MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

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INTEROFFICE COMMUNICATION

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TO: File for 2,4-dichlorophenoxyacetic acid (CAS # 94-75-7)

FROM: Doreen Lehner, Toxics Unit, Air Quality Division

SUBJECT: Screening Level for 2,4-dichlorophenoxyacetic acid (CAS # 94-75-7)

DATE: January 13, 2015

The initial threshold screening level (ITSL) for 2,4-dichlorophenoxyacetic acid is 35 µg/m^3 based on an annual averaging time, and a second ITSL is 100 µg/m^3 based on an 8-hour averaging time.

2,4-Dichlorophenoxyacetic acid (2,4-D) [CAS # 94-75-7] has multiple synonyms including: dacamine, chloroxone, agrotect, weedone LV4, and weedtrol. 2,4-D is a white to yellow powder with a molecular weight of 221.04 g/mol. "2,4-D is a common systemic herbicide used in the control of broadleaf weeds. It is one of the most widely used herbicides in the world. 2,4-D is a synthetic auxin (plant hormone), and as such it is often used in laboratories for plant research and as a supplement in plant cell culture media such as MS medium. 2,4-D was one of the ingredients in Agent Orange, the herbicide widely used during the Vietnam war. According to the US National Pesticide Information Center, "the controversy regarding health effects centered around the 2,4,5-T component of the herbicide and its contaminant, dioxin.(NPIC, 2008)." 2,4-D's mode of action is as an auxin. It is absorbed through the leaves and is translocated to the meristems of the plant, where it triggers uncontrolled cell division in vascular tissue, which leads to abnormal cell wall plasticity which causes stem curl-over, leaf withering, and eventual plant death (NPIC, 2008). 2,4-D can form toxic gases and vapors (such as hydrogen chloride and carbon monoxide) in the presence of heat (ACGIH, 2001).

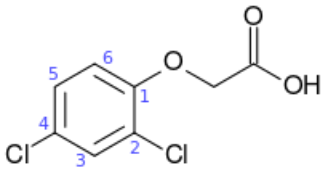

Figure 1. Structure of 2,4-dichlorophenoxyacetic acid.

A literature review was conducted to determine an initial threshold screening level (ITSL) for 2,4-D. The following references and databases were searched to derive the above screening level: Chemical Criteria Database (CCD), United States Environmental Protection Agency (US EPA) Integrated Risk Information System (IRIS), National Institute for Occupational Safety and Health (NIOSH), American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values and Biological Exposure Indices (TLV/BEI) 2012 Guide, National Toxicology Program (NTP) Study Database, International Agency for Research on Cancer

(IARC), Chemical Abstract Service (CAS) Online (searched 7/30/14), National Library of Medicine (NLM)-online, EPA Aggregated Computational Toxicology Resource (ACToR) Database, and EPA Toxic Substance Control Act Test Submission Database (TSCATS).

The ITSL is derived from an EPA RfD of 1 x 10^{-2} mg/kg/day which was based on a 90-day rat oral bioassay and 1-year interim report from a 2-year rat oral bioassay performed by the Dow Chemical Company in 1983.

> "Hematologic, hepatic, and renal toxicity were demonstrated in a study in Fischer rats (strain 344) during subchronic feeding performed at the Hazleton Laboratories in 1983. 2,4-D (97.5% pure) was added to the diet chow and fed to the rats for 91 days at doses calculated to be 0.0 (controls), 1.0, 5.0, 15.0, or 45.0 mg/kg/day. In each of the five groups there were 20 animals/sex and 40 animals/treatment group, for a total of 200 animals. Criteria examined to determine toxicity were survival, daily examination for clinical symptomatology, weekly change in body weights, growth rates, food intake, ophthalmologic changes, changes in organ weights, and clinical, gross and histopathologic alterations. The results of the study demonstrated statistically significant reductions in mean hemoglobin (both sexes), mean hematocrit and red blood cell levels (both sexes), and mean reticulocyte levels (males only) at the 5.0 mg/kg/day dose or higher after 7 weeks. There were also statistically significant reductions in liver enzymes LDH, SGOT, SGPT, and alkaline phosphatase at week 14 in animals treated at the 15.0 mg/kg/day or higher doses. Kidney weights (absolute and relative) showed statistically significant increases in all animals at the 15.0 mg/kg/day dose or higher at the end of the experimental protocol. Histopathologic examinations correlated well with kidney organ weight changes showing cortical and subcortical pathology. Increases in ovarian weights, T-4 levels, and a decrease in BUN were reported, but were not considered to be treatment related. In a second part of [the Dow Chemical Co., 1983 study], B6C3F1 mice (20/sex/group) were fed the diet chow mixed with 97.5% pure 2,4-D at 0.0, 5.0, 15.0, 45.0, or 90.0 mg/kg bw/day (calculated doses) for 91 days. Criteria used to determine toxicity were the same as for rats. The only effect reported at 5 mg/kg/day was increased weight of adrenals in females. Effects at 15 mg/kg/day included altered organ weights and hematologic effects. Kidney weights were not affected below 45 mg/kg/day." (EPA, 1988).

The EPA used the critical effect of hematologic, hepatic, and renal toxicity to determine a no observed adverse effect level (NOAEL) as the 1.0 mg/kg/day dose group and the lowest observed adverse effect level (LOAEL) as 5.0 mg/kg/day dose group. The EPA used a 100-fold uncertainty factor (10 for interspecies variability and 10 for interhuman variability) applied to the NOAEL of 1.0 mg/kg/day to determine the oral RfD of 1E-2 mg/kg/day. The EPA did not use a subchronic-to-chronic uncertainty factor, because "…an analysis of the 90-day and 1-year interim results suggests that the NOAEL would hold for the full 2-year duration…" (EPA 1988).

Rule 232(1)(b) was used to develop an ITSL, using the following equation:

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

$$ITSL = 1 \times 10^{-2}\ {}^{mg}/_{kg/day}\ \times \frac{70\ kg}{20\ m^3} = 0.035\ {}^{mg}/_{m^3} = 35\ {}^{\mu g}/_{m^3}$$

Rule 232(2)(b) states that an oral RfD has a default averaging time of 24 hours. However, this ITSL is based on 1-year interim results of a 2-year rat study; therefore, the averaging time is changed to annual and this chronic ITSL is coupled with an acute ITSL to better ensure health protection. ACGIH (2001) has established a threshold limit value – time weighted average (TLV-TWA) of 10 mg/m^3 for 2,4-D based on data from animal feeding studies. ACGIH also has listed 2,4-D as A4 – not classifiable as a human carcinogen (ACGIH, 2001). Rule 232(1)(c) can be used to derive an acute ITSL based on an occupational exposure level (OEL) using the following equation:

$$ITSL = \frac{OEL}{100} = \frac{10\ {}^{mg}/_{m^3}}{100} = 0.1\ {}^{mg}/_{m^3} = 100\ {}^{\mu g}/_{m^3}$$

Rule 232(2)(a) states that an 8-hour averaging time is to be used for an ITSL derived from an occupational exposure level. Therefore, the first initial threshold screening level (ITSL) for 2,4-D is 35 µg/m^3 based on an annual averaging time and the second ITSL is 100 µg/m^3 based on an 8-hour averaging time.

References:

ACGIH. 2001. 2,4-D. TLVs and BEIs Based on the Documentation of the Threshold Limit Values for Chemical Substances and Physical Agents & Biological Exposure Indices. ACGIH Worldwide Signature Publications.

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

EPA. 1988. Integrated Risk Information System. 2,4-Dichlorophenoxyacetic acid (2,4-D) (CASRN 94-75-7). Retrieved data on 12/30/2014. Available online at: http://www.epa.gov/iris/subst/0150.htm

NPIC. 2008. National Pesticide Information Center. 2,4-D Technical Fact Sheet. Available online at: http://npic.orst.edu/factsheets/2,4-DTech.pdf

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