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SUBJECT: COMMENTS ON U.S. EPA'S PRELIMINARY RISK ASSESSMENT FOR CHLORPYRIFOS: WITH A FOCUS ON EXPOSURE ASSESSMENT

The following is a summary of the review on United States Environmental Protection Agency's (U.S. EPA's) preliminary human health risk assessment draft document for the pesticide chlorpyrifos, entitled "*Chlorpyrifos Preliminary Human Health Risk Assessment* (DP No. D388070)".

1. In the human body, the organophosphate chlorpyrifos is biotransformed to chlorpyrifos oxon, which is reportedly responsible for most, if not all, of the cholinesterase (ChE) inhibition. ChE inhibition is one of the toxic endpoints of immediate concern listed in the U.S. EPA document. Chlorpyrifos oxon in the human body is also documented to be readily converted to another metabolite called TCP (3,5,6-trichloro-2-pyridinol), which is the metabolite typically used for biomonitoring of human exposure to chlorpyrifos.

   Some of the PoDs (points of departure) ≅ critical NOAELs (no-observed-adverse-effect-levels) used by U.S. EPA were based on *dosing directly with chlorpyrifos oxon*. In those cases, we suggest that the units for chlorpyrifos exposure (e.g., mg/kg/day) be expressed as units of chlorpyrifos oxon exposure. We acknowledge that structurally, the parent compound chlorpyrifos differs from its oxon only having its sulfur (S) atom replaced by an oxygen (O) atom; that is, both compounds have similar molecular weight (350.6 g/mol *vs*. 334.5 g/mol).

   We also believe that a key issue that warrants further discussion is the recovery of TCP. The U.S. EPA document states (p.24) that 84% of chlorpyrifos is excreted in the *rat* urine in the form of TCP, whereas only 70% of chlorpyrifos in the form of TCP is excreted in the *human* urine. This difference in TCP excretion suggests that more chlorpyrifos oxon molecules are available in the human than in the rat body per unit of exposure dose. For example, since the acute PoD is determined to be 0.5 mg chlorpyrifos (or 0.5 mg chlorpyrifos oxon) per kg of body weight per day based on juvenile animals (e.g., Table 7), then for human exposure to

this same dosage there appears to be (100%-70%) ÷ (100%-84%) = *1.9 times* more chlorpyrifos oxon molecules staying longer in the human body than in a juvenile animal's body to thereby cause more ChE inhibition there. Based on this information, it appears that chlorpyrifos is *nearly twice* as potent in humans as in rats (per unit of exposure dose).

2. It is expected that the Department of Pesticide Regulation's (DPR's) Medical Toxicology Branch will take a closer look at the various benchmark margins of exposure (MOEs) used throughout the U.S. EPA document. For example, U.S. EPA concluded that children are more susceptible to ChE inhibition than adults (p.37) and perhaps even more so than animals. However, it appears that Tables 19 through 21 each use the same LOC (level of concern ≅ benchmark MOE) for both adults and children.

3. U.S. EPA assumed a dermal absorption rate of 3% based on the ratio of oral LOAEL (lowest observed adverse effect level) of 0.3 mg/kg/day to dermal LOAEL (lowest-observed-adverse-effect-level) of 10 mg/kg/day and on the results (1 to 3%) observed in a human dermal absorption study conducted by Nolan et al. (1984). It is important to note that any underestimation of this dermal absorption rate would understate the risk from aggregate exposure (e.g., from dermal, oral, and inhalation combined) based on total internal dose (e.g., Table 19). *As elaborated on below, there is indication that this dermal absorption rate (3%) might have been underestimated*.

   In the Nolan study, the dose levels used to treat the human skin were 4,200 µg/cm^2 (n = 5) for the high dose and 390 µg/cm^2 (n = 1) for the low dose. This dose selection was not consistent with the dermal absorption study guidelines set forth by U.S. EPA (1998). The U.S. EPA guidelines clearly state that "*(Study) doses should span the range of doses expected in field exposure*". For fieldworkers and residents, for example, the average levels of exposure to pesticides typically range from about 25 µg per cm^2 down to *nano*grams per cm^2 (e.g., Thongsinthusak et al., 1999), far below the lower dose of 390 µg/cm^2 used in the Nolan study. It is also widely accepted among scientists that in most instances percent dermal absorption is *inversely* (but not necessarily linearly) proportional to dose level, with the lower dose potentially yielding a much greater percent dermal absorption value than the higher dose used in the same study (e.g., Thongsinthusak et al., 1999).

   Furthermore, there are at least four (4) uncertainties associated with using the ratio of oral LOAEL to dermal LOAEL (*whether or not as the only means*) to estimate a dermal absorption rate. These four uncertainties can be summarized as follows.

   a. Like with the LD_{50} (median lethal dose) ratio method, the accuracy of this LOAEL ratio method is contingent on *how* the LOAELs are accurately determined (or selected) in both the oral and the dermal toxicity study. There is no evidence or information given supporting that both the oral LOAEL and the dermal LOAEL used for the ratio each represented the *lowest* (i.e., the *true*) value *just right above* the *highest* (i.e., the *true*) value determined for their respective NOAEL. For example, in the chlorpyrifos case here, the

actual oral and dermal LOAELs could be, say, 0.28 mg/kg/day and 5.5 mg/kg/day, respectively, thus yielding a ratio of 5% (instead of 3%).

b. As commented earlier concerning the Nolan study, a lower dose generally would yield a substantially greater percent dermal absorption value. The dermal LOAEL used in the ratio method by U.S. EPA was in the range of 10 mg/kg/day. This dermal dose level is equivalent to roughly 200 to 800 $\mu g/cm^2$/day for a 250- to 1,000-gram rat with an exposed area of 12 cm^2 on the back; that is, using a level that still exceeded considerably the typical range (<25 $\mu g/cm^2$) of exposures experienced by most humans. (Note that the U.S. EPA document [p.127] listed only the exposed area of the rats used in the study, not their body weight.)

c. The oral LOAEL was determined in Spraque-Dawley (SD) rats (p.138), whereas the LOAEL from the dermal toxicity study was determined using Fisher 344 (F344) rats (p.127). It is not inconceivable that the skin of a F344 rat could be considerably less (or more) permeable to chlorpyrifos compared to the skin of a SD rat. For one thing, there are several studies supporting that SD rats are less susceptible to chemically-induced liver injury than F344 rats.

d. According to the U.S. EPA document, the oral LOAEL of 0.3 mg/kg/day was based on both a 41% red blood cells (RBC) and a 43% plasma ChE inhibition observed in the SD rats dosed for several weeks (pp.138-140). The exact day following the first day of dosing is not given (or not immediately transparent) for the above ChE inhibition observations. On the other hand, the dermal LOAEL of 10 mg/kg/day was based on both a 16% RBC and 45% plasma ChE inhibition observed in the F344 rats dosed for 4 days (p.127). To put it another way, the LOAEL ratio that U.S. EPA used to determine the dermal absorption rate in question is *not* supposed to be based *simply* on the dosages of 0.3 mg/kg/day from the oral *vs*. 10 mg/kg/day from the dermal route, without accounting for the difference in total effective dose delivered as due to dosing the animals to different days between the two routes. Also, the effect of 16% RBC ChE inhibition from the dermal route is not the same as, but actually about three times less than, the effect of 41% RBC ChE inhibition from the oral route. In other words, to use the ratio method, among other things the final amount of the chemical delivered into the body that can cause the same kind and same level of effect should be comparable between the oral and the dermal route. Frankly, this one comparability issue is even more uncertain or problematic when using the LD_{50} ratio method. This is because a much higher dermal dose level would then be needed on the very limited area of the rodent's back in order to induce a lethal effect, which may or may not be on the same tissue or organ as the lethal effect through the oral route will be on. Yet in the meantime, a higher lethal dermal dose level *per se* generally would cause or entail a much lower percent dermal absorption value.

In essence, in light of the above uncertainties U.S. EPA may need to request the chlorpyrifos registrants to conduct a dermal absorption study following the U.S. EPA Health Effects Test Guidelines – OPPTS 870.7600 Dermal Penetration.

4. In terms of all potential exposure scenarios in question, it appears that U.S. EPA has considered sufficiently the residential post-application exposures involved (Section 6.2). The exclusion of assessing quantitatively the exposure from residential ant mound treatment is deemed acceptable. The scientists at DPR's Worker Health and Safety Branch (WHS) concur that the contact of a treated ant mound by children is minimal, if any, in the sense that young children or their parents would know better not to be around a place where there are sufficient and large ant mounds calling for chlorpyrifos treatment.

5. In concept, U.S. EPA has duly considered the aggregate and cumulative exposures for the general public and bystanders (e.g., by including exposure from field volatilization).

6. For handler exposures, it appears that U.S. EPA has also considered sufficiently the potential scenarios involved (as reflected in Table 25 for agricultural use and in Table 26 for non-agricultural use). Biomonitoring of worker exposure to chlorpyrifos is by measuring TCP contents in the urine. However, TCP is a metabolite not unique to chlorpyrifos and can come from many sources including ambient air. For example, TCP is also a principal metabolite of the herbicide triclopyr. Therefore, when using the few available chlorpyrifos-specific bio-monitoring worker exposure studies even for comparison purposes (p.15), U.S. EPA may want to take the various potential sources of TCP into consideration.

7. For worker reentry exposures, U.S. EPA also seems to have considered sufficiently the potential exposures involved, as reflected in Table 27. However, at least a few typos are noticeably found in Table 27. For example, the estimated REI (restricted entry interval) for cherry (sour) in New York appears to be missing on the second page of the table (i.e., p.91). At the very beginning of the third page of the table (p.92), the name of a crop also appears to be missing.

8. Finally, it should be pointed out that this review of U.S. EPA's draft document came with no information on the way in which U.S. EPA actually calculated any of its exposure estimates. Therefore, WHS cannot make any specific comments regarding the assumptions and data used by U.S. EPA in its calculation of all the exposure estimates involved.

   Regardless, it is worth repeating here that the set of assumptions and data used to perform a pesticide exposure assessment can vary substantially across (regulatory) agencies, such as between U.S. EPA and DPR, partly due to differences in agency policies. These kinds of differences have been typically noted in the exposure appraisal section of the WHS exposure assessment documents prepared for most pesticide active ingredients (e.g., HS-1647 for endosulfan, HS-1527 for propargite).

References

Nolan RJ, Rick DL, Freshour NL, Saunders JH, 1984. Chlorpyrifos: Pharmacokinetics in Human Volunteers. *Toxicol. Appl. Pharmacol*. 73:8-15. (*This 1984 paper is assumed to be the same in contents as the 1982 study report referenced in U.S. EPA's document, which is not immediately assessable to WHS scientists.*)

Thongsinthusak T, Ross JH, Dong MH, 1999. Significance of dermal dose levels in dermal absorption studies of pesticides. HS-1801. Worker Health and Safety Branch, Cal/EPA Department of Pesticide Regulation, Sacramento, California.

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