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MEMORANDUM

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DATE: August 26, 2002

SUBJECT: COMMENTS ON THE DRAFT RISK CHARACTERIZATION DOCUMENT FOR AGGREGATE EXPOSURE TO METHYL BROMIDE

Thank you for the opportunity to review the draft risk characterization document (RCD) for aggregate exposure to methyl bromide prepared by the Department of Pesticide Regulation (DPR). This is the third of three draft RCDs prepared by DPR for methyl bromide exposure, the first draft RCD being for inhalation exposure and the second for dietary exposure. Our comments on the draft RCD for aggregate exposure to methyl bromide are provided in this memorandum.

Our primary concern with regard to this draft RCD is that the total estimated aggregate risk for inhalation plus oral exposure is lower than either inhalation or oral exposure alone. We think that this outcome is an artifact of the methodology employed in the RCD to estimate the aggregate risks and we recommend that an alternative method be used to aggregate inhalation and oral exposure to methyl bromide.

The U.S. Environmental Protection Agency (U.S. EPA) prepared guidelines for measuring and aggregating risk for single chemical, multi-route, multi-source assessments (U.S. EPA, 1999, 2001). The method used in the draft RCD to estimate risk of aggregate exposure to methyl bromide, called the "total margin of exposure (MOE_T) method," is based on the assumption that it is scientifically justified to combine exposures occurring by different pathways/routes only when the toxicological endpoints for the pathways/routes are related with respect to target organ and nature of adverse effect. When the relevant toxicological endpoints for all routes/pathways are not the same, U.S. EPA recommends that a separate aggregate assessment be conducted for each toxic effect of concern.

Following U.S. EPA's guidelines, the assessment for aggregate risk of acute exposure to methyl bromide in the draft RCD is based on a common toxicological endpoint for both inhalation and oral exposure, which is clinical signs of toxicity. These clinical signs were clearly attributed to neurotoxicity when inhalation exposure was involved, and according to the draft RCD could be attributed to neurotoxicity in the case of oral exposure. The acute no-observed-adverse-effect levels (NOAELs) used in this assessment are 22.8 mg/kg-day for inhalation exposure (based on a 23 to 30-day dog study) and 8 mg/kg-day for oral exposure (based on acute oral LD_{50} study in rats). In comparison, a NOAEL of 10.5 mg/kg-day for developmental toxicity, which is the most sensitive toxicological endpoint for acute methyl bromide exposure, was selected in the assessment of inhalation exposure alone. This acute NOAEL selected for use in the inhalation exposure RCD is two times lower than the acute NOAEL chosen for the inhalation component of the aggregate exposure assessment. The acute NOAEL of 8 mg/kg-day for oral exposure is used in both the dietary exposure RCD as well as the aggregate exposure RCD.

The developmental toxicity study used in the draft RCD for acute inhalation exposure was conducted with New Zealand white rabbits exposed to methyl bromide (99.6 percent) at 0, 20, 40, or 80 ppm for six hours per during days 7 to 19 of gestation. Equivalent absorbed doses used in this experiment were: 0, 5.2, 10.5, and 21 mg/kg-day. The developmental NOAEL is 40 ppm (10.5 mg/kg-day) based on omphalocele, hemorrhaging, retro-esophageal right subclavian artery, gall bladder agenesis, fused sternbrae, and decreased fetal body weight at 80 ppm (21 mg/kg-day). The data demonstrate that developmental toxicity caused by inhaled methyl bromide is a systemic effect and not a local effect.

In the oral developmental toxicity study in rabbits, methyl bromide (99.5 percent) was dissolved in corn oil and administered by gavage at (absorbed) dose levels of 0, 1, 3, or 10 mg/kg-day during days 6 to 18 of gestation (DPR's Summary of Toxicological Data, page 19). In this study "... the only fetal finding of interest was the observation that each of the three methyl bromide-treated groups had more fetuses with skeletal malformations than what was observed in the negative-control group. Skeletal malformations involving 2-3 litters in at least one methyl bromide-treated group included: splitting of the nasal/frontal/parietal bones; hemivertebra; fusion of the ribs/sternebrae; and absence of the metacarpal and phalangeal bones." Nevertheless, the Summary states "...the difference between the negative control and methyl bromide-treated groups appear too small to warrant further concern." However, it should be noted that highest absorbed dose used in the oral study is approximately the same as the NOAEL of 10.5 mg/kg-day (absorbed) identified from the inhalation study. Based on the comparison of doses, the highest dose used in the oral study is a NOAEL and therefore a similar effect would not have been expected in the oral study. In fact, some evidence for developmental toxicity, although not statistically significant, was reported in the oral developmental toxicity study even at the lower dose levels. Our approach is consistent with the National Academy of Sciences recommendation "to better be able to compare inhalation with the oral developmental

studies, it would be useful to calculate the estimated absorbed doses for these studies" (NAS, 2000).

The draft RCDs do not present data showing that the mechanism of toxicity for absorbed methyl bromide is different depending on the route of exposure. Likewise, we were not able to locate any data in the open literature that demonstrate the mechanism of action for developmental toxicity is exclusively related to inhalation of methyl bromide.

In summary, there is enough scientific support or there exist data gaps so that the following assumptions for acute exposure to methyl bromide are reasonable:

1. There is a greater variability in inhalation than dietary exposure for the two major groups of exposed individuals (i.e., workers and residents).

2. For occupational aggregate dose levels, the contribution from inhalation exposure is proportionately higher than dietary exposure for upper-end exposures (approximately 99 percent) but about the same for lower end exposures (approximately 50 percent).

3. For residential aggregate dose levels, the contribution from inhalation exposure is also proportionately higher than dietary exposure for upper-end exposures (approximately 77 percent) but lower or about the same for lower end exposures (approximately 25 to 50 percent).

4. The existing oral developmental toxicity study used absorbed dose levels that were at or below the NOAEL for absorbed methyl bromide determined from the inhalation developmental toxicity study.

5. The results of the oral toxicity study present some limited evidence of adverse developmental effects.

6. Developmental toxicity caused by methyl bromide exposure is systemic in nature.

7. Because neither DPR nor OEHHA were able to identify any studies that demonstrate differences, it is reasonable to assume that the mechanism of action of the developmental toxicity of methyl bromide is the same for oral and inhalation exposure.

Based on these assumptions, we recommend that the acute exposures estimated for methyl bromide from inhalation and ingestion be added and compared to the existing NOAEL for developmental toxicity from the inhalation study. As noted previously, we believe this approach is consistent with the recommendation of the National Academy of Sciences (NAS, 2000).

The situation for chronic toxicity from methyl bromide exposure is a little more complicated. The common toxicological endpoint used in the draft RCD for aggregate exposure to oral and inhaled methyl bromide is reduced body weight. The NOAELs (as absorbed doses) were 10 mg/kg-day (chronic inhalation study in rats) and 2.2 mg/kg-day (chronic oral study in rats) for inhalation and oral exposures, respectively. For chronic exposure to methyl bromide through inhalation alone, the critical endpoint is nasal cavity lesions in rats, yielding a NOAEL of 0.067 mg/kg-day (expressed as an absorbed dose). This NOAEL is 150-fold lower than the NOAEL of 10 mg/kg-day used for aggregate exposure. The NOAEL of 2.2 mg/kg-day for chronic oral exposure was used in both the aggregate RCD and the dietary RCD.

Unlike the acute toxicity data for developmental toxicity, the effects of long-term repeated inhalation of methyl bromide on the nasal cavity might be the result of a localized effect. Therefore, although the other assumptions we present above for acute exposure would likely also apply for chronic exposure to methyl bromide, further research should be conducted to ascertain the nature of the most sensitive toxicological endpoint from chronic exposure.

For chronic exposure to methyl bromide, we recommend that aggregate risks be estimated separately for different exposure scenarios based on the toxicological endpoints most sensitive for the prevalent route of exposure for each scenario. This approach is recommended by U.S. EPA (1999, 2001) for situations where there is more than one critical toxicological endpoint for a single chemical and where toxicological effects via different routes of exposure are not the same. Alternatively, the aggregate risk RCD should not include an aggregate risk assessment for chronic oral and inhalation exposure because the results in the draft RCD are confusing and not useful. If the latter option is chosen, then DPR should use the results of the inhalation RCD for methyl bromide in developing mitigation options as proposed in the draft RCD.

In reference to the aggregate risk estimate for chronic exposures, on pages 3 and 30 of the draft RCD the toxicological significance of animal weight loss is questioned due to a failure of the magnitude of the weight loss to increase with continued exposure. For methyl bromide (chronic rat study) the maximum reduction in high dose animals occurred during the first weeks of testing while "a further reduction in bodyweight relative to the controls did not occur despite continued exposure." However, in chronic studies, it is often the case that the magnitude of the body weight loss does not increase with increased time of exposure. Examples of chronic studies where weight loss in treated animals did not increase relative to controls with continued exposure include:[1]

[1] Source of information: DPR Website, Available Toxicology Summaries.

1. Mecoprop (chronic dog study): NOAEL based on "reduced bodyweight and bodyweight gain." Group mean body weight gains in high dose males were decreased 75 percent relative to controls between days 0 to 49, but decreased only 15 percent during days 0 to 364; group mean body weight gains in high dose females were decreased 25 percent relative to controls only between days 1 to 49.

2. Quinclorac (combined rat study): NOAEL is based on reduced body weight in females. The body weights were only lower than controls between days 518 to 658 (study went from 0 to 730 days).

3. Chlorpyrifos (combined rat): non-cholinesterase NOAEL based on body weight decreases in males; high dose males had reductions in body weights of "7-9% throughout study."

4. Diflufenzopyr (oncogenicity mouse): chronic NOAEL based on reduced body weight; mean body weight of high dose males were significantly lower than controls over 12 of the first 21 weeks, then no significant differences from controls.

We recommend the discussion on the toxicological insignificance of the reductions in body weight from chronic methyl bromide exposure be reconsidered in light of the examples where DPR has selected NOAELs based on the same endpoint for other active ingredients.

Thank you for the opportunity to review the draft risk characterization document for aggregate exposure to methyl bromide. If you have any questions regarding our comments, feel free to contact me or Dr. Michael DiBartolomeis at (510) 622-3200.

References

DPR, 1999. Summary of Toxicology Data for Methyl Bromide.

NAS, 2000. Methyl bromide risk characterization in California. National Research Council, National Academy Press, Washington, D.C.

U.S. EPA, 1999. Guidance for performing aggregate exposure and risk assessments, October 29, 1999. Office of Pesticide Programs, Environmental Protection Agency, Washington, D.C.
http://www.epa.gov/fedrgstr/EPA-PEST/1999/November/Day-10/6043.pdf

U.S. EPA, 2001. General principles for performing aggregate exposure and risk assessment, November 29, 2001. Office of Pesticide Programs, Environmental Protection Agency, Washington, D.C. http://www.epagov/pesticides/trac/science/aggregate.pdf

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