MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

May 11, 1999

TO: Chemical file for Di (2-ethylhexyl) adipate (DEHA) (CAS #103-23-1)

FROM: Robert Sills, Toxics Unit, Air Quality Division

SUBJECT: Screening Level Development

A screening level for DEHA has not been previously developed. A literature review for toxicity information was conducted, including standard references as well as searches for relevant toxicological information via the National Library of Medicine and CAS bibliographic databases. The resulting screening levels derived are an Initial Risk Screening Level (IRSL) of 3 ug/m^3 and a Secondary Risk Screening Level (SRSL) of 30 ug/m^3 (annual averaging).

The U.S. Environmental Protection Agency's (EPA) Integrated Risk Information System (IRIS) database (4/99 retrieval date) provides an oral reference dose (RfD) assessment and a carcinogenicity assessment, but not an inhalation reference concentration (RfC) assessment. The IRIS carcinogenicity assessment was last revised 12/1/94. That source indicates that DEHA has no human carcinogenicity data and limited animal carcinogenicity data, supporting a weight-of-evidence classification of "C; possible human carcinogen." This classification, and the supporting data presented in IRIS, satisfies the Rule 103(c) definition of a carcinogen for screening level development. The literature review did not provide compelling evidence that DEHA should not be regulated as a potential human carcinogen.

The EPA (1994) basis for cancer classification is primarily based on the weight-of-evidence provided by the National Toxicology Program (NTP) (1982). In that study, groups of 50 B6C3F1 mice/sex/dose were fed 0, 12,000, or 25,000 ppm DEHA in their diet for 104 weeks and observed for 106 weeks. The estimated doses for female mice were 0, 3222 and 8623 mg/kg-d, and for the male mice were 0, 2659 and 6447 mg/kg-d, respectively. A maximum tolerated dose (MTD) was achieved in the high-dose group of both sexes, as there was a significant dose-related decrease in the mean body weights of both dose groups in each sex. In females there was a statistically significant positive trend with dose for combined hepatocellular carcinoma and adenoma incidence; the incidences were 3/50, 19/50 and 18/49 for the control, low- and high-dose groups, respectively. Time-to-tumor analysis showed that the development time of carcinomas and adenomas in the dosed groups was significantly shorter (by pair-wise comparison test) than their development in the control group. In male mice, a statistically significant positive trend was seen in the incidence of hepatocellular adenomas and carcinomas

combined; the incidences were 13/50, 20/49 and 27/49 in the control, low- and high-dose groups, respectively. The incidence rate in the high-dose group did not differ greatly from the historical control rate in this laboratory (116/398), and time-to-tumor analysis did not show significant differences between the control and dose groups in males.

The NTP (1982) also performed companion bioassays in F344 rats (50/sex/dose), administered DEHA in feed at 0, 12,000, or 25,000 ppm for 103 weeks and observed for 106 or 107 weeks. The MTD appeared to be achieved in the high-dose groups, based on suppression of mean body weights. No differences in tumor incidence rates attributable to DEHA were observed in these bioassays.

The EPA (1994) indicates that DEHA has been found to be negative in a variety of genetic toxicity assays. The lack of mutagenicity of DEHA (as well as other structurally related compounds containing the 2-ethylhexyl moiety), combined with consistent findings of proliferation of hydrogen peroxide-generating peroxisomes, indicates that persistent proliferation of peroxisomes serves as an endogenous initiator of neoplastic transformation by enhancing oxidative stress.

Nevertheless, EPA (1994) employs the linearized multistage procedure as an extrapolation method for cancer risk. Recognizing the mechanistic information summarized above, the updated literature review conducted for the present assessment did not reveal any compelling information that another particular extrapolation approach is more appropriate than that selected by EPA (1994). Based on the combined hepatocellular adenomas and carcinomas in female mice (NTP, 1982), an oral slope factor of 1.2 E-3 per (mg/kg-d) is provided as the recommended quantitative estimate of carcinogenic risk (EPA, 1994). An equivalent inhalation unit risk of 3.4 E-7 per (ug/m^3) is derived as follows, per the equation of Rule 231(3)(f)(ii). It is noted that the absorption efficiency ratio a/b was the default value of 1/1 in this case.

$$\frac{1.2\text{ E-3}}{\text{mg/kg-d}} \times \frac{1}{70\text{ kg}} \times \frac{\text{mg}}{1000\text{ug}} \times \frac{20\text{ m}^3}{\text{d}} \times \frac{1}{1} = \frac{3.4\text{ E-7}}{(\text{ug/m}^3)}$$

The IRSL and SRSL are then derived as follows:

$$\text{IRSL} = \frac{1\text{E-6}}{3.4\text{E-7 (ug/m}^3)^{-1}} = 2.94\ \text{ug/m}^3 \approx 3\ \text{ug/m}^3\ \text{(annual averaging time)}$$

$$\text{SRSL} = \frac{1\text{E-5}}{3.4\text{E-7 (ug/m}^3)^{-1}} = 29.4\ \text{ug/m}^3 \approx 30\ \text{ug/m}^3\ \text{(annual averaging time)}$$

The assessment of noncancer effects for oral exposure summarized in EPA-IRIS (1992; retrieved April 1999) found that the critical effects for RfD development were reduction in body weight gain and increase in liver weight in adult rats; reduced ossification and kinked or dilated ureters in fetuses of treated rats; and reductions in offspring weight

gain, total liver weight, and litter size (ICI, 1988a, 1988b). The lowest-observed-adverse-effect level (LOAEL) for all of these effects was 12,000 ppm DEHA in feed (1080 mg/kg-d); the no-observed-adverse-effect level (NOAEL) was 170 mg/kg-d. The EPA (1992) derived an RfD of 0.6 mg/kg-d from this NOAEL and a total uncertainty factor of 300. The EPA assigned a medium confidence level to the key study, the database, and the RfD. If an initial threshold screening level (ITSL) were to be derived based on this RfD, the ITSL would be 2100 ug/m^3 (24 hr averaging time). An occupational exposure level for deriving an ITSL is not available. This information indicates that the derived IRSL and SRSL are expected to be protective of noncancer effects, and therefore establishment of an ITSL does not appear to be necessary.

REFERENCES:

EPA. 1992. IRIS database. Chemical file for di (2-ethylhexyl) adipate (103-23-1). Oral RfD assessment. Last revised 7/1/92.

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RS:SLB
cc: Cathy Simon, AQD