MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

January 15, 2016

TO: File for Chlopyrifos (CAS No. 2921-88-2)

FROM: Mike Depa, Toxics Unit, Air Quality Division

SUBJECT: Initial Threshold Screening Level

The chronic Initial Threshold Screening Level (ITLS) for chlopyrifos is 1 µg/m³ with annual averaging time. The short-term ITSL is 1 µg/m³ with an 8-hr averaging time is retained.

For information about the derivation of the 8-hr ITSL of 1 µg/m³ see the attached memo from Catherine Simon dated January 17, 2013.

The basis of chronic ITSL of 1 µg/m³ is a U.S. Environmental Protection Agency (EPA) Reference Dose (RfD) of 0.0003 mg/kg/day (EPA, 1992). Previously, the chronic ITSL was 10.5 µg/m³ with a 24-hr averaging time (briefly mentioned in attached memo from Cathrine Simon dated January 17, 2013). The previous RfD-based ITSL is now superceded by the new ITSL of 1 µg/m³.

The key study used to derive the current ITSL of 1 µg/m³ was summarized by EPA, (1992):

> Chronic Dietary Risk Assessment (Reference Dose)
> Study Selected: 2-Year Dog Feeding Study (McCollister et al. 1971 and Kociba et al. 1985)
>
> Executive Summary:
> The chronic toxicity study (MRIDs 00064933, 00146519) in dogs consisted of two phases. in Phase I, chlorpyrifos (97.2-98.8% a.i) as Dowco® 179 was administered to 3 beagle dogs/sex/dose in diet at dose levels of 0, 0.01, 0.03, 0.1, 1 or 3 mg/kg/day for one year. One dog/group was sacrificed at one year, and the remaining 2 dogs/group were sacrificed after a 3 month recovery period. In Phase Il. chlorpyrifos was administered to 4 beagle dogs/sex/dose al the same dose levels for a total of two years, at which time all dogs were sacrificed.
>
> There was a significant increase in the absolute and relative liver weights in the high dose males, although no concurrent histolopathological changes were observed. The male liver/body weight ratios were 2.6 for the control group and 3.47 for the highest dose group (which is less than a 2-fold increase). It is possible that changes in liver weight are an adaptive response. No other treatment related effects were noted other than cholinesterase inhibition. There were no treatment related effects on body weight, mortality, clinical signs, clinical chemistry, food consumption, hematology, urinalysis, or gross pathology. Plasma cholinesterase (ChE) activity in the one-year study was significantly and dose-dependently decreased in all male and female dogs except the 0.01 mg/kg/day group. Inhibition was apparent from 7 days on-ward. Plasma ChE inhibition for the 0.01, 0.03, 0.1, 1 and 3 mg/kg/day dose groups relative to controls were 16%, 26%, 5-42%. 34-56%, 49-77%, and 64-82%, respectively. Cholinesterase activity returned to normal levels

14 days after treatment cessation. Plasma ChE activity in the two-year study was similar to the one-year study. Plasma ChE inhibition of 6-42%, 28-54%, 41-69% and 68-85% was noted in both sexes of the 0.03. 0.1, 1 and 3 mg/kg/day groups, respectively. In the one-year study, red blood cell ChE inhibition of 27-45%, 10-47%, 2-48%, 34-75% and 24-82% was noted in both sexes of the 0.01, 0.03, 0.1,1 and 3 mg/kg/day groups, respectively. Red blood cell ChE activity in dogs of these groups returned lo normal after 92 days. Similar red blood cell ChE inhibition was observed in the two-year study, where inhibition was 1-17%, 6-41%, 37-75%, 43-87% for both sexes of the 0.03, 0.1, 1 and 3 mg/kg/day dose groups, respectively. Overall statistical significance for plasma ChE inhibition was reached at 0.03 mg/kg/day for some time intervals, while statistical significance was observed for RBC ChE inhibition at 0.1 mg/kg/day for some time intervals. Brain ChE activity was not markedly different from controls in the one-year study, although only one dog/sex/dose was evaluated. No significant brain ChE inhibition was noted in the two-year study, although mean inhibition in males relative to controls was 1.5, 6.7, 8.3, 7.2 and 20.8% for the 0.01. 0.03. 0.1, 1 and 3 mg/kg/day groups, respectively. In females, the brain ChE activities relative to controls were +7.1, +2.8, +1.2, +5.8 and -19.4%, respectively. The brain ChE inhibition in the high dose group is considered toxicologically significant.

The NOAELs for plasma, red blood cell and brain cholinesterase inhibition are 0.01. 0.03 and 1 mg/kg/day, respectively. The LOAELs for plasma, red blood cell and brain choline esterare inhibition are 0.03, 0.1 and 3 mg/kg/day, respectiely. The LOAEL and NOAEL for systemic effects are 3 and 1 mg/kg/day, respecthely based on alterations in absolute and relative liver weights, that could he an adaptive response.

The chronic toxicity study in dogs in conjunction with the addendum that contains supplemental information are acceptable-guideline and satisfy the guideline requirement (83-1b).

Dose/Endpoint for establishing the RfD: NOAEL = 0.03 mg/kg/day based on statistically significant or biologically significant decreases in plasma and red blood cell ChE activities in both sexes exposed to 0.1 mg/kg/day for 2 years. In addition, the ChE inhibition was noted at nearly all treatment periods at 0.1 mg/kg/day. Although, significant plasma ChE inhibition was also noted at 0.03 mg/kg/day, these effects were discounted because they were considered marginal and variable, and were not always statistically or biologically significant at all intervals.

Comments about Study and Endpint: Animal data were selected because the HIARC committee concluded that the 28 day human study (Coulston et al. 1972). selected previously as the basis of the chronic RfD, is not appropriate for the evaluation of lifetime dietary exposures because steady-state may not have been achieved. However, the Coulston et al. (1972) study provides some support for the animal data- In this study no effects were noted in humans exposed to 0.03 mg/kg/day for 21 days, while 36-82% plasma ChE inhibition and clinical signs of toxicity (blurred vision, feeling of faintness and runny nose) were observed in individuals exposed to 0.1 mg/kg/day for 9 days. Exposure of the 0.1 mg/kg/day dose group was discontinued on day 9, rendering this study of insufficient duration for assessing chronic exposures.

The NOAEL of 0.03 mg/kg/day and the LOAEL 0.1 mg/kg/day are supported by a 90 day rat study that observed marginal, but significant 22% plasma ChE inhibition at 0.025 mg/kg/day (Crown et al. 1985, MRID 40436406). and two other animal studies that observed no adverse effects at 0.01 mg/kg/day but significant plasma and/or RBC ChE inhibition at 0.22 mg/kg/day (90 day dog; Barker 1989. MRID 42172801) or 0.33 mg/kg/day (2 yr rat; Crown et al. 1990, MRID 42172801). Unfortunately, the large difference between low and mid dose groups (i.e., more than an order of magnitude) for two of these studies does not permit the evaluation of effects at 0.03 mg/kg/day. In addition, these studies are supported by the developmental neurotoxicity study that observed plasma and red blood cell inhibition of 43% and 41%, respectively relative to controls in dams exposed to 0.3 mg/kg/day (the lowest dose tested) from gestation day 6 (GD 6) through gestation day 20 (approximately 2 weeks)(Hoberman 1998a,b, MRID Nos- 44556901, 44661001).

Uncertainty Factor (UF): For chronic dietary risk assessment, the HIARC determined that an UF of 100 is required to derive the chronic RfD and that the inter-species extrapolation factor can not be altered. Although no effects were noted in both animals and humans at 0.03 mg/kg/day, the duration of exposure differs significantly (2 years for dogs and 21 days for humans). These data indicate the humans could be similarly or even more sensitive than animals to ChE inhibition. Although the human study did provide insight as to when ChE inhibition occurs, it was not rigorous enough for endpoint selection. The human study only included 4 male test subjects/dose and was determined to have limited test power and therefore, can only be used as supplemental data.

Chronic RfD = 0.03 mg/kg/day (NOAEL)/100(UF) = 0.0003 mg/kg/day EPA (1992)

Derivation of the Chronic ITSL

The chronic ITSL is calculated as follows:

ITSL = RfD x 70kg/20m^3

ITSL = 0.0003 mg/kg/day x 70kg/20m^3

ITSL = 0.00105 mg/m^3 x 1000µg/mg

ITSL = 1 µg/m^3 (with annual averaging time).

The averaging time (AT) assigned to chlorpyrifos is set to annual based on the nature and duration of the key study and the ITSL value derivation, as allowed under Rule 229(2)(b).

Reference

EPA. 1992. Memorandum. Subject: Chlorpyrifos - Replacement of Human Study Used in Risk Assessments - Report of the Hazard Identification Assessment Review Committee. FROM: Jess Rowland. Co-Chairman And Pauline Wagner, Co-Chairman Hazard Identification Assessment Review Committee Health Effects Division (7509C). TO: Steve Knizner, Branch Senior Scientist Re-Registration Branch 3 Health Effects Division (7509C). DATE: June 2, 1999. HED DOC. No. 013504

Attachment

MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

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INTEROFFICE COMMUNICATION

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TO: File for Chlorpyrifos (CAS No. 2921-88-2)

FROM: Cathy Simon, Air Quality Division

DATE: January 17, 2013

SUBJECT: Screening Level Update

Two initial threshold screening levels (ITSLs) for chlorpyrifos were established by the Air Quality Division in 1992. These included an ITSL of 2 µg/m^3 based on an 8-hour averaging time, and an ITSL of 10.5 µg/m^3 based on a 24-hour averaging time. The ITSL for chlorpyrifos, based on an 8-hour averaging time, has been changed from 2 µg/m^3 to 1 µg/m^3. This change is being made as part of a project to update ITSLs that are derived from outdated occupational exposure limits. The evaluation of data being done as part of this project is limited to identifying the most recent occupational exposure limit, and does not include a review of all the available scientific literature, nor does it include an updated evaluation of the ITSL based on a 24-hour averaging time.

The original ITSL (8-hour averaging time) for chlorpyrifos , set in 1992, was derived from the American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value (TLV) of 0.2 mg/m^3. This TLV of 0.2 mg/m^3 was first adopted by the ACGIH in 1975. The new ITSL is based upon the most recent TLV of 0.1 mg/m^3, which was adopted by the ACGIH in 2003, and represents the most up to date and scientifically based TLV available from the ACGIH (ACGIH, 2003). The new ITSL was derived as follows:

$$ITSL = \frac{TLV}{100} = \frac{0.1\ mg/m^3}{100} = 0.001\ mg/m^3 = 1\ \mu g/m^3$$

The above ITSL of 1 µg/m^3 (8-hour averaging time) was derived pursuant to Rule 229(2)(b) of the Michigan Air Pollution Control Rules, and is consistent with the methodologies of Rules 232(1)(c) and 232(2)(a).

References

ACGIH. 2003. *Chlorpyrifos. Documentation of the Threshold Limit Values and Biological Exposure Indicies.* 7th Edition. American Conference of Governmental Industrial Hygienists, Cincinnati, OH.

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