or 32 time mated CD rats were dosed with DEP in the feed at levels of 0, 0.2, 1.91, or 3.21g/kg/day on gestational day 6 through 15. Control feed was provided during gd 15 to 20 (Field et al., 1993). Animals were killed on day 20. No dams died during gestation. Pregnancy rates were 87-100% for all treatment groups. No significant adverse treatment-related maternal effects were observed with the exception of body weight effects. On gd 9 body weight was reduced in dams of both the 1.91 and 3.21 g/kg/day dose groups compared to controls and dams in the high dose group continued to weigh less than controls on gd 12, 15 and 18 ($P<0.05$). Body weight gains for the treatment period were significantly reduced in the high-dose group animals. Kidney and liver weights (absolute and relative to body weight) were not affected by DEP treatment. Food consumption was reduced in the 1.91 and 3.21 g/kg dose groups during gestational day 6-9 and in the 3.21 g/kg dose during gestational day 9-12. There was no effect of DEP treatment on indices of prenatal viability, such as resorption incidence, of live litter size. Percent male fetuses and mean fetal body weight per litter did not differ between treated and control groups. DEP treatment did not significantly increase the percentage of fetuses malformed per litter of the percentage of litter with malformations. The only embryo/fetal endpoint that displayed a treatment-related change was a significantly ($P<0.05$) greater incidence of variations in the high-dose group as compared to controls. The most frequent variation was an extra lumbar rib. A developmental NOAEL was identified as 1.91 g/kg/day. There was no maternal toxicity other than decreased weight gain

Pairs of male and female CD-1 mice were fed diets with dose levels of 0.0 (n=40), 0.25 (n=20), 1.25 (n=19), and 2.5% DEP (n=18) for 13 weeks in a continuous breeding reproductive study (Lamb et al., 1987). One male in the 1.25% group and two males and a female in the 2.5% DEP group died. By week 13 the high dose group (2.5%) weighed significantly less than controls (significance level not given). The weight gain of females was not significantly affected. Analysis of feed consumption for the pairs showed that between 5.0 and 5.6g of feed was consumed per mouse per day, regardless of treatment group. The average feed consumption was calculated to be 5.3g. Body weight data was provided for the control and high dose groups (male and female combined). This indicated that the dose for the 2.5% dose group (male and female combined) is approximately 3.7 g/kg/day (3700 mg/kg/day). Exposure of DEP did not alter the number of fertile pairs, the number of litters per pair, the number of pups per litter, the proportion of pups alive, or the live pup birth weight. Body weight was decreased in the 2.5% treated animals compared to controls (significance level not given). Since fertility and reproductive performance were not affected in the parental mice (F_0 generation), the fertility of the offspring were assessed once they reached sexual maturity. The final litters form the continuous breeding phase (F_1 generation) in the 0.0, and 2.5% DEP groups were weaned at 21 days of age. The F_1 generation animals had access to diets with the same levels of DEP as their parents until the end of the study. When the F_1 animals were approximately 10 weeks of age, pairs of control mice and pairs of 2.5% DEP-exposed mice were cohabited to evaluate reproductive function. The number of live pups per litter in the F_1 2.5% dose group was significantly different from controls ($p<0.50$). There was no difference in number of fertile pairs, live pup weight, or proportion of pups born alive. The F_1 mice were necropsied at the conclusion of the offspring assessment. In the male F_1 mice, body weight, liver, brain, pituitary, testis, epididymus, prostrate and seminal vesicles weight was analyzed. There was no significant difference from control in the male F_1 mice organ weights. The % motile sperm, sperm concentration and % abnormal sperm were also analyzed. The prostrate weight was significantly increased ($p<0.05$) and sperm concentration was significantly decreased ($p<0.05$) compared to control. In the female F_1 mice, body weight, liver and pituitary weight were

significantly different from control ($p<0.05$). There was no difference from control in the brain, uterus or ovary weights.

Discussion

The EPA IRIS RfD was last revised in 1993. The EPA (1995) HEAST database lists a subchronic oral RfD = 8 mg/kg/day, based on a NOAEL = 750 mg/kg/day via diet in rats for 16 weeks with a critical effect of decreased growth and decreased organ weights; a total UF = 100 was applied to derive the subchronic RfD. A chronic RfC and RfCs were not provided (EPA, 1995; HEAST). The ATSDR established the acute and intermediate MRLs in 1995. The toxicological data published since then is summarized in this document.

There was no published documentation of the derivation of the NIOSH REL (also 5 mg/m^3). After analyzing the ACGIH TLV documentation (ACGIH, 1993) it was found that the TLV was based on the data for di-sec-octyl phthalate, also called di-ethyl-hexyl phthalate (DEHP) (see Figure 2 for molecular structure). The ACGIH stated that there is little data on the toxicity of DEP, and that acute animal toxicity is low. The ACGIH also stated that, "Exposure of workers to the vapor of DEP may cause transient irritation of the nose and throat. Mixtures of phthalate plasticizers have caused polyneuritis and vestibular dysfunction." Since the ACGIH TLV is not based on toxicity data specific to DEP, and there was no information on how NIOSH derived the REL it was deemed inappropriate to base the ITSL on occupational exposure limits.

Special attention was made to find data relating to the absorption and metabolism of DEP in humans and animals in order to determine if it is appropriate to develop an inhalation screening level based on oral toxicity data. In the ATSDR (1995) review, there were no toxicity studies regarding the absorption, distribution or excretion of diethyl phthalate following oral or inhalation exposure. The ATSDR reported limited information regarding the metabolism of DEP. Respiratory tract absorption data was found for a similar dialkyl phthalate called di(2-ethylhexyl) phthalate (DEHP; see Figure 2). The ATSDR (1993) stated that, "[A]bsorbtion can occur through the lungs of humans as evidenced by identification of DEHP derivatives in the blood of infants exposed to DEHP during respiration therapy (Roth et al., 1988)." The ATSDR continued, "In rats, inhalation of an aerosol containing 1000 mg/m^3 of DEHP resulted in peroxisome proliferation (Merkle et al. 1988), indicating that absorption had occurred." It was reasoned that since di(2-ethylhexyl) phthalate is absorbed via the respiratory tract then it is likely that DEP would also be absorbed after inhalation exposures.

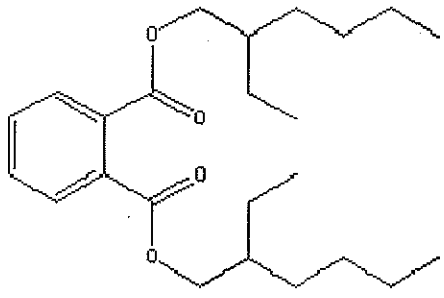

Figure 2. Chemical Structure of Di(2-ethylhexyl) Phthalate (CAS No. 117-81-7)

The ATSDR (1995) reviewed the reproductive and developmental toxicity of DEP. In a two-generation continuous breeding dietary reproductive toxicity study in mice, no adverse effect on any measured parameter of fertility was observed in either generation; however, 2nd generation reproduction was affected. The total number of live pups per litter was significantly lower in second generation litters at the lowest dose of 3250 mg/kg/day. In a developmental study performed in mice, the authors reported that there was no significant evidence of maternal

toxicity or neonatal developmental effects due to oral administration of 4,500 mg/kg/day on gestational days 6-13. In a developmental study in rats, dietary administration of up to 2.5% DEP (1,910 mg/kg/day) produced no embryonic or fetotoxic effects. In the same study at a dietary level of 5% (3210 mg/kg/day), treated embryos had an increased number of skeletal variations, particularly rudimentary (supernumerary) ribs. It was determined that the ITSL based on the RfD would also protect against the reproductive and developmental effects noted above.

The availability of inhalation toxicity data was limited to poorly reported occupational exposures. ACGIH stated that exposure to DEP vapor causes irritation to the eyes and throat. These effects cannot be accounted for in oral dose studies. Consequently, there is significant uncertainty concerning the level of protection provided by a screening level based on oral effects. However, no data were found that indicated that the oral to inhalation route extrapolation was inappropriate. Therefore, due to a lack of inhalation data, the EPA (1993) RfD was used to calculate the ITSL according to Rule 232 hierarchy. The screening level was calculated pursuant to Rule 232(1)(b) as follows:

ITSL = Oral RfD x 70kg/20m^3

ITSL = 0.8 mg/kg x 70kg/20m^3

ITSL = 2.8 mg/m^3

ITSL = 2.8 mg/m^3 x 1000µg/mg

ITSL = 2800 µg/m^3

The ITSL for diethyl phthalate is 2800 µg/m^3 based on a 24 hour averaging time.

References

ACGIH (1993) Documentation of threshold limit values and biological exposure indices. Cincinnati, OH. pages 467-8.

ATSDR. (1993) Toxicological profile for di(2-ethylhexyl) phthalate. U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, Division of Toxicology/Toxicology Information Branch. 1600 Clifton Rd NE, E-29, Atlanta, Georgia 30333.

ATSDR. (1995) Toxicological profile for diethyl phthalate. U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, Division of Toxicology/Toxicology Information Branch. 1600 Clifton Rd NE, E-29, Atlanta, Georgia 30333.

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Morrissey RE, Lamb JC, Morris RW, Chapin PE, Dushyant KG, Heindel JJ. 1989. Results and evaluation of 48 continuous breeding reproductive studies conducted in mice. Fundamental and Applied Toxicology. 13: 747-777.

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