MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for Di-n-octyl phthalate (DnOP) [CAS# 117-84-0]

FROM: Doreen Lehner, Toxics Unit, Air Quality Division

DATE: February 3, 2017

SUBJECT: Di-n-octyl phthalate (DnOP) [CAS# 117-84-0] ITSL change in the averaging time from 24 hours to annual

The initial threshold screening level (ITSL) for di-n-octyl phthalate (DnOP) is 470 µg/m^3 based on an annual averaging time. The ITSL was originally established on 7/26/2007 and was based on a Poon et al, (1997) 13 week oral study in male and female rats. The critical effect of DnOP is liver toxicity. As the key study used to derive the ITSL is a 13 week oral study, the averaging time is appropriately set at annual. Therefore, the averaging time is being changed from 24 hours to annual.

References:

Act 451 of 1994, Natural Resources and Environmental Protection Act and Air Pollution Control Rules, Michigan Department of Environmental Quality.

Poon R, Lecavalier P, Mueller R, Valli VE, Procter BG, and Chu I. 1997. Subchronic oral toxicity of di-n-octyl phthalate and di(2-ethylhexyl) phthalate in the rat. Food & Chemical Toxicology 35:225-239.

MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: Memo to File 117-84-0, Di-n-octyl phthalate (DnOP)

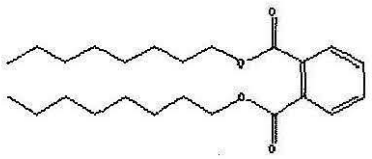
FROM: Margaret M Sadoff

RE: Derivation of Screening Level

DATE: July 26, 2007

A search of the literature and the following databases was performed for information regarding Di-n-octyl phthalate (DnOP). American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values, National Institute for Occupational Safety and Health (NIOSH) Pocket Guide to Hazardous Chemicals, EPA Integrated Risk Information System (IRIS), EPA High Production Volume Information System, Registry of Toxic Effects of Chemical Substances (RTECS), Environmental Protection Bureau Library, International Agency for Research on Cancer (IARC) Monographs, CAS Registry Online, Hazardous Substance Data Bank (HSDB), National Library of Medicine/Toxline, National Library of Medicine ToxSeek, Health Effects Assessment Summary Tables (HEAST), National Toxicology Program (NTP) Study Database, Entrez PubMed, Scirus, IPCS Intox Databank and CalEPA's Toxicity Values Database

The ITSL for di-n-octyl phthalate [177-84-0] is 470 ug/m3, 24 hr average.



MW = 390

Uses, Exposure, Environmental Fate

Sources: (1) NTP Center for the Evaluation of Risks to Human Reproduction Phthalates Expert Panel Report (2003). Monograph on the Potential Human Reproductive and Developmental Effects of Di-n-octyl phthalate (DnOP). NIH Publication No. 03-4488. (2) NLM Toxline HSDB.

DnOP exists as a clear oily liquid which may give off irritating vapors at high temperatures. It is one of a group of industrially important phthalates used as plasticizers for commercial uses. There are commercially important mixture C6-10 phthalates. This mixture is used in a variety of no commercial uses for pure DnOP but it makes up approximately 20% of the commercial products such as flooring and carpet tiles, tarps, pool liners and garden hoses. DnOP is approved by the FDA as an indirect food additive since it is used in seam cements, bottle cap

liners, and conveyor belts that come into contact with food and drugs. Occupational exposure may occur through inhalation of aerosols or dermal contact. Environmental exposure may occur through dietary intake of contaminated food or drinking water, dermal contact with products containing DnOP or, less likely, through inhalation of vapor or particulate bound DnOP. Like other phthalates, DnOP is readily absorbed from the GI tract, rapidly metabolized and excreted. n-Octanol is the main metabolite of DnOP.

A NIOSH Survey (1981-1983) estimated that 7,678 workers (1,296 of these are female) are potentially exposed to DnOP in the US(1).
[(1) NIOSH; National Occupational Exposure Survey (NOES) (1983)]**PEER REVIEWED**

DnOP was detected in human adipose tissue collected throughout the US during the 1982 National Human Adipose Tissue Survey(1).
[(1) Phillips LJ, Birchard GF; Arch Enciron Contam Toxicol 21: 159-68 (1991)]**PEER REVIEWED**

If released to air, a measured vapor pressure of 1.4E-4 mm Hg at 25 deg C suggests that DnOP may exist in both vapor and particulate phases in ambient air. Vapor-phase DnOP degrades in the atmosphere by reaction with photochemically-produced hydroxyl radicals with an estimated atmospheric half-life of 19 hours. Particulate-phase DnOP is physically removed from the atmosphere by wet and dry deposition. Water solubility has been reported by EPA as 0.2 mg/L (@ 25C).

Phthalate Human Exposure Study

A pilot study was performed in 2000 in which urine levels of certain phthalate metabolites, including those of DnOP, were analyzed and from which environmental exposure concentrations were extrapolated. The initial study included 289 subjects that were 56% women, 20 to 60 years of age, and mostly composed of minorities. The study revealed that median and 95th percentile DnOP exposures were 0.01 and 1.0 ug/kg/day, respectively. These estimates are significantly lower than NTP-CERHR estimates of between 3 and 30 ug/kg/day (based on extrapolation from DEHP data). Mean levels were below detection limits (0.9 ng/mL). A subsequent study of more than 2500 individuals yielded similar results to that of the reference group. A much smaller sampling of approximately 1 year-old infants (n=19) and children ages 6-11 (n=328) also found mean levels below the detection limit. Overall, the panel concluded that phthalate exposure to the general population was of minimal to negligible concern.

In addition, the panel reviewed some data on toxicokinetics of phthalates between primates and rodents. It seems that the higher molecular weight phthalates (> C8) are absorbed in primates at a significantly lower rate than in rats. Further, primates excrete phthalates in the bile to a much greater extent than do rodents. Therefore, much of what is absorbed in primates may not be distributed to the target organs identified from rodent studies (i.e. testes). This helps to explain why testicular atrophy normally seen in rodents exposed to phthalates has not been observed in primates. The panel concluded that, at least for the higher molecular weight phthalates, humans would be expected to have lower internal doses and lower target organ doses than rodents at the equivalent external exposure levels. Furthermore, the Panel surmised that the relatively large internal doses of high molecular weight phthalates associated with rodent effects may not be achievable in humans under any conditions.

Human Toxicity Data

There is no human toxicity data on exposure to DnOP. There are no U.S. occupational standards but there are emergency values: TEELs 0,1,2,3 are 15, 50, 400 and 500 mg/m3, respectively. Norway and Sweden have OELs of 2-3 mg/m3. ATSDR has developed an acute oral MRL of 3 mg/kg/day (Lake et al., 1986) and an intermediate oral MRL of 0.4 mg/kg/day (Poon et al., 1995) based on liver effects in animals.

Very limited anecdotal evidence for human toxicity consists of a case report of eye and upper respiratory tract irritation of workers exposed to phthalates (including dioctyl phthalate, isomer unspecified), poorly documented studies on neurological and reproductive effects in small groups of workers exposed to mixed phthalates, and poorly documented clinical dermal studies with human volunteers noting skin irritation and sensitization upon contact with dioctyl phthalate (isomer unspecified). There is one reported case study of a worker with continuous exposure to dioctyl phthalate during the manufacture of imitation leather who developed an asthmatic reaction to the substance. It is not clear whether this exposure is to DnOP or DEHP (diethylhexyl phthalate) which is sometimes reported in the literature as dioctyl phthalate. Source: Canadian EPA Priority Substances List Assessment Report on Di-n-octyl phthalate (1993).

General/Acute Toxicity in Experimental Animals

Sources: (1) NLM Toxline HSDB (2) RTECs (3) NTP Center for the Evaluation of Risks to Human Reproduction Phthalates Expert Panel Report (2003). Monograph on the Potential Human Reproductive and Developmental Effects of Di-n-octyl phthalate (DnOP). NIH Publication No. 03-4488.

DnOP is generally considered to be of low toxicity via the oral and dermal routes. It is a mild eye and mucous membrane irritant. Skin sensitization is of minor concern. At high doses, central nervous system depression may occur. Its low vapor pressure usually precludes inhalation of any significant amount of DnOP except perhaps as an aerosol adsorbed to airborne particulates.

A probably lethal human dose is estimated to be between 500 and 15,000 gm/kg in a 70 kg adult. LD50s in experimental animals have been reported as follows:

Rat = 30,000 mg/kg; 47,000 mg/kg; 53,700 mg/kg
Mouse = 6,513 mg/kg; 13,000 mg/kg

Dermal LD50 values for guinea pigs are reported as 75 mL/kg.

There is mention in the literature of one small inhalation study in mice exposed to unspecified concentrations of DnOP in air for up to 16 weeks. No overt signs of toxicity were noted and microscopic examination of lungs revealed normal tissue. No further information is available. Source: Canadian EPA Priority Substances List Assessment Report on Di-n-octyl phthalate (1993).

Four-week old male Wistar rats were exposed to 20,000 ppm DnOP in the diet for 3, 10 or 21 days. An effect level of 1,821 mg/kg-bw/day was calculated based on observable effects after 3 days. Liver changes were noted including slight but significant liver enlargement, significantly

increased liver weights at 10 and 21 days of treatment and histological and serum chemistry changes at all three assessment times.

Source: Mann AH, Price SC, Mitchell FE, Grasso P, Hinton RH, Bridges JW. (1985). Comparison of the short-term effects of di(2-ethylhexyl phthalate) and di (n-octyl) phthalate in rats. Toxicol Appl Pharmacol 77:116-132.

Marginal increases in liver weight as well as liver metabolism and biochemical changes associated with peroxisome proliferation were observed in rats treated with 1,000 mg/kg DnOP for 14 days. (Lake et al., 1986).

Developmental Toxicity in Experimental Animals

Source: NTP-CERHR, 2003.

One IP study in Sprague-Dawley rats found reduced fetal weights and gross malformations that were dose-dependent such as missing tail, twisted hind legs and hematomas. Doses were massive at 4,890 and 9,780 mg/kg.

A gavage study in CD-1 mice found reduced litter size and reduced weight gain after exposure to 9,780 mg/kg/day on gestational days 6-13.

A third study investigated the prenatal toxicity of n-octanol, a primary metabolite of DnOP. No fetal abnormalities were reported but there were nervous system symptoms and maternal deaths at 650, 945 and 1,300 mg/kg/day.

Taken as a whole, the NTP Panel concluded there was insufficient data to show developmental toxicity in experimental animals by gavage or IP administration after very high doses of DnOP. Experiments either had small sample size or only one exposure group. Additionally, no maternal toxicity was reported in these studies.

A review by NTP-CERHR indicates emerging evidence that testicular effects of some phthalates may be a consequence of reduced testosterone biosynthesis rather than direct toxic injury, with the timing of the exposure determining the nature of the effect. For example, late gestation exposure would result in structural malformations during the critical period of testicular development whereas exposure during the period of sexual maturation would tend to produce testicular atrophy (McKee, et al 2004).

Subchronic & Reproductive Toxicity in Experimental Animals

There is one continuous breeding study in 20 pairs/dose level M/F CD-1 Swiss mice fed DnOP in the diet at 0, 1.25, 2.5 or 5% (w/w) (approximately 1800, 3600 and 7500 mg/kg-bw/day). There was no effect on number of litters, mean number of live pups per litter, proportion born alive, live pup weight, or days to delivery. In the absence of reproductive toxicity, the second generation mating was not carried through. The only remarkable finding was a 12% decrease in seminal vesicle weight in F1 treated males. Other relevant findings were increased relative liver and kidney weights in females and increased absolute and relative liver weights in males. A reproductive NOAEL was identified as 7,500 mg/kg/day. The study concluded that there was no apparent effect on reproductive function in animals exposed to DnOP at levels sufficient to cause significant increase in liver weight (Heindel et al. 1989).

Systemic effects were studied in 4-6 week old Sprague-Dawley rats. 10/sex/group were fed DnOP at dietary concentrations of 0, 5, 50, 500 or 5,000 ppm (corresponds to 0, 0.4, 3.5, 36.8 and 350 mg/kg/day for males and 0, 0.4, 4.1, 40.8 or 403 mg/kg/day for females) for 13 weeks. No clinical signs of general toxicity were noted. DnOP exposure did not affect organ or body weight at any concentrations. No hematological changes were noted. Gross and histopathology were evaluated as well as several hematology and clinical chemistry parameters. At the highest dose tested, mild liver and thyroid changes were observed along with increases in liver enzyme activity (3-fold in females and 12-fold in males). After 13 weeks of oral exposure, the amounts of DnOP in the liver were either below the detection limit (3ppm) or barely detectable for rats fed 500 ppm or 5,000 ppm. Adipose tissue concentration of DnOP in the 5,000 ppm rats was 3-6 times higher than the liver. Notably, no changes in testes were observed (adverse effects were expected based on DnOP's similarity to DEHP and testicular atrophy related to phthalate exposure, in general). However, review of the data by CERHR revealed that the male rats were past the age of maximum sensitivity to phthalate-induced testicular damage. A reproductive NOAEL was identified as 350 mg/kg/day. Subchronic NOAELs in rats from this study are 37 and 40 mg/kg/day in males and females, respectively. ATSDR developed an intermediate MRL of 0.4 mg/kg/day based on the Poon study (rounding the NOAEL to 40 and using a total uncertainty factor of 100).

Source: Poon R, Lecavalier P, Mueller R, Valli VE, Procter BG, Chu I. (1997) Subchronic oral toxicity of di-n-octyl phthalate and di (2-ethylhexyl) phthalate in the rat. Food Chem Toxicol 35: 225-239.

Carcinogenicity/Mutagenicity

There is inadequate data from which to evaluate the potential carcinogenic effects of DnOP in humans. In 1995, EPA assessed the carcinogenic risk from DnOP. The review was for the purpose of communicating health risks related to Superfund sites. EPA reviewed several mechanistic studies that were suggestive of the tumor promoting potential of DnOP in the rat liver but were not designed to examine complete carcinogenicity. There was also inconclusive evidence of some initiating capability of DnOP based on data from one study. The weight of evidence is that lack of good data in animals renders DnOP not classifiable as to potential for human carcinogenicity.

Source: Letter from EPA/ORD to Gary Hurlburt, SWQD, MDNR, July 3, 1995.

DnOP has given negative results in standard Ames mutagenicity tests.

Screening Level Development

Using a weight of evidence approach, NTP surveyed the toxicological data available on the reproductive and developmental toxicity of DnOP and concluded that DnOP is not likely to be a reproductive effector in humans based on negative evidence in rats and mice. There is limited evidence in experimental animals for its developmental toxicity.
(NTP-CERHR, 2003)

Adequate data on liver and thyroid indicate adverse effects to this major organ have been observed at lower doses than have been employed in developmental and reproductive studies with negative or equivocal results. Therefore, an ITSL protective of liver and thyroid effects should be protective of any potential for developmental and reproductive effects.

The Poon et al. study is an adequate subchronic study from which to derive an RfD-based ITSL. Use of a feeding study is appropriate given the lack of data on inhalation toxicity, the limited water solubility of DnOP, and the systemic effect of liver toxicity. An ITSL pursuant to R232(1)(b) is

$$\frac{\text{NOAEL 40 mg/kg/day}}{\text{*Total UF 300}} \times \frac{\text{70 kg}}{\text{20 m3}} = \text{0.47 mg/m3 OR 470 ug/m3, 24 hr average}$$

3 interspecies differences (reduced from 10 due to toxicokinetic differences that suggest lower internal doses for primates as compared to rodents)
10 intraspecies differences
10 lack of chronic study

The ITSL for di-n-octyl phthalate [177-84-0] is 470 ug/m3, 24 hr average.

Selected References:

ATSDR Toxicological Profile for Di-n-octylphthalate (September 1997).

Heindell JJ, Gulati DK, Mounce RC, Russell SR & Lamb JC. (1989). Reproductive toxicity of three phthalic acid esters in a continuous breeding protocol. Fundamental & Applied Toxicology 12: 508-518.

Hellwig J & Jackh R. (1997). Differential prenatal toxicity of one straight-chain and five branched-chain primary alcohols in rats. Food Chem Toxicol 35: 489-500.

Kavlock R, Boekelheide K, Chapin R, Cunningham M, Faustman E, Foster P, Golub M, Henderson R, Hinberg I, Little R, Seed J, Shea K, Tabacova S, Tyl R, Williams P & Zacharewski Tm. (2002). NTP Center for the evaluation of risks to human reproduction: Phthalates expert panel report on the reproductive and developmental toxicity of di-n-octyl phthalate. Reproductive Toxicology 16: 721-34.

Lake BG, Gray TJB, Gangolli SD. (1986). Hepatic effects of phthalate esters and related compounds-in vivo and in vitro correlations. Environmental Health Perspectives 67: 283-90.

McKee RH, Butala JH, David RM & Gans G. (2004). NTP center for the evaluation of risks to human reproduction reports on phthalates: Addressing the data gaps. Reproductive Toxicology 18: 1-22.

NTP Center for the Evaluation of Risks to Human Reproduction Phthalates Expert Panel Report (2003). Monograph on the Potential Human Reproductive and Developmental Effects of Di-n-octyl phthalate (DnOP). NIH Publication No. 03-4488.

Poon R, Lecavalier P, Mueller R, Valli VE, Procter BG & Chu I. (1997). Subchronic oral toxicity of di-n-octyl phthalate and di(2-ethylhexyl) phthalate in the rat. Food & Chemical Toxicology 35: 225-239.

MS:lh