Office of Environmental Health Hazard Assessment

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MEMORANDUM

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Agency Secretary

Gray Davis
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TO: Gary Patterson, Ph.D., Chief
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FROM: Anna M. Fan, Ph.D., Chief
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DATE: July 27, 2001

SUBJECT: COMMENTS ON THE DEPARTMENT OF PESTICIDE REGULATION'S DRAFT METHYL BROMIDE RISK CHARACTERIZATION DOCUMENT FOR DIETARY EXPOSURE

We have reviewed the draft methyl bromide risk characterization document (RCD) for dietary exposure prepared by the Department of Pesticide Regulation (DPR). Methyl bromide is a multipurpose fumigant used for pest control in structures such as warehouses, ships, freight cars, and homes and in postharvest treatment of commodities. It is also used in the preplant treatment of soil in fields and greenhouses to control insects, nematodes, weeds, bacteria, and fungi. On an average, 17 million pounds of methyl bromide is used annually in California. Approximately 96 percent is for soil fumigation, 3 percent is for structural use and 1 percent is for commodity and nursery fumigation.

Methyl bromide is a known stratospheric ozone depleter. Under the United Nations Montreal Protocol, it is scheduled to be phased out of use in the United States by 2005. In California, it is regulated under: Health and Safety Code Sections 39650 to 39670 (Toxic Air Contaminants, Assembly Bill 1807), Food and Agriculture Code Section 13134 (Dietary Risk Assessment, Assembly Bill 2161); Birth Defect Prevention Act of 1984 (Senate Bill 950), and Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65).

The draft methyl bromide RCD for dietary exposure submitted by DPR for the Office of Environmental Health Hazard Assessment's (OEHHA's) review is volume II of the projected three-volume document. The first volume on risk characterization for inhalation exposure was reviewed by OEHHA in August 1999. The third volume on risk characterization for aggregate exposure will be developed after completion of volumes I and II. The draft RCD for dietary exposure consists of two parts: a main document and an attachment with two appendices. The two parts discuss acute and chronic dietary analysis, respectively.

A summary of our comments is presented below. More detail is provided in the attachment.

1. We recommend that the draft dietary RCD for methyl bromide include the ranges of methyl bromide concentrations for particular commodities which are health protective for all consumer groups, especially for children. Such ranges could serve as a reference source in the future to see whether the proposed or approved tolerance values meet the safety requirements.

2. We recommend that the draft dietary RCD include a brief discussion on subpopulations at greater risk from methyl bromide exposure in the diet.

3. We recommend that the draft dietary RCD include a brief discussion comparing the pharmacokinetics, toxicity, and the lowest levels of methyl bromide causing adverse effects from inhalation and dietary exposure. Alternatively, this discussion could be included in volume III.

4. A discussion on polymorphism in glutathione transferase activity among humans and its implications on toxicity of methyl bromide in exposed individuals would enhance the risk characterization of this chemical. In addition, the lack of correlation between the strong mutagenic activity and the negative results in cancer bioassays for methyl bromide should be discussed. We recommend these topics be included in volume III.

Thank you for the opportunity to review the draft RCD for dietary exposure to methyl bromide prepared as volume II of a three volume set for this active ingredient. If you have any questions regarding our comments, or would like to set up a meeting to discuss them, feel free to contact me or Dr. Michael J. DiBartolomeis at (510) 622-3200.

Attachment

cc: Val F. Siebal
Chief Deputy Director
Office of Environmental Health Hazard Assessment

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ATTACHMENT

Comments on the Draft Methyl Bromide Risk Characterization Document for Dietary Exposure

Methyl bromide is a multipurpose fumigant used for pest control in structures such as warehouses, ships, freight cars and homes and in postharvest treatment of commodities. It is also used in the preplant treatment of soil in fields and greenhouses to control insects, nematodes, weeds, bacteria, and fungi. On an average, 17 million pounds of methyl bromide are used annually in California for pest control. Approximately 96 percent is for soil fumigation, 3 percent is for structural use and 1 percent for commodity and nursery fumigation.

COMMENTS

Dietary versus inhalation exposure risks

The toxicological database for methyl bromide allows for the assessment of risk from exposures to methyl bromide from different routes of exposure. The risks from inhalation exposures (volume 1) were based on studies with inhalation exposures. The risks from dietary exposure to methyl bromide (volume 2, currently under review) was based on studies with oral exposures. In general, we support this approach. We also believe that the overall health risks from all routes of exposure to methyl bromide will be based on the absorbed doses of methyl bromide from all routes of exposures. According to the draft dietary risk characterization document (RCD), aggregate exposures will be assessed in volume III of the RCD.

The comparison of critical no-observed-adverse-effect-levels (NOAELs) and endpoints chosen for risk assessment for oral and inhalation exposures showed that these two parameters are very different for the two routes of exposure (see Table 8 on page 25). For oral exposure, both acute and chronic NOAELs (8 mg/kg and 0.02 mg/kg-day, respectively) selected for risk assessment were lower than acute and chronic NOAELs for inhalation exposure (11 mg/kg and 0.14 mg/kg-day, respectively). The toxicological endpoint used for acute oral exposure was clinical signs in rats while the endpoint for inhalation exposure was developmental toxicity. For chronic oral exposure the most sensitive toxicological endpoint used in risk assessment was enlarged spleens in rats while the most sensitive endpoints for chronic inhalation exposure were nasal epithelial hyperplasia and degeneration.

We recommend that the RCD include a comparison of the pharmacokinetics, toxicity, and the lowest levels causing adverse effects from exposure to methyl bromide via inhalation or in the diet. Alternatively, this discussion might be more appropriate for volume III, the aggregate exposure assessment.

Tolerance assessment

The draft dietary RCD does not include an assessment of tolerances because the existing tolerances established by the United States Environmental Protection Agency (U.S. EPA) for methyl bromide are based on inorganic bromide which U.S. EPA believes to be of no toxicological concern. There are no current official tolerances established for methyl bromide. However, there are prepared tolerances submitted to U.S. EPA by the registrant that could be presented. They range from 0.1 ppm (vegetables, small fruits and berries, and stone fruits) to 50 ppm (green cocoa beans). (Note: tolerance assessment issues are addressed in the draft RCD on pages 30 and 31.)

We recommend that the dietary RCD provide the range of methyl bromide concentrations for particular commodities which are health protective for all consumer groups, including but not limited to children and infants. Such ranges could serve as a reference source in the future to see whether the proposed or approved tolerance values meet the safety requirements.

Susceptible populations

The draft dietary RCD does not identify groups of people more susceptible to the toxic effects of methyl bromide. In the first volume of the draft RCD for methyl bromide from inhalation exposure, the issue of the increased sensitivity of the young to methyl bromide was addressed under the heading Pre-and Post-natal Sensitivity (as noted in volume II, pages 123 and 124). Dietary exposure analyses presented in volume II showed that children one to six years old had the highest potential acute and chronic dietary exposure to methyl bromide residues in the diet among the 20 groups analyzed. Although the risks for this group from the dietary exposure to methyl bromide were still within the acceptable range, we recommend that a brief discussion of the issue be included in the dietary RCD.

Conjugation of methyl bromide with glutathione

The conjugation with glutathione appears to be an important part of metabolism and the toxification/detoxification process for monohalomethanes including methyl bromide (Hallier et al., 1990). This reaction is catalyzed by glutathione transferase. There is a broad genetically determined polymorphism in glutathione transferase activity among humans (Hallier at al., 1993). Approximately 75 percent of people have red blood cells with a form of this enzyme (GST1-1), which is selective for the conjugation of methyl bromide with glutathione (fast conjugators) (Garnier et al., 1996). About 25 percent of the population does not have this enzyme phenotype (slow conjugators) (Garnier et al., 1996). There are ethnic differences in the prevalence of the genotype (Nelson et al., 1995).

The polymorphism of glutathione transferase activity may result in different dose responses among individuals in a population with varying toxic responses to methyl bromide exposure. Therefore, these differences in metabolism (conjugation) may be a factor in identifying susceptible subpopulations that would require more consideration in the risk assessment.

Although the amount of data on the subject matter is limited, we recommend that such a discussion be included in volume III.

Genotoxic and oncogenic effects of methyl bromide

The oncogenic potential of methyl bromide has been studied extensively through inhalation (two long-term chronic toxicity studies in rats) as well as through dietary routes of exposure (at least four chronic toxicity studies in rats, mice, and dogs). Chronic toxicity and oncogenicity of methyl bromide were discussed in volume I (pages 55 to 64).

There was no clear evidence of oncogenicity in the currently available studies. This is puzzling because methyl bromide is a direct-acting mutagen, especially in *in vitro* systems (see volume I pages 65 to 69). It was found positive in *Salmonella typhimurium* strains TA 100 and TA 1535, *Escherichia coli* strains Sd-4 and WP2her, and in *Saccharomyces cerevisiae*. It also produced a dose-dependent induction of sex-linked recessive lethality in *Drosophila melanogaster*. In *in vivo* assays methyl bromide was found to cause dominant lethal mutations, an increase of micronuclei, and a dose-related increase in the frequency of sister chromatid exchanges in bone marrow. DNA adducts were detected in liver, lung, stomach, and forestomach of rats exposed to high concentration of methyl bromide by inhalation.

We recommend that a discussion of the lack of correlation between strong mutagenic activity and no clear evidence of carcinogenicity be included in volume III.

References

Garnier, R., M.O. Rambourg-Schepens, A. Muller and E. Hallier (1996). Glutathione transferase activity and formation of macromolecular adducts in two cases of acute methyl bromide poisoning. Occup. Environ. Med. 53(3): 211-215.

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