File

Office of Environmental Health Hazard Assessment

Joan E. Denton, Ph.D., Director
Headquarters • 301 Capitol Mall, Rm. 205 • Sacramento, California 95814-4308
Oakland Office • Mailing Address: 1515 Clay Street, 16th Floor • Oakland, California 94612

Winston H. Hickox
Secretary for Environmental Protection

Gray Davis
Governor

MEMORANDUM

TO: Gary T. Patterson, Ph.D., Chief
Medical Toxicology Branch
Department of Pesticide Regulation
830 K Street
Sacramento, California 95614-3510

FROM: Anna M. Fan, Ph.D., Chief MMP for AMF
Pesticide and Environmental Toxicology Section

DATE: September 1, 1999

SUBJECT: COMMENTS ON THE DEPARTMENT OF PESTICIDE REGULATION'S DRAFT RISK CHARACTERIZATION DOCUMENT FOR INHALATION EXPOSURE TO THE ACTIVE INGREDIENT METHYL BROMIDE

We have completed our review of the draft risk characterization document (RCD) for methyl bromide prepared by the Department of Pesticide Regulation (DPR). Methyl bromide is a soil, structural, and commodity fumigant used for the control of insects, rodents, nematodes, weeds, and other organisms. From 1991 to 1997, an average of 15 to 19 million pounds of methyl bromide was used per year in California. The majority of use was for soil fumigation (96%), with lesser amounts used for structural (3%), and commodity and nursery fumigation (1%). Methyl bromide is a class one ozone depleter and its use is regulated by the U.S. Clean Air Act and the United Nations Montreal Protocol. In California, it is regulated under the Health and Safety Code Sections 39650 to 39670 (Toxic Air Contaminants, AB 1807), the Food and Agriculture Code Section 13134 (Dietary Risk Assessment, AB 2161), the Birth Defect Prevention Act of 1984 (SB 950), and for structural use only, the Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65).

The package submitted to the Office of Environmental Health Hazard Assessment (OEHHA) for review consists of the draft RCD (March 1, 1999) and various appendices (A through I). These appendices include, among other documentation, a summary of toxicology data for methyl bromide (March 5, 1999) and an exposure assessment dated January 11, 1999, prepared by the Worker Health and Safety Branch. Furthermore, on July 14, 1999, staff of DPR and OEHHA met at U.C. Davis to discuss the draft RCD and technical issues identified by OEHHA.

The draft RCD is one of the more comprehensive and well-written characterizations prepared by DPR under SB 950 to date. However, based on our review of the draft RCD and the July 14 discussion, we still feel that the document needs significant revision before finalization. Our major technical comments are as follows. More detailed comments are provided in the attachment.

1. The draft RCD addresses only inhalation exposures to methyl bromide and states that the potential risk from dietary exposure to methyl bromide residues in food will be addressed in a separate document. This underestimates the potential risk posed by methyl bromide use. A more complete risk assessment would include characterization of oral and dermal exposures in addition to inhalation for methyl bromide. This is especially important for those scenarios in which dermal contact is the primary source of exposure. However, OEHHA concurs with the use of inhalation exposure alone for now, in order to expedite actions to protect public health against the identified hazards of methyl bromide.

2. Application of an additional uncertainty factor to protect infants and children appears to be warranted based on the acute neurotoxic effects of methyl bromide and the data gap for a developmental neurotoxicity study under Federal Insecticide, Fungicide and Rodenticide Act (FIFRA).

3. The methyl bromide RCD does not include adequate information on chloropicrin toxicity, exposure, and interaction with methyl bromide to address the risk of the formulations containing methyl bromide and chloropicrin. This is especially important for those formulations that contain a large proportion of chloropicrin (up to 1:1 with methyl bromide in some cases). Because chloropicrin is much more acutely toxic than methyl bromide (up to about 50 times more potent as an irritant), the acute hazard from the use of some mixtures will be dominated by the effects of chloropicrin. Without this information, the development of mitigation measures might be based on an insufficient analysis of the toxicity of the formulated products. However, the calculated margins of exposure based on methyl bromide alone are so small that any further delay to address the chloropicrin toxicity issues would be counterproductive.

4. Concerns regarding the reliability of the recovery calculations add significant uncertainty to the exposure calculations. Based on information presented at a symposium in June, methyl bromide exposure levels using the results of past ambient air sampling appear to be at least 40% greater than presented in the draft RCD, with correspondingly lower margins of exposure (MOEs).

5. The inclusion of "reference exposure levels" (RELs) with observed exposure levels would be appropriate in order to compare health-based exposure levels with measured air levels. Some

discussion of these limitations is needed in the technical summary and risk appraisal sections. When possible, additional analysis (such as for a characterization of dermal exposures) would be helpful. Inclusion of a summary of chloropicrin toxicity would be important in order to provide an adequate characterization of the risks posed by the use of methyl bromide-containing products in California.

Most of the MOEs for worker exposure scenarios presented in the draft RCD are less than 100, and some are below 1.0, especially for acute exposures (Tables 21 to 24). Assuming that the document was revised to address our technical concerns, these MOEs would be even lower. Given the very low MOEs, it is not clear how the use and exposure pattern could be changed to protect workers. We request an opportunity to comment on the draft mitigation proposals for methyl bromide before they are finalized.

Thank you for the opportunity to comment on the draft RCD for methyl bromide. If you have any questions about our comments, please contact Dr. Michael J. DiBartolomeis or me at (510) 622-3170.

Attachment

cc: Joan E. Denton, Ph.D., Director, OEHHA
Val F. Siebal, Chief Deputy Director, OEHHA
George V. Alexeeff, Ph.D., DABT, Deputy Director for Scientific Affairs, OEHHA
Michael J. DiBartolomeis, Ph.D., PETS/OEHHA

Attachment

Comments on the Draft Toxic Air Contaminant Document
for Methyl Bromide

General Comments

The draft risk characterization document (RCD) for methyl bromide is one of the more comprehensive and well-written risk characterizations prepared by DPR under SB 950 to date. We agree with the selection of critical studies and their respective lowest-observed-adverse-effect-levels (LOAELs) or no-observable-adverse-effect-levels (NOAELs). We also acknowledge that the developmental effects of methyl bromide have been discussed extensively. The citation and incorporation of relevant information from the published literature is much more comprehensive than in earlier documents. However, a few other articles may be worth noting, as listed at the end of these comments.

The draft RCD addresses only inhalation exposures to methyl bromide and this is appropriately reflected in the title of the document. The rationale that the Department of Pesticide Regulation (DPR) provides for only considering inhalation exposures in this document is that the majority of exposures to methyl bromide are via inhalation and other exposures such as from dietary residues would be relatively small. We have been informed that a dietary risk characterization is under preparation. Nevertheless, a complete assessment of the risk of methyl bromide from airborne exposures would include characterization of at least dermal exposures to methyl bromide. This is especially important for those scenarios in which dermal contact is the primary source of exposure, such as for workers who wear respirators in areas with relatively high concentrations of methyl bromide (see specific comments).

The application of an additional uncertainty factor to protect infants and children appears to be warranted based on the acute neurotoxic effects of methyl bromide. Neurotoxicity is a major effect of methyl bromide in critical acute, short-term, and subchronic toxicity studies. There is evidence suggesting that children may be more sensitive to these effects than adults. There is also a lack of appropriate neurotoxicity studies to assess the risks of methyl bromide exposure to infants and children. Under the Federal Insecticide, Fungicide and Rodenticide Act, there is a data gap for a developmental neurotoxicity study. We agree with the conclusions in the draft RCD that the calculated margins of exposure (MOEs) categories of workers are extremely low and present a potential health hazard to workers. However, we conclude that the benchmark of 100 for an MOE, which is stated in the draft RCD, is not adequate for short-term exposures of methyl bromide to infants and children. Therefore, we recommend the use of an additional uncertainty factor for potential developmental neurotoxicity, where appropriate.

Recent information presented by DPR staff at a symposium on June 29, 1999 indicated that methyl bromide exposures using ambient air sampling are likely to be underestimated because the

analyses utilized inaccurate recovery estimates. We interpret these findings to mean that actual exposures are at least 40% greater than estimated in the draft RCD, with correspondingly lower MOEs (see specific comments). We recommend that these recent results on air monitoring be described in the RCD.

Chloropicrin is used with methyl bromide in various products at ratios varying from approximately 1:400 to 1:1. Because chloropicrin is much more acutely toxic than methyl bromide (up to about 50 times more potent as an irritant), the acute hazard from the use of some mixtures will be dominated by the effects of chloropicrin. Additive or even synergistic effects are possible, but are not adequately discussed in the draft RCD (mentioned only in Table 7, Appendix E). The minimal discussion of this co-active ingredient in methyl bromide formulations leaves a major gap in the characterization of the toxic potential resulting from use of methyl bromide products. However, because of the magnitude of the hazard as described, we do not recommend delays in completion of this document to address the additional concerns about combined exposures.

An MOE of 100 based on the use of animal studies is generally considered to be a "benchmark MOE" and adequately health-protective by DPR. However, during our joint meeting on July 14, 1999 in Davis, we agreed that an MOE of 100 is not adequately health-protective in all situations for all persons. Therefore, we recommended that in addition to MOE calculations, the RCD include reference exposure levels (RELs) which include appropriate uncertainty factors to protect the health of the most susceptible individuals. When measured or estimated exposure levels are compared to RELs, it is easier to determine by how much an actual or estimated exposure is above or below a health-protective exposure level. The inclusion of RELs should give a more complete characterization of risk than the inclusion of MOEs alone.

While not a part of this draft RCD, we reviewed the document entitled "Toxicological Endpoint Evaluation and Exposure Assessment for Methyl Bromide" prepared by the Methyl Bromide Industry Panel (MBIP) of the Chemical Manufacturer's Association. We also read DPR's memorandum (dated September 25, 1998) containing comments on MBIP's document. We agree with DPR's evaluation of MBIP's document.

Specific Comments

We found the organization of the draft RCD, particularly in the appendix section, to be confusing. For example, duplication of appendices with the same letters (appendices to the draft RCD and sub-appendices to Appendix E) presented some difficulty. This problem is only partially solved by the page numbering (E1, E2, etc.), and the double numbering of many pages lends additional confusion. We recommend using two independent systems for identifying the respective appendices, such as A, B, C and I, II, III.

A discussion of the potentially increased sensitivity of the more susceptible subpopulations, as provided on page 124, should be added to the technical summary on page 7.

We note that 2.8 million pounds of chloropicrin were used in 1997, compared to 15.7 million pounds of methyl bromide (Pesticide Use Report, DPR, 1997). This is particularly relevant in applications to strawberries, for which methyl bromide use in 1997 was 4.1 million pounds, and chloropicrin use was 1.9 million pounds (presumably applied together). Because the volatility and evaporation rate of chloropicrin is lower than that of methyl bromide, it is likely that chloropicrin persists longer in the environment. Therefore, measured levels of methyl bromide in ambient air would not accurately predict chloropicrin levels based on the initial mixture ratio. For example, the observed methyl bromide to chloropicrin ratio after soil fumigation was 1.66 (1133/681 = 1.66) and 37.8 (900/23.8 = 37.8) in the field and 20 yards away from the field, respectively (page 17, first paragraph, last line). Therefore, it appears that the longer-duration inhalation exposures from use of the combined products could be essentially chloropicrin exposure. Due to the low margins of exposure calculated for the inhalation exposure alone, any further delay to address methyl bromide and chloropicrin co-exposure would be inappropriate. However, these issues could be addressed in the RCD dealing with exposures to methyl bromide in food.

III.D.1. Inhalation - rat

There are some discrepancies between the description given in the toxicology summary for the inhalation toxicity study in rats and in the discussion in the text of the draft RCD. For example, there is no discussion of granular cell myoblastoma at the 30 ppm dose level in the draft RCD as indicated in the toxicology summary.

III E.4. In vitro and in vivo human studies

The draft RCD provides a discussion of the polymorphism of glutathione-S-transferase and its effects on methyl bromide toxicity and mutagenicity. Since glutathione also activates chloropicrin (Schneider et al., 1999), an overall discussion of these two chemicals and the effects of glutathione-S-transferase polymorphism would have been appropriate in this section. We acknowledge, as discussed at the July 14 workshop in Davis, that the effect of this polymorphism on human sensitivity cannot be determined at this time. Nevertheless, we still recommend that additional discussion in the document, such as what was presented by the primary author of the draft RCD at the workshop, would be useful.

III F. & G. Reproductive and developmental studies

It would be worth noting and citing the other rat and rabbit developmental toxicity studies for which data have been submitted to DPR (Appendix D). At least two of these data sets have also been reported in the published literature (Kaneda et al., 1993, 1998).

IV.B. Exposure assessment

Risk evaluations in the draft RCD are based on the inhalation route and occupational exposures only, and do not account for other routes and aggregate exposures. It is possible that a soil fumigant worker could live in a nearby home and have additional residential exposures to methyl bromide. This could be discussed in the context of number of days exposed in the exposure assessment.

Information presented by DPR staff at a methyl bromide symposium on June 29, 1999 indicated that methyl bromide exposures using ambient air sampling with charcoal tubes are likely to be underestimated because the analyses utilized inaccurate recovery estimates. One of the authors of the report entitled "Evaluation of charcoal tube and SUMMA canister recoveries for methyl bromide air sampling" (DPR, EH 99-02) raised the issue that due to the inaccurate recovery estimates, actual exposures may be at least 40% greater than earlier estimates (as presented in the draft RCD). This was based on a mean methyl bromide recovery from field spikes using charcoal tubes of 49%, compared to the previously used values of 69% to 88% (pages E51 to E95). Data from one six-hour day time collection (EH 99-02, Table 6) showed average recoveries of only 23%. The authors conclude "To account for these differences, DPR will review air concentrations listed in past studies and make appropriate adjustments, and will review the methyl bromide sampling methodology used in future studies." The authors also state, "The fact that 6-hour sampling with charcoal tubes during the day recovered less methyl bromide than 12-hour sampling with charcoal tubes at night needs further study" (EH 99-02, page 5). We agree with these conclusions and recommend that the exposure calculations presented in the draft RCD be re-evaluated based on the new recovery data. Based on the discussion at the symposium, the MOEs for methyl bromide that rely on the results of the ambient air monitoring are likely to be significantly lower than those presented in the draft RCD.

We cannot comment much on the quantitative significance of dermal exposure to methyl bromide and the potential risks of consuming treated produce because these analyses were outside the scope of the draft RCD. Some discussion of these additional exposure routes and mechanisms would be useful in the document.

For example, the draft RCD assumed a personal protection factor of 10,000 (based on the NIOSH guidelines for self-contained breathing apparatus) used during space fumigation at a brewery (page E92, Table 32). This appears to be the protection factor for respiratory hazard only, which would not incorporate the potential for dermal exposures. However, methyl bromide can be absorbed through skin and high concentrations have been noted to cause dermal toxicity (page 15, paragraph four). Chloropicrin also has a high skin hazard rating. Assuming under the conditions of space fumigation that dermal exposure would provide about 1 to 5% of the unprotected inhalation dose, dermal exposure would be 100 to 500 times greater than that received by inhalation during this task assuming the mask truly provides a 10,000-fold inhalation protection factor. Therefore, the acute MOEs for the brewery activities would be in the range of about 1 to 10, rather than 241 to 1,458, as stated in the draft RCD. Failure to address the potential hazard from dermal exposures when working in a high-concentration environment, wearing respiratory protection, is a significant limitation of the RCD. This specific analysis should be included

regardless of the extent of the general discussion on dermal exposure that is added based on our previous comments.

IV.C. Risk characterization

MOEs for approximately 25% of the acute, 26% of the short-term, and 50% of the seasonal exposure estimates are below 100 (Tables 21 to 24). Most of these MOEs are in the range of 1 to 50 and some are even less than 1.0, especially for the seasonal exposure scenarios. Actual exposures will vary widely from the mean values given, and are likely to be underestimated because of the apparently erroneous methyl bromide analytical recovery values used for these calculations in the draft RCD. This suggests an ongoing hazard to workers from the use of this pesticide.

Limitations and uncertainties of the exposure assessment are presented in Appendix E (Exposure Appraisal, page E35). For example, the use of repeated estimates from one location, lack of recovery study and standards, missing application rates, and limited data on frequency and duration of exposures might affect the MOEs. While this is a useful qualitative discussion, it could be improved by adding a more quantitative discussion of the variability of the exposure estimates (i.e., the distribution of potential acute, short-term, and seasonal exposures).

In several instances a default exposure estimate of 210 ppb has been used in the exposure assessment calculation (see page E103, Table 37) because of its designation as a "regulatory limit under permit conditions" (page 13, paragraph four). The calculated MOEs should be based on actual or estimated exposures, not on a "regulatory limit" that might not be solely health-based. We recommend that risk estimates calculated based on the "regulatory limit" of 210 ppb also be calculated based on actual or estimated exposures, providing a range of values in the RCD if necessary.

V. Risk appraisal

The risk appraisal is well written and comprehensive for inhalation exposures. As already noted the need for further incorporation of other exposure routes (especially dermal exposures), and combined exposures with chloropicrin should be acknowledged in the risk characterization and Executive Summary.

References

De Vreede et al. (1998). Exposure to methyl bromide during greenhouse fumigation on Crete, Greece. Arch Environ Contam Toxicol 35(3):539-547.

Dimitriou and Tsoukali (1998). Personal and environmental air sampling of methyl bromide during experimental greenhouse fumigation. J Environ Health B 33(3):267-277.

Garry et al. (1990). Preparation for human study of pesticide applicators: sister chromatid exchanges and chromosome aberrations in cultured human lymphocytes exposed to selected fumigants. Teratogen Carcinogen Mutagen 10(1):21-29.

Goldman et al. (1987). Acute symptoms in persons residing near fields treated with the soil fumigant methyl bromide and chloropicrin. West J Med 147(1):95-98.

Horowitz et al. (1998). An unusual exposure to methyl bromide leading to fatality. J Toxicol Clin Toxicol 36(4):353-357.

Kaneda et al. (1993). A two generation reproduction study in rats with methyl bromide fumigated diet. Food Chem Toxic 31:533-542.

Kaneda et al. (1998). Oral teratogenicity studies of methyl bromide in rats and rabbits. Food Chem Toxicol 36(5):421-427.

Schneider et al. (1999). Glutathione activation of chloropicrin in the Salmonella mutagenicity test. Mut Res 439:233-238.

Wilson et al. (1998). Methyl bromide: 1-year dietary study in dogs. Food Chem Toxicol 36(7):575-584.

Wong et al. (1984). Mortality of workers potentially exposed to organic and inorganic brominated chemicals, DBCP, TRIS, PBB, and DDT. Brit J Indust Med 41:15-24.