MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for Dinoseb [CAS# 88-85-7]

FROM: Doreen Lehner, Toxics Unit, Air Quality Division

DATE: January 12, 2017

SUBJECT: Dinoseb [CAS# 88-85-7] ITSL change in the averaging time from 24 hours to annual

The current ITSL for dinoseb (4 µg/m^3) has a justification (attached) dated March 19, 2004. The averaging time (AT) assigned at that time was 24 hours. The current file review concludes that the averaging time may appropriately be set at annual, as this screening level is based on chronic studies. Therefore, the AT is being changed from 24 hours to annual at this time.

MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

March 19, 2004

TO: File for dinoseb (88-85-7)

FROM: Marco Bianchi

SUBJECT: Initial Threshold Screening Level

The Initial Threshold Screening Level (ITSL) for dinoseb is 4 $\mu g/m^3$ based on a 24 hr averaging time. The following references or databases were searched to identify data to determine the ITSL/IRSL: IRIS-online, HEAST, NTP Management Status Report-online, RTECS, EPB-CCD, EPB library, CAS-online, NLM-online, IARC-online, NIOSH Pocket Guide, and ACGIH Guide.

Dinoseb is an herbicide used to control various kinds of seedling weeds. Although the EPA established a reference dose (RfD) for this compound in 1987 of 1E-3 mg/kg/day, it was subsequently suspended from use due to its environmental persistence and potential developmental/reproductive risks. It is unclear at this time whether Dinoseb is banned from use for all formulations, or just from its use as a pesticide. In order to facilitate the air permit application process, a screening level will be derived for non-pesticide uses. The studies presented below are two of the many toxicity studies all showing similar results. The Irvine and Armitage (1981) 3-generation rat study was the key study that EPA used to establish an RfD.

A review of the available literature indicates that the most appropriate study for criteria derivation is the 3-generation study in rats by Irvine and Armitage (1981). Groups of 25 male and 25 female rats (2 littering groups/generation) received dinoseb in their diet at concentrations of 0, 1, 3, and 10 mg/kg/d for 29 weeks. There was a compound-related depression in parental body weight gain at the high dose in both sexes during the pre-mating period in all three generations. The mean fetal weights showed a high degree of variability. Decreased weights were observed or suggested in the F_0 to F_{1b}, the F_1 to F_{2a} and the F_2 to F_{3a} littering groups with the F_0 to F_{1b} pup weights diminished (combined sexes) at day 21 at all dose levels. Since the treated pup weights at birth were similar to controls, the subsequently depressed pup weight gains indicated a reproductive effect during the lactation period. A reproductive LOAEL of 1 mg/kg/d was determined. In continuation of the 3-generation study, a 2-generation reproductive study was conducted. Adverse effects included inconsistency between increased body weight changes in the 2-generation study and the previous 3-generation study and consistent decreases in gonadal

weights and gonadal weights/body weight ratios at all dose levels. A systemic LOAEL of 1 mg/kg/d was reported based on dose-related reductions in relative parental body weights with significant decreases at low and high doses in F_3 females.

Hazleton Laboratories (1977) conducted a 2-year feeding study using groups of 60 albino rats/sex (Charles River CD) exposed to dinoseb at dose levels of 0, 1, 3, and 10 mg/kg/day (purity not given). Adverse effects included hunched appearance, staining of the fur, and polypnea in all treated animals (particularly females) during the first year of the study. Mean body weight gains of males receiving the mid and high doses and females receiving all doses were significantly lower than those of controls during the first year of the study. At the end of the study, body weights were not significantly different from controls. No treatment related effects on survival, food consumption, hematology, clinical chemistry, and urinalysis were observed in the study. Mean organ weights of treated animals were similar to control animals except there were significantly dose-related decreases in mean thyroid weight at all dose levels in male rats. No histopathological changes were detected in the liver, kidneys. Based on a significant decrease in thyroid weights in male rats, 1 mg/kg/d was designated as a LOAEL.

In August 2003, a literature review was conducted by an EPA contractor to find more recent toxicity data that may be pertinent in re-evaluating the RfD for Dinoseb. According to the contractor, 3 studies were found that may provide additional information that could potentially change the RfD. After reviewing these studies it is doubtful that this new data could be used to establish a revised RfD. In the first study (Daston et al, 1988), the route of administration was intraperitoneal (ip) injection rather than oral or inhalation. The second study (Bordas et al, 1990) was from a Romanian journal (abstract in English) that appeared to use one dose group. The third study (Giavini et al, 1986) consisted of three separate experiments differentiated by the method of administration. In one experiment, five groups rats were dosed by gastric intubation at 0, 2.5, 5, 10, and 15 mg/kg/day between day 6 and day 15 of gestation. Results showed that the only dose related increase was skeletal anomalies (extra ribs) that became statistically significant at the 10 mg/kg/day dose group. A NOEAL or LOAEL was not established for this study.

A review of the existing data, including the three studies mentioned by the EPA contractor, shows that the Irvine and Armitage (1981) study is still the most appropriate toxicity study to use to derive a screening level. The Water Division (WD) of MDEQ also concurs with this assessment. In January 2001, a WD human non-cancer value was derived based on this key study. Therefore, it is appropriate at this time to use the RfD to derive an ITSL. An RfD of 0.001 mg/kg/day was established with a 1000-fold uncertainty factor (UF). The UF includes uncertainties in the extrapolation from laboratory animals to humans (factor of 100), as well as concern for the lack of a NOEL in the reproduction study (factor of 10). The critical effect was decreased fetal weight.

The ITSL was derived as follows:

RfD = 0.001 mg/kg/day

$$ITSL = RfD \times \frac{70\ kg}{20\ m^3}$$

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$$ITSL = 0.001\ mg/kg \times \frac{70\ kg}{20\ m^3}$$

$$ITSL = 0.0035\ mg/m^3$$

Conversion of mg/m^3 to ug/m^3

$$ITSL = 0.0035\ mg/m^3 \times \frac{1000\ ug}{1\ mg} = 3.5\ ug/m^3$$

The ITSL for dinoseb = 4 $\mu g/m^3$ based on a 24 hr averaging.

References:

1. Irvine, L.F.H. and A. Armitage. 1981. 2-sec-butyl-4,6-dintrophenol (dinoseb): Three generation reproductive performance study in the rat (dietary). Hazleton Laboratories Europe, Ltd. Prepared for Agricultural Chemical, Dow Chemicals Pacific, Ltd. Hong Kong. EPA Accession No. 259499. As cited by U.S.EPA. 1992. Final Drinking Water Criteria Document for Dinoseb

2. Hazleton Laboratories. 1977. Hazleton Laboratories America, Inc. 104-week dietary study in rats: Dinoseb DNBP. Prepared for the Dow Chemical Co., Midland, MI. EPA MRID 00025582. As cited by U.S.EPA. 1992. Final Drinking Water Criteria Document for Dinoseb.

3. Bordas, E. and Zeic, A. 1990. The effects of Dinoseb pesticide on the kidneys and adrenal glands of white rats. Rev Ig Med Muncii Med Soc Bacteriol Virusol Parazitol Epidemiol Pneumoftiziol Ser Ig Med Muncii Med Soc 39[1], 25-29.

4. Daston, G. P., Rehnberg, B. F., Carver, B., Rogers, E. H., and Kavlock, R. J. 1988. Functional teratogens of the rat kidney. I. Colchicine, dinoseb, and methyl salicylate. Fundam Appl Toxicol 11[3], 381-400.

5. Giavini, E., Broccia, M. L., Prati, M., and Vismara, C. 1986. Effect of Method of Administration on the Teratogenicity of Dinoseb in the Rat. Archives of Environmental Contamination and Toxicology 15[4], 377-384.