MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

January 27, 2016

TO: File for a Clopyralid (CAS # 1702-17-6)

FROM: Mike Depa, Air Quality Division, Toxics Unit

SUBJECT: Initial Threshold Screening Level

The Initial Threshold Screening Level (ITSL) for Clopyralid is 500 µg/m³ with an annual averaging time.

The basis for the ITSL is the same as that which formed the basis as a previously calculated ITSL (see attached memo from Marco Bianchi, dated October 17, 1994; hereafter referenced as Bianchi, 1994). The NOAEL was properly identified as 15 mg/kg/day from a 2-year (chronic) dietary study in mice and rats (Bianchi, 1994). However, using a 7-day study equation, even if the uncertainty factor was reduced from 35 to 10, is overly conservative. A chronic Reference Dose (RfD) can be derived from this study using typical U.S. Environmental Protection Agency (U.S. EPA, 2002) uncertainty factors as follows:

RfD = NOAEL/UF1xUF2
RfD = (15 mg/kg/day)/(10x10)
RfD = 0.15 mg/kg/day

Where UF1 is an uncertainty factor (UF) of 10 to convert from animals to humans, and UF2 is an UF of 10 for the extrapolation to account for sensitive individuals.

The ITSL is calculated from the RfD pursuant to Rule 232(1)(b):

ITSL = RfD x 70kg/20m³
ITSL = 0.15 mg/kg/day x 3.5 x 1000µg/mg
ITSL = 525 µg/m³
ITSL = 500 µg/m³, rounded to 1 significant figure

The current file review concludes that the averaging time (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.

Reference

U.S. EPA. 2002. A Review of the Reference Dose and Reference Concentration Processes. U.S. Environmental Protection Agency, Risk Assessment Forum, Washington, DC, EPA/630/P-02/002F, 2002.

Attachment

MICHIGAN DEPARTMENT OF NATURAL RESOURCES

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INTEROFFICE COMMUNICATION

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OCTOBER 17, 1994

TO: File for a Clopyralid (CAS # 1702-17-6)

FROM: Marco Bianchi

SUBJECT: Initial Threshold Screening Level

The initial threshold screening level (ITSL) for clopyralid is 15 µg/m³ based on an annual averaging time.

The following references or databases were searched to identify data to determine the ITSL: IRIS, HEAST, NTP Management Status Report, RTECS, EPB-CCD, EPB library, CAS-online, NLM-online, IARC, NIOSH Pocket Guide and ACGIH Guide.

A complete literature search was conducted for clopyralid, but only limited information was available. Dow Chemical Company did submit a two year dietary toxicity and oncogenicity study in rats and mice for clopyralid, in an abstract format. Clopyralid was fed in the diet to 70/sex/group for both B6C3F1 mice and Fischer-344 rats at dose levels of 0, 100, 500, or 2000 (mice) and 0, 15, 150, or 1500 (rats) mg/kg body weight/day for up to 2 years. In the mice, the only evidence of toxicity was body weight depression in males of the highest dose group. In top dose rats, decreased food consumption and body weights, increased liver and kidney weights, and pathologic, but non-tumorigenic, macroscopic and microscopic stomach changes occurred. The microscopic changes also occurred in the stomachs of a few middle dose rats. The gross change consisted of increased prominence of the gastric limiting ridge. The histopathologic change consisted of hyperplasia and thickening of the epithelium of the anterior surface of the limiting ridge, more steadily apparent in males. No evidence that clopyralid causes malignant or nonmalignant tumors was found in either rats or mice. The stomach changes in the rats did not occur in the mice. The no-observed-effect-level (NOEL) was 500 and 2000 mg/kg/day in male and female mice, respectively, and 15 mg/kg/day in both male and female rats. A NOEL of 15 mg/kg/day for rats will be used to derive an ITSL. However, because both male and female rats have the same NOEL, the ITSL will be determined by using the female rat body weight and inhalation rate. This will result in a more conservative ITSL than using the male rat data.

Other data sources reviewed such as RTECS, revealed an oral rat LD50 of 4300 mg/kg taken from the Agrochemical Handbook. However, when this handbook was obtained,

no references were listed to support this data. A NLM search listed a TSCA acute oral rat submittal study for clopyralid and other pesticides. This study has been ordered, but it is doubtful this information will supersede the 2 year Dow Chemical study. Hayes et al., (1984) conducted a teratogenic study on Fisher 344 rats and New Zealand White rabbits. Rats were given 0, 15, 75, or 250 mg clopyralid/kg/day by gavage on Days 6-15 of gestation while rabbits were given 0, 110, or 250 mg clopyralid/kg/day on Days 6-18 of gestation. Maternal toxicity, as evidenced by decreased body weight gain, was observed among pregnant rats in the 250 mg/kg/day group. No evidence of maternal toxicity was observed among treated rabbits. A teratogenic effect was not detected in either species. This study would have been used to establish a LOEL for an ITSL determination had it had not been for a study submitted by Dow Chemical Company.

The ITSL was derived as follows using Rule 232(1)(h):
NOEL = 15 mg/kg/day
W_A = Body weight of experimental animal in kilograms (kg).
I_A = Daily inhalation rate of experimental animal in cubic meters/day.
Body weight of Fischer-344 female rat = 0.25 kg.
Daily inhalation rate of Fischer-344 rat = 0.256 m^3/day

A safety factor of 10 is used instead of 35, because the study was conducted for 2 years.

ITSL = (NOEL mg/kg/day)/(10 x 100) x W_A/I_A

ITSL = 15 mg/kg/day/(10 x 100) x 0.25 kg/0.256m^3/day = 0.0146 mg/m^3

0.0146 mg/m^3 x 1000µg/mg = 14.6 µg/m^3

The ITSL for clopyralid = 15 µg/m^3 based on annual averaging.

References:

Barna-Lloyd T et al., (191(7). Clopyralid: Chronic Dietary Toxicity and Oncogenicity in Rats and Mice (Abstract). The Toxicologist, 7:1; 188.

Hayes, FA et al.. (1984). Teratologic Evaluation of 3,6-Dichloropicolinic Acid in Rats and Rabbits. Fundamental and Applied Toxicology, 4:91-97.

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