MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

March 15, 2016

TO: File for 2-ethylhexanoic acid (149-57-5)

FROM: Mike Depa, Air Quality Division, Toxics Unit

SUBJECT: Initial Threshold Screening Level

The Initial Threshold Screening Level (ITSL) for 2-ethylhexanoic acid (2-EHA) is 70 µg/m³ based on an annual averaging time.

The following references or databases were searched to identify data to determine an ITSL: IRIS-online, HEAST, NTP Management Status Report-online, RTECS, EPBCCD, EPB Library, CAS-online, NLM-online, IARC-online, NIOSH pocket Guide, and ACGIH Guide. 2-Ethylhexanoic acid is used primarily as a raw material in the production of 2-ethylhexanoate soaps, peroxy esters, and additives that are used in paints, inks, varnishes and enamels. This compound is a clear liquid with a low vapor pressure.

2-EHA did not induce mutations in Ames testing, and despite its metabolic similarity to DEHP, is not known to be carcinogenic. The acute oral toxicity of 2-ethylhexanoic acid is low, with an oral LD50 of about 1.6 to 3 g/kg in rats and 1.3 g/kg in rabbits. Rats (sex not specified) exposed by inhalation to a nominal concentration of 2.36 mg/l (400 ppm) for 6 hours and observed for 14 days showed no signs of toxicity.

In a subchronic oral toxicity study, groups of 10 male and 10 female Fischer 344 and B6C3F1 mice were fed diets containing either, 0.0, 0.1, 0.5 or 1.5% 2-EHA for 13 weeks. Additional groups of 10 male and 10 female rats or mice were fed either 0.0 or 1.5% 2-2-EHA for 13-weks followed by a 4-week recovery (non-treatment) period. Based on food consumption and body weight, the 2-EHA diets provided doses of 61, 303, or 917 mg/kg day for male rats and 71, 360 or 1068 mg/kg/day for female rats. The 2-EHA diets provided doses of 180, 885, or 2728 mg/kg/day for male mice and 205, 1038, or 3139 mg/kg/day for female mice. No mortality or significant clinical signs of toxicity were observed during the study. Body weights and food consumption of both rats and mice fed 1.5% 2-EHA were lower beginning after the first week of treatment, consistent with a reduction in food consumption. Other groups were unaffected by treatment. After 13-weeks, lower triglyceride levels occurred in male mice fed 1.5% 2-EHA and female mice fed 0.5 or 1.5% 2-EHA, but not in other groups. Cholesterol levels were higher in all male rats test groups and in female rats and male and female mice fed either 0.5 or 1.5% 2-EHA, although this effect was reversible following a 28-day recovery period. The principal effects of 2-EHA involved the liver or metabolic processes associated with the liver. The 0.5 and 1.5% diets in both rats and mice were associated with increased relative liver weight and histological changes in hepatocytes, specifically hepatocyte hypertrophy and reduced cytoplasmic vacuolization. Observed histopathological and

clinical pathological changes were reversible following recovery. These results indicate that 2-EHA does not produce persistent, overt toxicity in rats or mice following subchronic dietary exposure at concentrations up to 1.5% in feed. The no-observed-adverse-effect level (NOAEL) for male rats was 61 mg/kg/day and the NOEL for female rats was 71 mg/kg/day, while 180 and 205 mg/kg/day represent NOELs for male and female mice, respectively.

Oral gavage reproductive and developmental toxicity studies were similar to the dietary studies. Maternal and fetotoxicity were dependent upon dose. In one developmental study, pregnant female Wistar rats were treated by oral gavage with a single dose of 0, 1.0, or 2.0 ml/kg 2-EHA (approximately 900 or 1800 mg/kg) on day 12 of gestation and the dams euthanized on day 20. The high-dose level produced embryo- and fetotoxicity. The incidence of malformed fetuses increased from 0 in control animals to 67.8% in the high-dose level dams; no apparent toxic or teratogenic effect was observed at the low-dose level. No information was presented on maternal effects or effects on the sex of fetuses. In a similar study, Sprague-Dawley rats were gavaged on days 6 to 15 of gestation with 2-EHA (900 or 1200 mg/kg/day) in corn oil. The dams were allowed to deliver, and their litters were examined through postnatal day 6. Effects on development included delayed parturition (day 22 instead of day 21), decreased progeny viability, reduced pup weights, and induced malformations of the vertebrae and ribs. These effects, however, occurred at highly maternally toxic doses. Maternal effects included mortality (27 and 40 percent at 900, and 1200 mg/kg, respectively), decreased body weight or body weight gain, maternal respiratory toxicity (rales or dyspnea), and transient signs of depressed motor activity (e.g., ataxia, lethargy). In another study, no evidence of teratogenicity was observed in Fischer 344 rats treated by oral gavage with 0, 100, 250, or 500 mg/kg of 2-EHA on days 6 through 15 of gestation. No mortality or effect on maternal body weights and feed consumption occurred, although high-dose-level dams experienced hypoactivity, ataxia, and audible respiration, and liver weights. No embryotoxic effects were noted, and total implants, preimplantation loss, and viable fetuses were comparable among groups. Fetal body weights were <10% and were probably attributable to a higher average litter size in high-dose dams. There were no treatment related increases in the incidence of malformations. Increases in some common variations occurred in treated rats, but the total number of visceral or skeletal variations was not significantly altered by treatment. The NOAEL for maternal animals was 250 mg/kg/day and the NOEL for offspring was 100 mg/kg/day.

In biochemical toxicity studies, [2-14C-Hexyl]2-ethylhexanoic acid in corn oil was administered to female Fischer 344 rats either as a single oral gavage at 100 or 1000 mg/kg, or after 14 days of oral unlabeled 2-ethylhexanoic (100 mg/kg only). An aqueous solution of [2-14C-Hexyl]2-ethylhexanoic acid was applied topically at either 100 or 1000 mg/kg and another group of rats received 2-ethylhexanoic acid by intravenous injection (1 mg/kg). Urine, feces, and blood were collected at various intervals for 96 hours. Results showed that approximately 72 to 75% of the oral dose was excreted in the urine within 24 hr, and <10% was excreted after 24 hours. About 50% of the 14C was excreted in the first 8 hours after the 100 mg/kg dose versus 20% after the 1000mg/kg dose. Fecal excretion accounted for 7 to 12% of both doses. After intravenous injection, 64% of the 14C was excreted in the urine and 2% in the feces. Repeated dosing with unlabeled 2-ethylhexanoic acid (100 mg/kg) appeared to reduce the urinary elimination of 14C slightly to 55% in urine, whereas the fecal excretion increased to 15% in the first 24 hours. After dermal application, approximately 30% of the applied dose was excreted in the urine during the first 24 hours, followed by an additional 8 and 17% from 24 to 96 hours for the 100- and 1000-mg/kg doses, respectively. Fecal excretion was 7% for both dose levels. Dermal absorption was estimated to be 63 to 70% relative to intravenous administration. After dermal application,

peak blood levels of 14C occurred about 5.7 hours after application and the absorption half-life was 3.2 hours. Major urinary metabolites included the glucuronide of 2-ethylhexanoic acid, the glucuronides of 2-ethyl-6-hydroxyhexanoic acid and 2-ethyl-1,6-hexanedioic acid, and unmetabolized 2-ethylhexanoic acid. The proportions of each metabolite changed with the dose and route of administration.

Derivation of the Screening Level

Data from the 13-week dietary study provided the best data to derive a screening level that will adequately protect sensitive subpopulations. This study followed the 1992, U.S. Toxic Substance Control Act, Health Effects Testing Guidelines for Subchronic Oral Toxicity Studies. The lowest LOAEL of 61 mg/kg/day was established for male rats.

There was no data to suggest that oral route of exposure would be inappropriate to use for the inhalation route of exposure. The ITSL was derived from the Reference Dose (RfD). The RfD was derived as follows:

$$RfD = LOAEL/(UF_1 x UF_2 x UF_3 x UF_4)$$

Where, UF_1 = 3 for LOAEL to NOAEL conversion
UF_2 = 10 for animal to human (interspecies)
UF_3 = 10 for sensitive individuals (intraspecies)
UF_4 = 10 for subchronic to chronic duration

RfD = (61 mg/kg/day)/(3x10x10x10)
RfD = 0.02 mg/kg/day

Pursuant to Rule 232(1(b), the ITSL is calculated from the RfD as follows:

ITSL = RfD x 70kg/20m^3
ITSL = 0.02 mg/kg/day x 70kg/20m^3
ITSL = 0.071 mg/m^3 x 1000µg/mg
ITSL = 70 µg/m^3 (rounded to 1 significant figure)

The current file review concludes that the AT 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). Therefore, the AT is set to annual.

References:

Juberg DR, et al. 1998. 2-Ethylhexanoic Acid: subchronic oral toxicity studies in the rat and mouse. Food and Chemical Toxicology 36: 429-436.

Patty's Industrial Hygiene and Toxicology. 1994. Aliphatic carboxylic acids. Volume II, Part E. 3553-3559.