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Office of Environmental Health Hazard Assessment

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MEMORANDUM

TO: Chuck Andrews, Chief
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FROM: Anna M. Fan, Ph.D., Chief MMF for AMF
Pesticide and Environmental Toxicology Section

DATE: March 11, 2003

SUBJECT: COMMENTS ON THE RISK CHARACTERIZATION DOCUMENT FOR INHALATION EXPOSURE TO METHYL BROMIDE, ADDENDUM TO VOLUME I, PREPARED BY THE DEPARTMENT OF PESTICIDE REGULATION

As part of its public notification process, on February 25, 2003, the Department of Pesticide Regulation (DPR) made available the document entitled "Methyl Bromide: Risk Characterization Document Inhalation Exposure, Addendum to Volume I." The February 2003 document is an addendum to the original methyl bromide (MeBr) inhalation risk characterization document (RCD), which the Office of Environmental Health Hazard Assessment (OEHHA) submitted comments in September 1999 (OEHHA 1999). OEHHA has obtained a copy of the 2003 RCD addendum and has reviewed relevant sections of the document. It should be noted that OEHHA did not receive this document as part of its consultation and peer review authority and function under the Health and Safety and Food and Agricultural Codes, but rather as a member of the public at large. Furthermore, because of the short time frame for reviewing and providing comments on the MeBr RCD addendum, we have limited our comments in this memorandum to only those we consider most essential to the rulemaking process. Overall, OEHHA does not agree with the main scientific findings in the RCD addendum, as discussed in greater detail below and in the attachment.

OEHHA previously reviewed and submitted comments on the three-part RCD for MeBr prepared by DPR over a period of approximately three years. As you know, the three-part document consists of an RCD for inhalation exposures (volume I), an RCD for dietary exposures (volume II), and an aggregate exposure (inhalation plus dietary) RCD (volume III). The inhalation RCD for MeBr characterizes the risks for acute, short-term (one week), subchronic (greater than one month), and chronic exposures in humans (DPR 2002). For assessing

short-term (one week) inhalation exposure to MeBr, a no-observed-adverse-effect level (NOAEL) of 20 ppm was selected from the toxicology data and used in the RCD to calculate margins of exposure (MOEs). This NOAEL is based on neurotoxicity (convulsion, paresis) in rabbits at the next highest dose used in the study (70 ppm) for one week (Sikov et al. 1981). For subchronic exposure of longer duration (greater than one month) a NOAEL of 0.5 ppm was estimated from a lowest-observed-adverse-effect level (LOAEL) of 5 ppm for decreased responsiveness in two out of eight dogs observed after 34 exposure days (Newton 1994). It should be noted that in the review draft of volume III of the MeBr RCD (aggregate exposure), subchronic exposures to MeBr were not addressed.

In the 2003 addendum to the MeBr inhalation RCD, DPR identified a new study and critical effect level to use in the characterization of MeBr risk and for estimating public health protective target levels for mitigation. The 2002 MeBr inhalation RCD used the LOAEL of 5 ppm for the most sensitive toxic effect of neurotoxicity in dogs from the Newton (1994) study to estimate a NOAEL of 0.5 ppm. The 2003 addendum to the inhalation RCD identifies three possible NOAELs of 5, 10, or 20 ppm from the Schaefer (2002) study, depending on the endpoint selected. The target air concentration level chosen from the risk assessment will drive regulations that are developed to protect residents and workers from subchronic (seasonal) exposures to MeBr.

Under Food and Agriculture Code, Section 13129, DPR is required to grant to OEHHA access to the mandatory health effects studies and other health effects studies on file at DPR. OEHHA, based on its review of the data provides advice, consultation, and recommendations to DPR concerning the risks to human health associated with exposure to the substances tested. Under this authority, we obtained and reviewed relevant portions of the Schaefer (2002) study. We have included our analysis in the attachment to this memorandum.

Based on our review of the Schafer (2002) and the Newton (1994) studies, the relevant documentation prepared by DPR, information provided by several reviewers of the study, and the guidelines for conducting toxicity studies developed by the U.S. Environmental Protection Agency (U.S. EPA) we have arrived at the following conclusions. Although, neither the Newton (1994) nor the Schaefer (2002) study meets the U.S. EPA guidelines for conducting a subchronic (90-day) inhalation study or for the neurotoxicity screening battery, there were no reported problems in study design or conduct to suggest that the finding of reduced responsiveness at 5 ppm in Newton (1994) was not reliable. We are unable to identify any scientific basis for giving more weight to the finding of decreased proprioceptive placing at 10 ppm in Schaefer (2002) compared to the toxic effect noted at 5 ppm in the Newton (1994) study. In fact, the results of the Schaefer (2002) study support the selection of 5 ppm from the Newton (1994) study as a LOAEL.

Therefore, for the purposes of risk assessment and mitigation, OEHHA finds that the results of the Newton (1994) study provide sufficient evidence for the most sensitive toxic effect of MeBr (i.e., decreased responsiveness in dogs) to be used as an end point for subchronic (seasonal) exposures. We do not agree that the results of the Schaefer (2002) should be used for risk assessment or as the basis for developing worker health and safety standards or field fumigation regulations and mitigation measures. We also find that the available toxicology data for subchronic exposures in non-rodent species are generally of poor quality.

In addition to the selection of the appropriate toxicity endpoint for risk assessment, we note that the addendum to volume I of the RCD still leaves unresolved two major concerns we had concerning the original RCD, which we previously raised (OEHHA 2000) about the health effects of chloropicrin and MeBr mixtures and the protection of infants and children. Data obtained from a developmental neurotoxicity study for MeBr could help clarify the degree of susceptibility of this vulnerable subpopulation. Furthermore, we recommend that subchronic aggregate (oral, dermal and inhalation) exposures be estimated and compared to subchronic risks of exposure to MeBr by inhalation alone.

Based on our review, we support the use of 1 ppb as the target air concentration for subchronic exposures due to the overall poor quality of the data, the uncertainty in the protection of infants and children, and the uncertainty in the evaluation of MeBr/chloropicrin formulations.

If you have any questions concerning our comments or recommendations, please 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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Deputy Director for Scientific Affairs
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Michael J. DiBartolomeis, Ph.D.
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Attachment

Comparison of Two Inhalation Toxicity Studies in Dogs for use in Risk Assessment of Methyl Bromide

The February 2002 risk characterization document (RCD) for methyl bromide (MeBr) (DPR 2002a) estimates a no-observed-adverse-effect level (NOAEL) of 0.5 ppm from 5 ppm, which was identified as a lowest-observed-adverse-effect level (LOAEL) from a six-week inhalation dog study (Newton, 1994). The NOAEL of 0.5 ppm was used by the Department of Pesticide Regulation (DPR) to calculate margins of exposure (MOEs) for subchronic (seasonal) MeBr exposure in the RCD. The Newton study utilized a dose range including controls (no exposure) and 5, 26, 53, 103, and 158 ppm methyl bromide. In this study, female dogs exhibited reduced absolute spleen weights and two of the four female Beagle dogs exhibited decreased responsiveness at the lowest dose of 5 ppm after 30 exposure days. This latter observation was made by a trained neurologist as part of a series of scheduled neurological exams performed at pretest, after four weeks and after six weeks of exposure. Importantly, the endpoint of reduced activity and responsiveness demonstrated a dose response for time of onset, with earlier onset as the dose was increased (DPR 2003, Appendix E, page 74, Table 1). In our September 1, 1999 comments, we stated, "we agree with the selection of critical studies and their respective lowest-observed-adverse-effect-levels (LOAELs) or no-observable-adverse-effect-levels (NOAELs)" (OEHHA 1999).

The results of the Newton (1994) study in dogs raises concerns about the neurotoxic effects of MeBr inhalation exposure at 5 ppm. In a review commissioned by DPR, at least one member of the Subcommittee for the Review of the Risk Assessment of Methyl Bromide for the National Academy of Sciences (NAS) believed that the results of the Newton (1994) study were "subjective and spurious" because a formal protocol for neurological examination and/or testing was not followed, and the objective of the study was to determine tolerable exposure levels for a proposed long-term inhalation toxicity study (NRC 2000). This opinion was expressed primarily by Dr. Janice Chambers. In her evaluation of the Newton (1994) study, Dr. Chambers stressed that the Newton (1994) study was only a pilot study with the focus on determining exposure levels for a chronic study, which never was conducted subsequently. In our opinion, these criteria for rejection of Newton (1994) are not widely upheld in the scientific community and do not invalidate its use to identify a NOAEL for risk assessment purposes.

In response to the NAS report, the Alliance of the Methyl Bromide Industry commissioned a supplemental study to further examine the neurotoxic effects in dogs ("A Six-Week Inhalation Toxicity Study of Methyl Bromide in Dogs," Schaefer, 2002). According to Schaefer (2002), the rationale for conducting this study was that the observation of decreased responsiveness in two female dogs were "unscheduled observations" (i.e., not planned as part of a formal protocol) from Newton (1994) and, therefore, the study results are equivocal. Dr. Chambers was retained by the registrant to review the Schaefer study protocol and results. The results of the Schaefer (2002) study were subsequently submitted to DPR in 2002 for consideration.

According to the study investigators, the inhalation study in dogs (Schaefer, 2002) was specifically designed to evaluate neurotoxic effects within a time period of six weeks. In this study, groups of four male and four female Beagle dogs were exposed to MeBr at targeted air concentrations of 5, 10, or 20 ppm. A control group of four male and four female dogs was exposed to clean, filtered air under comparable conditions as the MeBr exposed animals. The dogs were exposed on a seven-hour/day, five-day/week basis for six consecutive weeks. According to the documentation we reviewed, clinical examinations were performed at least once daily. Tabletop functional observation and measurement, open field observation, and locomotor activity assessments (all part of a functional observation battery or FOB) were conducted in weeks 2, 4 and 6 after the start of exposure. Physical exams were conducted weekly and necropsies were performed on all animals. Neurologic tissue was examined microscopically. As described in Table 1 (DPR 2003, page 7), various peer reviewers of the study made one of three observations about the results: 1) the lowest dose of 5 ppm is a LOAEL based on tremors, twitching and emesis in a single animal; 2) the lowest dose of 5 ppm is a NOAEL based on a dose responsive decrease in proprioceptive placing beginning at 10 ppm; or 3) the highest exposure level of 20 ppm is a NOAEL based on the absence of adverse effects at any exposure level (DPR 2003, page 7, Table 1).

The Office of Environmental Health Hazard Assessment (OEHHA) independently reviewed the Schaefer (2002) study in order to make a determination as to its usefulness for risk assessment and for developing mitigation options. In reviewing the Schaefer (2002) study, we asked the following questions:

1. In comparing the two studies, is the Schaefer (2002) study clearly superior to the Newton (1994) study in terms of study design for addressing neurotoxicity according to U.S. Environmental Protection Agency (U.S. EPA) guidelines (U.S. EPA, 1998a)?

2. Does the Schaefer (2002) study meet the requirements for a subchronic inhalation study according to U.S. EPA guidelines (U.S. EPA, 1998b)?

3. Should the results of the Schaefer (2002) study replace the results of Newton (1994) for use in risk assessment?

4. Should the results of the Schaefer (2002) study be used to support or revise mitigation measures and field fumigation regulations?

Table 1 summarizes some basic design features of the two available toxicity studies (Newton, 1994 and Schaefer, 2002) for evaluating seasonal (i.e., subchronic) inhalation MeBr exposure. We compared the design of the two studies with the guidelines developed by U.S. EPA for a neurotoxicity testing battery (U.S. EPA, 1998a) and for 90-day inhalation toxicity studies (U.S. EPA, 1998b) under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Toxic Substances Control Act (TSCA).

Table 1. Comparison of the "Subchronic" Methyl Bromide Inhalation Toxicity Studies Dogs

	Newton (1994)	Schaefer (2002)	U.S. EPA Guidelines (1998a)	U.S. EPA Guidelines (1998b)
Study type	Pilot study for chronic inhalation toxicity study.	Designed to test for neurotoxicity in dogs following "subchronic" inhalation exposure.	OPPTS Number 870.6200 "Neurotoxicity Screening Battery."	OPPTS Number 870.3465 "90-Day Inhalation Toxicity."
Length of exposure	34 exposure days (six weeks total)	30 exposure days (six weeks total)	90 days for subchronic inhalation toxicity study.	Refer to guidelines for subchronic testing.
Exposure levels	24 days: 0, 11, 26, 53, or 103 ppm. 30 days: dogs treated w/11 ppm dosed w/ 158 ppm for 6 more days. 34 days: 0 or 5 ppm.	30 days: 0, 5, 10, or 20 ppm	Doses levels should be adequately spaced and selected to maximally support detection and dose-response relations.	At least 3 dose levels plus control. Doses levels should be adequately spaced.
Selection of dose levels	Dose-response observed for decreased responsiveness.	Dose-response observed for decreased proprioceptive placing.	High dose should result in significant neurotoxic effects.	Intermediate dose levels should produce gradation of toxic effects and the highest dose tolerated (not fatal).
Number of animals[1]	4 Beagle dogs/sex/ group	4 Beagle dogs/sex/group	At least 10 male and 10 female animals for each dose and controls.	At least 10 male and 10 female animals for each dose and controls.

Newton (1994) is a pilot study designed to determine exposure levels for a long-term chronic toxicity study. It was not designed to specifically address neurotoxicity and therefore the study design does not meet the criteria for the neurotoxicity screening battery. We did not find

[1] The rat is the preferred species for mammalian testing for inhalation exposures. If another species is used, justification for its selection should be provided although the guidelines for neurotoxicity screening state "not all of the battery may be adaptable to other species."

guidelines published by U.S. EPA for conducting pilot (dose-range finding) studies. Because of the study duration and the number of animals used (see Table 1), Newton (1994) also does not meet the guidelines for conducting a subchronic inhalation study (90 days). However, the use of the results from this study for assessing risks from seasonal exposures to MeBr, as was done in the initial inhalation RCD (DPR 2002a) is justified because: 1) frank toxicity was observed at the higher and intermediate doses, 2) a dose-response was demonstrated, and 3) the toxicity (e.g., behavioral effects) was consistent with the demonstrated neurotoxic potential of MeBr in other species.

We agree that the intent of the Schaefer (2002) study design was to address neurotoxicity concerns from subchronic MeBr inhalation exposure. However, the Schaefer (2002) study does not meet some basic design parameters for either the U.S. EPA guidelines for neurotoxicity screening battery or for conducting a 90-day inhalation toxicity study (Table 1). DPR (2002b) also points out major study deficiencies in its review of the Schaefer (2002) study. These flaws include a failure to control the MeBr concentration during some exposure intervals, possible variability in the cumulative hours of exposure per week prior to behavioral testing, inadequate positive control data for the FOB and motor activity measurements, inadequate histological evaluation, and failure to adequately document purported idiopathic febrile necrotizing arteritis in a single male dog exposed to 5 ppm MeBr. Schaefer (2002) also does not meet U.S. EPA guidelines for subchronic (90-day) inhalation testing. Not only is the dose selection narrow, but the number of animals per dose level per sex is too small. Furthermore, the study was conducted for six weeks and not for 90 days as stated in U.S. EPA's guidelines.

In our opinion, both the Newton (1994) and Schaefer (2002) studies have limitations in study design. The same conclusion was reached by DPR in its review of the two studies (DPR 1994; 2002b). In our evaluation of the two studies, we conclude that neither meets the U.S. EPA guidelines for a properly conducted subchronic (90-day) inhalation study or for the neurotoxicity screening battery. Both have been designated "Supplemental" by DPR with major study deficiencies (DPR 1994; 2002b). However, none of the reported problems in study design or conduct suggest that the finding of reduced responsiveness at 5 ppm in Newton (1994) was anything less than reliable. Therefore, OEHHA was unable to identify any scientific basis for giving more weight to the finding of decreased proprioceptive placing at 10 ppm in Schaefer (2002) compared to the toxic effect noted at 5 ppm in the Newton (1994) study. In fact, the results of the Schaefer (2002) study support the selection of 5 ppm from the Newton (1994) study as a LOAEL. Therefore, for the purposes of risk assessment and mitigation, OEHHA determines that the results of the Newton (1994) study provide evidence for the most sensitive toxic effect of MeBr, (i.e., decreased responsiveness in dogs) to be used as an end point for subchronic (seasonal) exposures. Furthermore, this behavioral endpoint exhibited a dose response and agrees well with other studies demonstrating MeBr neurotoxicity in a variety of species (DPR 2003).

In conclusion, OEHHA continues to support the use of the Newton (1994) results, from which a LOAEL of 5ppm is identified, for subchronic risk assessment of MeBr. The Schaefer (2002) results provide additional support for the neurobehavioral effects seen in the Newton (1994) study, but should not be used to replace the results of the Newton study.

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