Appendix A - Comments submitted

1. Ann Katten (California Rural Legal Assistance Foundation)
2. William Mendez (private citizen)
3. Anna Fan (Pesticide and Environmental Toxicology Section, Office of Environmental Health and Hazard Assessment, OEHHA)
4. Val F. Siebal (Office of Environmental Health Hazard Assessment)
5. Linda McElver (with additional comments from Karl Kempton and Michael Kaplan)
6. Judy Buelke-Sam (Toxicology Services, submitted by the AMBI)
7. Gerald Schaefer (WIL Research Laboratory Study Director, submitted by AMBI)
8. Vince Piccirillo (VJP Consulting, Inc., submitted by AMBI)
9. Bob Klein (California Pistachio Commission)
10. Rodger Wasson (California Strawberry Commission)
11. California agricultural groups

#003-0025

California Rural Legal Assistance Foundation

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February 21, 2003

Paul Helliker, Director
Department of Pesticide Regulation
Sacramento CA 95814

Dear Mr. Helliker:

The discussion section of the DPR Methyl Bromide Toxicology Study Evaluation Worksheet (6 week Dog study) dated August 16, 2002 requests the following additional information about the study from the sponsor and laboratory. I would like to know whether or not additional information has been provided to DPR by the study sponsors in each of these areas. I am also writing to request copies of any supplemental DPR evaluations of this study including but not limited to evaluations of any additional data submitted by the sponsor or laboratory.

Summary of additional information requested from study sponsors in Toxicology Study Evaluation Worksheet:

1) Individual temperature data (for the dogs) showing the date (with time of day) when (temperature was) recorded. (pg 22 pt VI.A.1.a)

2) The basis for classifying (dog) ID no 8738 as lethargic should be explained and this should be compared to the degree of lethargy that has been described in the literature for dogs exhibiting febrile necotizing arteritis. (pg 22 pt VIA.1.b)

3) The basis for classifying ID no 8738 as having stiffness should be explained fully. All data and protocol-deviation documentation should be submitted and an explanation for how this could have been missed by personnel who did FOB testing should be supplied.(pg 22 pt VIA.1.c)

4) Hematology data should be supplied including whether or not any followup blood tests were conducted to verify the diagnosis of idiopathic febrile necrotizing arteritis. (pg. 23 pt VIA.1.d)

5) Negative control histological data for male beagle dogs of comparable age should be supplied (pg. 23 pt VIA.1.e)

6) Data concerning observations of diarrhea in ID no 8738 on nonexposure days should be supplied (pg 24 pt VIA.1.e)

7) Data on chamber loading patterns and all GC readings through Jan 11 should be supplied. (pg 24 pt. VIA.2.a,b)

8) Information as to whether the two dogs which were replaced were monitored for effects.

9) What happened (with mebr generating system) after December 27 (with GC) data and how it was corrected should be explained.

10) Positive control data for dog FOB testing and nervous system pathology should be supplied.

11) Identities of the FOB evaluators and operators of the motor activity measurement aparatus should be provided (via initials) with synopses of the training they received.

12) Information on how many hours of exposure occurred for each animal before each FOB testing should be supplied.

13) Fine motor activity data and ambulatory data should be reported separately and analyzed separately using statistics.

14) How the findings from record 132821 were used to guide the histological work should be explained.

15) Histological work involving the nervous system should be extended to include testing with an appropriately selected battery of specialty stains. If this can not be done, the reasons should be explained. (pg. 27 c2)

16) Further information on clinical exams should be provided including whether personnel who did the mid exposure and postexposure clinical exams on these Sundays were the same who did the weekday exams.

Please contact me at 446-7904 x 19 if you have any questions about this request.

Sincerely,

Anne Katten

Anne Katten, MPH
CRLA Foundation

CC: Tobi
Gary
PG
PH

"What Should Be The Subchronic Regulatory Goal For Methyl Bromide And Why?" – Comments submitted to CDPR Workshop on Risk Management Considerations for Methyl Bromide Subchronic Toxicity, February 27, 2003

Introduction

My name is William Mendez, Jr. I am an environmental scientist employed by ICF Consulting of Fairfax, Virginia. I have a Ph.D. in Biochemistry from the University of Chicago and over 20 years of experience in science and policy consulting and environmental risk assessment. I have conducted a number of risk assessment for pesticides and air pollutants for the U.S. Environmental Protection Agency and other clients.

In agenda for this meeting, attendees were invited to answer the question "What should be the Subchronic Regulatory Goal for Methyl Bromide?" This is a very broad question, and rather than presume to give an answer, I will instead comment briefly on the toxicological information and analyses presented in the CDPR Addendum to the Risk Characterization Document (CDPR 2003), and suggest concerns that have arisen in the course of my review.

My comments focus on apparent differences in the approach taken by CDPR from methods recommended in the most current Federal EPA guidance and recommendations (US EPA 2002a,b). Specifically, I believe that there are sufficient uncertainties in the toxicological database to warrant the use of one or more additional uncertainty factors for the protection of children's health in the RfC derivation, and that there are plausible grounds for characterizing the 5 ppm endpoint in the Shaefer dog study as a LOAEL instead of a NOAEL. If either of these suggestions is adopted, the result would be setting an RfC lower than that recommended in the Addendum to the Risk Characterization Document.

OVERVIEW OF TOXICOLOGICAL DATABASE FOR METHYL BROMIDE

I believe that the available data leaves a high degree of uncertainty regarding potential human health impacts from subchronic exposures, particularly in children, judging by commonly applied standards. I reach this conclusion because:

- While it is well-established that methyl bromide is a neurotoxin in animals and humans, that it is a reproductive toxin and teratogen, available human data are weak, and to my knowledge, there have been no studies on potential methyl bromide impacts on children,
- Animal studies indicate substantial interspecies variability in response,
- Available studies in most sensitive species (dogs) are of marginal quality,
- Important questions exist about the identification and significance of the critical toxicological endpoint in the dog studies,
- The developmental neurotoxicity of methyl bromide has not been evaluated, and
- The biochemical mechanisms through which methyl bromide produces adverse effects are not well understood

I believe that these limitations in the toxicological data suggest a higher level of caution may be appropriate in establishing acceptable subchronic exposure levels than has been adopted by CDPR in the Addendum. There are established procedures for addressing uncertainties in toxicity and exposure data, however...

THE NEED TO INCORPORATE CONSIDERATION OF UNCERTAINTIES RELATED TO EFFECTS ON CHILDREN INTO THE RfC DERIVATION

CDPR elected not to use additional uncertainty factors to protect against possible adverse effects in children when deriving the RfC for this group. It appears that this decision is not consistent with current practice. Most recent EPA guidance (US EPA 2002a) suggests that protectiveness to children be incorporated into pesticide risk assessment at two stages:

- During database evaluation, when the quality and quantity of data relating potential health impacts in adults and children should be incorporated into conventional uncertainty factors, including the "database uncertainty factor" (note that this is a standard practice for all assessments, independent of the specific provisions of the "FQPA"),
- During risk characterization, remaining concerns related to potential adverse effects in children should be considered, and may be addressed through the use of a "special FQPA factor"

CDPR elected not to include a Database Uncertainty Factor in the RfC calculation, despite the limitations of the toxicological database noted above. Of particular concern, in my judgement are:

- The marginal quality of Schaefer study, whose limitations were clearly noted by CDPR staff
- The data set for methyl bromide does not include a developmental neurotoxicity study
- The RfC was not set based on a developmental end point

I believe that the combination of these factors clearly warrant the incorporation of a database uncertainty factor into the RfC derivation. Doing so would reduce the estimated RfC for children by as much as factor of ten.

CDPR also elected not to include a "Special" FQPA factor to take into account concerns for children's health effects not addressed by the other uncertainty factors. This decision was taken despite the demonstrated neurotoxicity, teratogenicity, and reproductive toxicity of methyl bromide, factors which normally would have been considered in such a decision. Use of a special FQPA factor could also have resulted in as much as a ten-fold reduction in the estimated RfC.

There may be adequate reason not to use both the database factor and the special FQPA factor in the same assessment, but the decision to use neither seems to be inconsistent with the level of uncertainty in the data and concern about children's health effects.

IDENTIFICATION OF 5 PPM AS THE NOAEL FOR PROPRIOCEPTIVE PLACING

There is also substantial question about whether to characterize 5 ppm in the Shaefer study as a NOAEL instead of a LOAEL. This question arises both from the shortcomings of the study itself, and questions about its interpretation. The limitations of the Shaefer study are discussed in detail by CDPR staff in Appendix E, and I will not repeat that discussion here, but simply note that most of the problems with the study tend to reduce its sensitivity, and the ability to accurately characterize dose-response relationships.

The specific technical reasons why it might be more appropriate to characterize 5 ppm as a LOAEL rather than LOAEL include:

- Emesis and eye discharge at 5 ppm were dismissed as not compound-related, despite staff interpretation that these effects could be part of a "spectrum of effects"
- A LOAEL of 5 ppm for reduced activity was found in Newton (1994) dog study
- Data from the Newton and Shaefer studies taken together suggest increasing incidence/severity of adverse effects with increased duration of exposure at lower exposure levels; that is, a case can be made that if Schaefer the study had gone longer, adverse effects could well have been clearly established at 5 ppm. This possibility is also noted by the CDPR staff in Appendix E.

If 5 ppm were characterized as a LOAEL instead of a ~~L~~NOAEL, the derived RfC could have been three- to ten-fold lower than the level selected by CDPR.

In closing, I want to stress that my review of the toxicological data and CDPR's proposed RfD decisions has been undertaken primarily with reference to current Federal EPA guidance and policy, and not in terms of the specific policy choice confronting CDPR. The views expressed are entirely my own and do not reflect the views of the ICF or any of our clients. Thank you.

References:

CDPR (2003), *Methyl Bromide Risk Characterization Document Addendum to Volume 1*, Medical Toxicology Branch, February 3.

US EPA (2002a), *Determination of the Appropriate FQPA Safety Factor(s) in Tolerance Assessment*, Office of Pesticide Programs, February 28.

US EPA (2002b), *A Review of the Reference Dose and Reference Concentration Processes*, Risk Assessment Forum, May.

LIVINGSTON & MATTESICH

WM. J. THOMAS
ATTORNEY AT LAW

March 4, 2003

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Paul Helliker
Director
Department of Pesticide Regulation
1001 "I" Street
Sacramento, California 95814

Paul Gosselin
Chief Deputy Director
Department of Pesticide Regulation
1001 "I" Street
Sacramento, California 95814

Dear Messrs. Helliker and Gosselin:

In follow up to our recent meeting on the Methyl Bromide dog study and determination of an appropriate NOEL we herewith submit a written report from Dr. Buelke-Sam, one of the nation's leading experts on FOB studies. Please add that to the weighty pile of real expertise which supports that the reflex observation of one dog is not an effect determination and that 20 pp6 is the appropriate NOEL. The counter position from the UCD reviewers, who have no background experience or expertise in these study areas, pales by comparison.

We would also suggest that you contact EPA's Dr. Virginia Moses, who does have expertise in this study area and determine her assessment. She has informed us that she would be willing to review this issue but can only do so upon an EPA or DPR request.

Sincerely,

William J. Thomas/sma

WILLIAM J. THOMAS

WJT:sma
Enclosure
cc: Gary Patterson (w/encl.)

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Toxicology Services

February 22, 2003

Joseph Holson, Ph.D.
WIL Research Laboratories
1407 George Road
Ashland, OH 44805-9218

Dear Dr. Holson:

At your request, I have reviewed the report and data tables for Schaefer (2001) "A six-week inhalation toxicity study of methyl bromide in dogs," a study conducted by WIL Research Laboratories. In addition, I have reviewed the two expert opinions on interpretation of study results prepared by Drs. Kent E. Pinkerton and Jerold Last, both of whom are associated with the University of California, Davis. Both opinions include reference to a study interpretation/comments provided by Professor Janet Chambers, Mississippi State University; I did not receive the Chambers' commentary for review.

My interpretation of the results of this study agrees with the scientific judgments of the report author and the conclusions referred to from Dr. Chambers.

1) The veterinary diagnosis of beagle pain syndrome in dog #8738 from the 5-ppm exposure group seems clear and reasonable, and is the only potential finding that occurred in the low-exposure group.
2) The isolated occurrences of post-exposure lack of "visual placing" in 1/8 dogs from the 10-ppm exposure group and 2/8 dogs in the 20-ppm group are the only findings that occurred in the mid- and high-exposure groups.
3) There is no dose-dependent or time-dependent pattern of effects to suggest neurotoxicity occurred at any level of methyl bromide in this study.

The rationale for my interpretation of study results is discussed briefly below.

Method of Assessment. The functional observation battery (FOB) used in this study includes many components standard to neurological examinations routinely conducted in large animal toxicity studies, and additional components standard to many rodent FOBs designed for use in adult and developmental neurotoxicity studies. This particular battery included eight (8) individual assessments that rely on one or more aspects of visual function in these dogs: "menace" reaction, pupillary reflex, tracking, pupillary size, nystagmus, ocular position, cliff avoidance, "proprioceptive" placing. The manner in which the proprioceptive placing assessment occurred includes a visual component. The opinions of Drs. Pinkerton and Last suggest that visual neurotoxicity occurred in this study at exposure levels of 10 and 20 ppm In my experience, and as stated in veterinary diagnosis texts [1], animals that are comfortable being held in the position for this assessment may or may not display a "normal" visual placing response. There were no other indications of exposure-related findings to suggest a **pattern** of effects on the other seven (7) indicators of visual function, or

Toxicology Services:
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Greenfield, IN 46140
Buelke19@insightbb.com

on the many other tests that include proprioceptive or overall sensory function. In addition, a more specific, and in my estimation appropriate evaluation of proprioceptive placing would not include the visual component of the assessment as conducted here, but test the animal in a blinded (blindfolded) manner. Therefore, I do not consider the isolated findings to indicate any exposure-related effect on either visual or proprioceptive function.

Time-Response Effects. There was no FOB assessment of the animals following the first daily 7-hour exposure to assess any potential acute effects of methyl bromide in this study. The isolated findings of "visual placing" effects in 1/8 dogs each in the 10- and 20-ppm groups during 2-week and 4-week assessments did **not** occur at the final 6-week assessment – in my judgment the time interval for assessment required to demonstrate a specific, repeated exposure-related effect on this combined visual/proprioceptive response. Only a single dog in the 20-ppm group did not display the visual placing response at all three assessment periods. A single dog displaying a consistent, isolated post-exposure alteration in only one of many apical behavioral tests, regardless of exposure group, does not convince me that 20-ppm may be a LOEL for neurotoxicity in this study. The fact that this individual dog responded "normally" in the pre-exposure assessments is most likely due to handling and testing experience in this animal.

Dose-Response Effects. I do agree that, very often, functional indicators of neurotoxicity may be expected to occur at doses or exposure levels below those resulting in morphologic or histopathologic findings. I also agree that a single, isolated finding **may** have some relevance in estimating LOELs, but **only** if these occur in some dose-related or time-related pattern. In this study there was no expectation to define a very high-exposure effect to include pathologic indicators of exposure-related effects, since the exposure levels selected for use in this study of methyl bromide were rather low and were chosen to help delineate more clearly a NOEL/NOAEL following sub-chronic inhalation exposure in dogs. There also is no indication of any cross-assessment **pattern** of either visual or proprioceptive findings at any exposure level tested to suggest a dose-related response in this study. Therefore, I find no indication of any dose-response adverse effect at exposure levels up to and including 20-ppm methyl bromide.

Sincerely,

Judy Buelke-Sam
Toxicology Services
710 N. Spring St.
Greenfield, IN 46140

Reference:

J.E. Oliver, Jr., and M.D. Lorenz. Handbook of Veterinary Neurologic Diagnosis. Philadelphia, W.B. Saunders Co., p. 30.

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Garden Rose Council

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March 10, 2003

Paul Helliker, Director
California Department of Pesticide Regulation
1001 I Street
Sacramento, CA 95812

Re: Methyl Bromide Field Fumigation Regulations

Dear Mr. Helliker:

I am writing on to you on behalf of the Garden Rose Council and California's rose plant production industry, regarding the workshop on Risk Management Considerations for Methyl Bromide Subchronic Toxicity, held on February 26, 2003, in Sacramento. Methyl bromide is a critical tool for California's rose growers. Its use is essential to producing disease free nursery stock to meet state, national and industry certification requirements as well as to provide healthy plants for the consumer.

The methyl bromide phase-out mandated by the Montreal Protocol would eliminate the use of methyl bromide in 2005. However, the Parties to the Protocol, as well as the U.S. EPA recognized that certain methyl bromide uses are essential and must not be eliminated. Thus, the Protocol itself, as well as the U.S. Congress, created an exemption for "quarantine and preshipment" uses of methyl bromide. Moreover, the U.S. EPA has recently applied to the parties of the Montreal Protocol for a Critical Use Exemption (CUE) for the consumption of 22,000,000 pounds of methyl bromide after the phase out in 2005. The EPA determined that certain of these uses, including pre-plant fumigation for roses, were essential for agriculture throughout the United States. The CUE application indicates the importance of methyl bromide to agriculture. In fact, at this point, the California rose production industry depends on methyl bromide for survival. For this reason, California's rose growers have been following closely the scientific discussion that will determine the content of the next amendments to the methyl bromide regulations.

It is our understanding that the Reference Concentration (RfC) for sub-chronic exposure to methyl bromide, established in DPR's Risk Characterization Document (RCD) for Methyl Bromide at 1ppb for children and 2 ppb for adults, is being reconsidered based on

a new dog inhalation study (Schaeffer study). We also understand that highly qualified toxicologists, including Dr. Janice Chambers (a member of the NAS committee that reviewed the DPR RCD), agreed that the new study demonstrated a No Effect Level (NOEL) of 20 ppm which would lead to a RfC of 40 ppb in children. However, DPR, in its presentation at the methyl bromide workshop , proposed that the NOEL for the Schaefer study is 5 ppm, leading to an RfC of 9 ppb for children. DPR's conclusion was apparently based upon some external discussions and on the opinion of two individuals from U.C. Davis.

During the workshop, it became evident that, early in the review process, a DPR reviewer raised some concerns about the Schaeffer study, which were made known to the study sponsors on February 24, 2003. We further understand that the laboratory that conducted the study is responding to the questions raised by the reviewer. It is unclear to what extent these concerns influenced DPR's derivation of the reference dose. However, we urge DPR to fully consider the response of the performing laboratory to its questions and interpretation of the new study and to consider the views of other outside scientists who are qualified to comment on the interpretation of the neurotoxicity studies. We believe that the evidence will indicate that a reference concentration for methyl bromide in children around 40 ppb is fully protective of health.

California already has the most stringent rules governing the use of methyl bromide in the world. Rose growers in California must compete with growers in other states and nations that don't face these regulatory requirements. We are concerned that new regulations, if based on an unnecessarily low reference concentration, may further erode the competiveness of the rose industry

The rose production industry recognizes and supports the fact that DPR must make regulatory decisions that protect the health of California citizens. However, we ask the department to carefully consider all of the information available, and allow time for additional responses from the laboratory in question and other qualified experts before establishing an RfC that has the potential to significantly affect our industry.

Sincerely,

Michael McCaffrey

Michael McCaffrey
President, Garden Rose Council

Cc: Governor Gray Davis
Secretary Winston Hickox
Secretary Bill Lyons
Secretary Lon Hatamiya

LPG DPH

CALIFORNIA PISTACHIO COMMISSION

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March 7, 2003

Paul Helliker, Director
California Department of Pesticide Regulation
1001 I Street
Sacramento, CA 95812

Dear Mr. Helliker:

RE: Methyl bromide field fumigation rules

Methyl bromide is one of the most important tools enabling California growers and processors to efficiently produce food for both domestic and export consumption. It's use is also essential in field and commodity fumigations in order to comply with many state, national and international requirements. The methyl bromide phase-out mandated by the Montreal Protocol would eliminate the use of methyl bromide in 2005. However, the Parties to the Protocol, as well as the U.S. EPA recognized that certain methyl bromide uses are essential and must not be eliminated. Thus, the Protocol itself, as well as the U.S. Congress, created an exemption for "quarantine and preshipment" uses of methyl bromide. Moreover, the U.S. EPA has recently recommended to the parties of the Montreal Protocol that the production and use of 22,000,000 pounds of methyl bromide be declared "critical" for the year 2005. EPA made this recommendation after rigorous examination of the various uses of methyl bromide and the available alternatives. The EPA determined that certain of these uses were essential for agriculture throughout the United States. The extent of this recommendation indicates the importance of methyl bromide to agriculture.

We want to be sure that DPR understands the devastating effect that its methyl bromide regulations can have on significant segments of California agriculture. These segments depend on methyl bromide for survival. Therefore, regulatory decisions must be based upon the latest available data and the proper scientific evaluation of this data.

In its Risk Characterization Document (RCD) for Methyl Bromide, Volume 1, issued in August 2002, DPR established a Reference Concentration (RfC) for sub-chronic exposure to methyl bromide at 1ppb for children and 2 ppb for adults. These levels were based on the so-called "Newton study" of inhaled methyl bromide in dogs. After the National Academy of Science (NAS) subcommittee reviewed the draft RCD and characterized the Newton study as "equivocal" and recommended a new study, the Alliance of the Methyl Bromide Industry (AMBI) conducted such a study (the "Schaefer study") and submitted it to DPR for review in June, 2002.

It is our understanding that the study director (Dr. Gerald Schaefer), Dr. Janice Chambers (a member of the NAS review committee, Dr. Nancy O'Malley (industry) and at least one DPR toxicologist agreed that the Schaefer study demonstrated a No Effect Level (NOEL) of 20 ppm which would lead to a RfC of 40 ppb in children. It appears that DPR, however, in its Addendum to Vol. 1 of the RCD, concluded that the NOEL for the Schaefer study is 5 ppm, leading to a RfC of 9 ppb for children. DPR's conclusion was apparently based upon some external discussions and on the opinion of two individuals from U.C. Davis. We are concerned because we believe that the Davis reviewers lack the same experience and expertise in the evaluation of the neurotoxicity studies as Doctors Schaefer, Chambers and O'Malley.

Furthermore, it is our understanding that the laboratory which completed the Schaefer study in June, 2002, was not informed of DPR's concerns about the study until February 24, 2003, yet these concerns were apparently raised by DPR scientists in August, 2002. We understand that, despite these lingering questions, DPR continued to use its own interpretation of the Schaefer study to shape its derivation of the reference dose without notifying or even calling the laboratory or the study sponsor.

We have been repeatedly assured that DPR will use sound science as the basis for its proposed new regulations. However, in this case we are concerned that the regulations may be inconsistent with the most accurate interpretation of the study results. It is essential for fairness and sound science, even at this late date, that DPR fully consider the response of the performing laboratory to its questions and interpretation of the Schaefer study, and that DPR consider the views of other outside scientists who are qualified to comment on the interpretation of the neurotoxicity studies. We believe that the evidence will indicate that a reference concentration for methyl bromide in children around 40 ppb is fully protective of health.

California already has the most stringent rules governing the use of methyl bromide in the world. Despite the ingenuity and commitment of California's growers, the competitiveness of the state's agricultural industry has already been eroded by the overly stringent regulations on the use of methyl bromide. Moreover, Governor Davis has stated his concerns regarding taking action that will lead to further erosion of California agriculture's competitive position. He has also promised to provide a "level playing field" for the use of methyl bromide by California growers. We are concerned that the new regulations may further damage the agricultural industry and make the playing field so "unlevel" that California will no longer be the leader in the production and export of fresh fruit, vegetables, nuts, grains and other agricultural commodities.

We are eager to provide any additional information you need to make the regulatory decision that protects the health of California citizens. We believe that for the State to regulate beyond what is safe and reasonable is

unwarranted and inconsistent with past regulatory policy. Moreover, such "over-regulating" in this instance would be crippling to the most economically significant industry in California. Furthermore, it would arguably be indefensible from a regulatory standpoint.

We look forward to working with you to protect the food supply and health of Californians.

Sincerely,

Bob Klein

Bob Klein, Ph.D.
Director of Research

MEMORANDUM

TO: Chuck Andrews, Chief
Worker Health and Safety Branch
Department of Pesticide Regulation
P.O. Box 4015
Sacramento, California 95812-4015

FROM: Anna M. Fan, Ph.D., Chief
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:

1) 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.

2) 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.

3) 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

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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.

[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."

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

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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March 11, 2003

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VIA HAND-DELIVERY

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Chief Deputy Director

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Medical Toxicology Branch
California Department of Pesticide Regulation
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Sacramento, CA 95814

RE: RESPONSE TO ISSUES RAISED CONCERNING THE *6-WEEK INHALATION TOXICITY STUDY OF METHYL BROMIDE IN DOGS*

Dear Mr. Gosselin and Mr. Patterson:

Attached please find a responsive memorandum Dr. Vince Piccirillo prepared regarding the toxicology issues identified at the recent methyl bromide workshop. I think you will find them to be dispositive on these recently divulged issues.

Sincerely,

WILLIAM J. THOMAS

WJT:ad
cc: Alliance of the Methyl Bromide Industry

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DATE: March 7, 2003

TO: William Thomas, Livingston & Mattesich
David McAllister, Great Lakes Chemical Corporation

FROM: Vincent J. Piccirillo, Ph.D., DABT

SUBJECT: CDPR Methyl Bromide Workshop

The California Department of Pesticide Regulation held a workshop on February 26, 2003 to present its review of the "6-Week Inhalation Toxicity Study of Methyl Bromide in Dogs" and to solicit comments from interested parties regarding the review. At that workshop, several questions pertaining to the toxicity of methyl bromide and the adequacy of the toxicology database were raised by one of the commenters. The purpose of this memorandum is to address the following questions:

1. Is methyl bromide a teratogen?
2. Should additional uncertainty (safety) factors be include in the risk assessment to protect childrens health and to cover database uncertainties?
3. Are the results of the Schaefer study consistent with results of other neurotoxicity studies with methyl bromide?
4. Is the mechanism of toxicity known for methyl bromide?

IS METHYL BROMIDE A TERATOGEN?

The teratogenic potential of methyl bromide has been evaluated in rabbits (Breslin et.al.,1990a and1990b) and rats (Sikov et.al.,1981)

The Breslin study was conducted in two phases. In the initial phase, pregnant New Zealand White rabbits were exposed for six hours/day to methyl bromide concentrations of 0, 20, 40, and 80 ppm on days seven through 19 of gestation. In the second phase, pregnant does were exposed to 0 or 80 ppm only. Cesarean delivery was performed on day 28 of gestation. In the first phase, maternal toxicity, evidenced by decreased bodyweight gain and clinical signs of neurotoxicity, was seen in three of the does from the 80 ppm group. The clinical signs consisted of right-sided head tilt, ataxia, slight lateral recumbency and lethargy. In the second study, a significant decrease in bodyweight during gestation was the only evidence of maternal toxicity in the 80 ppm

group. Minimal developmental findings (gall bladder agenesis and fused sternebrae) were seen in maternally toxic 80 ppm group only. The relevance of these findings to methyl bromide exposure have been debated in several forums (California EPA, 1993). A number of experts have presented their views and direct relationship of the gall bladder agenesis and fused sternebrae findings to methyl bromide treatment remains questionable in light of the maternal toxicity.

Sikov et.al. (1981) reported results from a developmental toxicity study in rats. A CDPR reviewer raised a question regarding a higher frequency of delayed skull ossification (a variation rather than a malformation) being a possible treatment related effect. Sikov et.al had concluded that methyl bromide concentrations at concentrations up to 70 ppm (the highest tested concentration) produced no effects on female rats nor evidence of embryotoxicity or teratogenicity. This conclusion has been supported by several experts (California EPA, 1993). The overall conclusion that can be drawn from these studies is that methyl bromide is not a developmental toxin.

SHOULD ADDITIONAL UNCERTAINTY (SAFETY) FACTORS BE INCLUDED IN THE RISK ASSESSMENT TO PROTECT CHILDRENS HEALTH AND TO COVER DATABASE UNCERTAINTIES?

In performing human risk characterization, regulatory authorities consider the overall strength of the toxicology database. To account for variability between animals and humans, uncertainty factors are built in to the risk assessment. The primary uncertainty factors used for risk assessment are a 10-fold uncertainty (or safety) factor for interspecies variation and 10-fold uncertainty (or safety) factor for intraspecies variation. Additional uncertainty factors may be included. The Food Quality Protection Act provides USEPA the ability to use an additional 10-fold safety factor, when taking in account the potential for pre- and post-natal toxicity (increased sensitivity of young and juvenile animals) and the completeness of the toxicology and exposure databases. For purposes of the discussion below, each criterion will be discussed separately.

Increased Sensitivity of Young and Juvenile Animals

Developmental toxicity studies and reproductive toxicity studies are used to evaluated an increased sensitivity for young animals as compared to adults. The developmental toxicity studies with methyl bromide were discussed above. In the Breslin study, the NOELs for maternal toxicity and developmental toxicity were the same. In the Sikov study, the study authors indicated that the NOELs for maternal toxicity and developmental toxicity were the highest tested dose. In a two generation reproduction study, male and female Sprague Dawley rats were exposed to methyl bromide by whole body inhalation exposure, six hours/day, five days/week at concentrations of 0, 3, 30 or 90 ppm in a two-generation reproduction study (American Biogenics Corporation, 1986). The NOEL for adults and for pups was 3 ppm. Collectively, the results from these studies do not indicate an increased sensitivity of young and juvenile animals and an uncertainty factor on this basis is not warranted.

Completeness of the toxicologic and exposure database

In cases where the toxicologic database is incomplete, a database uncertainty factor may be applied. Methyl bromide has an extensive regulatory database and the literature contains many studies reporting toxicologic results for methyl bromide exposure. Some of the studies are summarized in Table 1. The toxicology database for methyl bromide has been summarized in several documents (ATSDR, 1991; WHO, 1995; Piccirillo, 2001). With such a robust database, a database uncertainty factor is not warranted for methyl bromide.

The primary regulatory studies were conducted via inhalation as this was considered the most likely route of significant human exposure. The inhalation studies included acute neurotoxicity in rats, acute and short term toxicity in dogs, six-week neurotoxicity study in dogs, subchronic neurotoxicity in rats, developmental toxicity in rats and rabbits, reproductive toxicity in rats, dominant lethal evaluation in rats and carcinogenicity studies in rats and mice. Chronic toxicity studies by oral exposure have been conducted in rats and dogs. An extensive battery of mutagenicity studies have also been reported. These studies have been reviewed by the California Department of Pesticide Regulation and USEPA and were included as part of the EU SIDS program in 2001.

ARE THE RESULTS OF THE SCHAEFER STUDY CONSISTENT WITH RESULTS OF OTHER NEUROTOXICITY STUDIES WITH METHYL BROMIDE?

The Schaefer study was conducted to resolve issues related to an equivocal observation of neurotoxicity (decreased responsiveness) seen in two female dogs exposed at 5 ppm for 6 weeks in a previous inhalation toxicity study in dogs (Newton, 1994). The Schaefer study was specifically designed as a neurotoxicity study in dogs. Rather than subjective animal observations, the study dogs were evaluated using validated Functional Observation Battery (FOB) and motor activity assessments comparable to those used in standard acute and subchronic neurotoxicity studies in rats.

The exposure concentrations in the Schaefer study were selected to resolve the question surrounding the equivocal findings seen at 5 ppm seen previously and to establish the most appropriate No Observed Effect Level (NOEL) for methyl bromide in dogs. Therefore, all three of the test concentrations in the Schaefer study were selected to potentially be NOELs based on observations from other dog inhalation studies rather than to reproduce toxicologic effects seen at much higher concentrations in previous studies. For this reason, the results from the Schaefer study are not consistent with other inhalation toxicity studies with methyl bromide in which significant neurotoxicity was seen, at higher concentrations than tested in the Schaefer study.

In other methyl bromide studies, the intent was to cover a range of exposure that would elicit no effect, minimal effects and clear evidence of toxicity. The results from numerous repeated inhalation exposure studies in rats, mice, rabbits and dogs clearly demonstrate that the toxicologic effects from methyl bromide exposure are threshold based. Upon exceedance of the threshold, effects from methyl bromide exposure have a very steep dose response curve. The toxic responses in dogs observed in the Newton study at high concentrations (150 ppm) were consistent with neurotoxicity findings seen in studies in rats and mice.

It should be noted, however, that the exposure levels used in this study are within the range of NOELs seen from numerous other studies. The DPR document (CDPR, 2003) states that the NOELs seen in other studies ranges from <5 ppm (Newton, 1994) to <30 ppm (Norris et. al., 1993). Collectively, the results from other studies show that it was likely that inhalation exposures in the range of 5 ppm to 20 ppm would be NOELs as seen in the Shaefer study. On this basis, the lack of findings in the Shaefer study is consistent with other studies.

IS THE MECHANISM OF TOXICITY KNOWN FOR METHYL BROMIDE?

The mechanism of toxicity for methyl bromide, like many chemicals, is not well understood. Proposed mechanisms include direct cytotoxicity of methyl bromide or one of its metabolites to target tissue. For example, the necrosis seen in the nasal olfactory epithelial upon inhalation exposure suggests a direct cytotoxic response. Honma et. al. (1985) concluded that the central nervous system effects seen in rats may be due to methyl bromide or the methyl moiety from methyl bromide or methyl bromide itself being incorporated into tissue.

Methyl bromide per se is a reactive chemical that readily methylates S- and N-groups in biological tissues. The reaction of methyl bromide with key intracellular components such as sulhydryl enzymes, protein, lipids and other cellular components has also been proposed as a potential mechanism. Such reactions upset normal cell function inducing cytotoxic responses.

Glutathione is a tripeptide found in many mammalian tissues that serves as a scavenger for reactive chemicals such as methyl bromide and provides a major protective role in xenobiotic metabolism. Glutathione reactions are both enzymatic and nonenzymatic (Sipes and Gandolfi, 1991). Andersen et. al.(1980) reported that methyl bromide uptake follows first order kinetics indicative of rapid, nonenzymatic metabolism consistent with a methyl bromide-GSH reaction. It has been hypothesized that the metabolism of methyl bromide may result in the formation of a reactive metabolite through the methyl bromide-glutathione conjugation process and that the reactive metabolite may induce toxic responses in target cells. Another proposed mechanism is that high exposure concentration of methyl bromide leads to a depletion of glutathione permitting reaction with cellular components and inducing toxicity.

Even though the exact mechanism of toxicity for methyl bromide is unknown, it is important to note that the risk assessments for methyl bromide are conducted using the No Observed Effect Levels, not levels at which toxicity occurs and, therefore, knowledge of the exact mechanism may not be an important consideration.

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March 11, 2003

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VIA HAND-DELIVERY

Paul Gosselin — *Response Without Attachments*
Chief Deputy Director

Gary Patterson, Branch Manager — *Response Includes Attachments*
Div. of Registration and Health Evaluation,
Medical Toxicology Branch
California Department of Pesticide Regulation
1001 I Street
Sacramento, CA 95814

RE: RESPONSE TO ISSUES RAISED CONCERNING THE *6-WEEK INHALATION TOXICITY STUDY OF METHYL BROMIDE IN DOGS*

Dear Mr. Gosselin and Mr. Patterson:

Attached please find a responsive memorandum Dr. Gerald Schaefer, the WIL Research Laboratory Study Director has compiled with extensive materials responding to the issues raised at the workshop.

Sincerely,

WILLIAM J. THOMAS

WJT:ad
cc: Alliance of the Methyl Bromide Industry

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RESPONSE TO THE CALIFORNIA DEPARTMENT OF PESTICIDE REGULATION IN REFERENCDE TO:

A 6-Week Inhalation Toxicity Study of Methyl Bromide in Dogs

Background:
Methyl bromide is a gaseous pesticide used to fumigate soil, crops, commodity-warehouses and commodity-shipping facilities. Because as much as 17 million pounds of methyl bromide are used annually in California to treat various crops, the Department of Pesticide Regulation (DPR) of the California Environmental Protection Agency (EPA) regulates its use and has a vested interest in determining its potential toxicity. The DPR, in reviewing toxicology studies conducted on methyl bromide, has concluded that the critical target organ for acute and repeated exposure to methyl bromide is the nervous system. A National Academy of Sciences review[1] also concluded that the dog may be the most sensitive species of the laboratory animals studied, and that the inhalation route is more appropriate than other routes, such as oral gavage. The conclusion of the NAS review of the methyl bromide data was that a well-controlled inhalation study in dogs with repeated and well-defined behavioral and neurological endpoints, as well as a comprehensive histopathological evaluation was warranted. This was based on its finding that the previous study conducted by Newton [2] was not adequate to answer these questions.

Expertise:
Within this context, a group of senior scientists at WIL Research Laboratories, Inc. (WIL) developed a protocol that would remedy the weaknesses articulated by the NAS report.[3] Members of the WIL team consisted of Gerald Schaefer, Ph.D., J.D., with 30 years experience in behavioral neuroscience and neuropharmacology/neurotoxicology; Joseph Holson, Ph.D., with 30 years experience in regulatory toxicology; Christopher Chengelis, Ph.D., D.A.B.T., with 25 years experience in pharmacology and toxicology; Daniel Kirkpatrick, Ph.D., D.A.B.T., with 20 years experience in inhalation toxicology: and Mark Nemec, B.S., D.A.B.T., with 20 years experience in developmental neurotoxicology. This broad and overlapping base of expertise produced a protocol that was consistent with the directives of the NAS, and one that was reviewed by the DPR. In contrast, the academicians used by DPR as outside reviewers have no documented experience in either neurotoxicology or in veterinary l medicine.

Technical Aspects:
In the WIL neurotoxicology study, dogs were exposed to methyl bromide by whole body inhalation at concentrations of 0, 5, 10 and 20 ppm five days per week for seven hours per day for 6 weeks. Potential adverse effects of this exposure were assessed by a neurological examination of the dog known as a functional observational battery (FOB), and by an assessment of spontaneous locomotor activity.

In the FOB, one of eight dogs in the 10 ppm group, and two of eight dogs in the 20 ppm group were observed to lack proprioceptive placing. No other effects in the FOB were noted. There were no other findings to suggest proprioceptive placement changes were

related to methyl bromide exposure. Subsequently, these data were reviewed by Janice Chambers, Ph.D., D.A.B.T., Fellow A.T.S., who is a widely-recognized expert with 25 years experience in neurotoxicity assessment, and by Judy Buelke-Sam M.A., who is widely-recognized expert in neurobehavior assessment with 30 years experience. Both scientists agreed with our interpretation of the data (reviews enclosed). Consequently, had we or the other reviewers interpreted the data on proprioceptive placing as a test-article effect, the scientific method would have been violated by ignoring the weight of evidence generated by the FOB, as well as our collective experience with the conduct of the FOB in both rodents and in dogs. To further ensure that our scientific methodology and data interpretation are sound, we have recommended that Virginia Moser, Ph.D., D.A.B.T. review our report. Dr. Moser has many years experience with the US Environmental Protection Agency as a neurotoxicologist. She is co-editor of the Training Video and Reference Manual for a Functional Observational Battery, co-sponsored by the USEPA and the Neurotoxicology Subcommittee of the American Industrial Health Council. While she was pleased that we requested her to review our data, Dr. Moser declined because of her concern about a potential conflict of interest with USEPA. However, Dr. Moser said that if DPR requested her to review the report, she would be happy to do so.

The FOB, which was developed for use in rodents approximately 35 years ago is both an objective and a subjective testing paradigm that consists of some 30 different parameters scored by highly trained observers. The FOB parameters are categorized into patterns or functional domains such as sensorimotor observations, neuromuscular observations and physiological observations[4]. As has been emphasized in the rodent FOB by Dr. Moser, it is essential to determine whether there are mutually consistent patterns within a given functional domain. The assessment of central nervous system (CNS) effects is sometimes subjective and responses can be inconsistent. However, determinations of inter-observer reliability are conducted in our laboratory to ensure consistent ratings by the technicians. Even though there are obvious size differences between the dog and the rat that result in differences in the FOB, the concept of patterns of consistent changes in the FOB is the same for both species. For example, if the parameter of gait is found to be altered, then other parameters such as the time it takes the animal to take its first step in an enclosed space should also be affected. Similarly, if proprioceptive placing is altered, one would expect to see significant changes in wheel barrowing or hemistanding/hemistanding parameters, as well as visual alterations in ocular position or cliff avoidance. It follows, of course, that when a single parameter in isolation is scored as positive without additional parameters in that domain also scored as positive, then the significance of the isolated occurrence is not confirmed. Furthermore, before biological significance is attached to an isolated finding, it is important to determine whether the effect is consistent between both sexes, whether the effect increases with increasing concentrations of the test article, and whether the effect is observed with repeated testing.

Following the FOB, all dogs were tested in a computer-monitored instrument that objectively measured spontaneous locomotor activity over the course of 60 minutes. Like the FOB, automated testing of spontaneous locomotor activity has been conducted for the past 30 years. In our laboratory, we use a device that is engineered after similar

devices used to test rodents. No statistically significant differences were found in spontaneous locomotor activity at any time during exposure to methyl bromide. Had the animals in this study had any difficulty in ambulation, it would have been recorded and the changes would have been correlated with the changes in proprioceptive placing.

During the conduct of this study, veterinary care was provided by Barbara Smith, D.V.M., M.S., Ph.D., D.A.C.V.S., D.A.C.L.A.M., who diagnosed one dog in the 5 ppm group with idiopathic febrile necrotizing arteritis [5,6,7,8,9,10,11] (also know as "beagle pain syndrome"). This syndrome, which is known to occur in laboratory beagles, has been shown to occur in our laboratory in control animals both prior to and since the conduct of this study with methyl bromide. In the professional opinion of Dr. Smith, the clinical signs observed in the dog in this study were not related to exposure to methyl bromide. Even though WIL Research Laboratories, Inc. is accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International, and despite best practices by the veterinary staff, idiopathic diseases can occur.

At the end of six weeks of methyl bromide exposure, all dogs were euthanized and whole-body *in-situ* perfusion with 4% paraformaldehyde and 1.5% glutaraldehyde was conducted. The use of *in-situ* perfusion provides the optimal preservation of cellular integrity of both peripheral and central nervous system tissues to detect neuropathological changes. The microscopic histopathology was conducted by Karen Regan, D.V.M., D.A.B.T., D.A.C.V.P., who has extensive experience in both tissue preservation and tissue evaluation. There were no neuropathological lesions observed in any of the dogs. The only histopathological finding was that of beagle pain syndrome in the one dog exposed to 5 ppm, and this was not considered to be related to methyl bromide exposure.

Responses to specific issues outline in the letter of February 26, 2003 (William J. Thomas):

1. "Pretesting data...indicate that is rare for untreated dogs not to exhibit this response, especially in a repetitive manner."

Although there are not a lot of data available on FOB testing in the beagle, we have seen this observation on another occasion, both prior to and following drug exposure (data enclosed). Furthermore, our dog FOB is based on a neurological examination in the dog. As reported by Oliver and Lorenz (1983), (page 30)[12] some dogs will ignore the table and not place their front paw on the surface of the table if they become accustomed to being held. This is particularly the case when the animal can see the table, as opposed to being blind-folded (an alternative technique described by Oliver and Lorenz).

2. "Major deficiencies include:
   i. Positive control data regarding FOB testing... were either inadequate or not provided

   The use of the beagle FOB is a recent extension of the FOB conducted in rodents. There is not an extensive database. However, we are providing data from six studies

on both FOB and locomotor activities in dogs. Furthermore, it needs to be emphasized that our study was clearly more rigorous than that conducted by Newton [2].

ii. The histological examination of the nervous system did not include special stains.

As described in the protocol, special stains were to be used at the discretion of the pathologist to further characterize lesions and changes. Since none were found, special stains were not used.

iii. Some methods, data and a protocol deviation regarding the male presumed to be exhibiting idiopathic febrile necrotizing arteritis were not provided.

Enclosed is a memorandum from Dr. Smith detailing the medical history of the dog diagnosed with beagle pain syndrome. Also note that seven research articles are being submitted describing this syndrome.

3. "The diagnosis of idiopathic febrile necrotozing arteritis was not well substantiated.

a. See the response directly above. Also note that we have found animals with a microscopic diagnosis of beagle pain syndrome in eight studies conducted here at WIL (see enclosed data table). Furthermore, we had previously contacted Ridglan Farms and confirmed that they have seen this syndrome in some of their dogs. In the dog diagnosed in this study, the animal had both clinical signs (see memo from Dr. Smith) and confirmatory macroscopic and microscopic signs (see section 6.7.3 of the final report). Clearly both veterinarians, Dr. Smith and Dr. Regan, were qualified to make this diagnosis. Furthermore, previous methyl bromide studies using dogs were more than adequate to assess systemic toxicity, but did not produce any evidence of the beagle pain syndrome.

b. "There were problems...exposure atmospheres"

Please see enclosed description of atmosphere conditions from Dr. Kirkpatrick.

c."It was unclear how many dogs were in a given chamber."

There were eight dogs in each chamber, four on top and four on the bottom. The positions (left to right) within the top or bottom were systematically rotated for the animals on each day of exposure.

d. There were no pretest individual data for clinical signs.

Individual pretest data for clinical signs are not normally produced in the report, only summary data. However, enclosed is a listing of individual pretest clinical signs for this study.

e. There were no positive control data for the FOB... and (no) details regarding the staff conducting the test were provided.

Positive control groups are not normally conducted unless specifically requested by the Sponsor, and the addition of a positive control group was not included in the protocol reviewed by DPR. However, the enclosed studies contain positive control data for the FOB. The staff used to conduct FOB in this study were: Julie Braddock, Amanda Davis, Tracy Ebert, Victoria Johnson, Chip Kopp, Dawn Linder and Mike Sexton. They were the same individuals throughout the study. Prior to the initiation of the study, these trained observers underwent inter-observer reliability training using positive controls (doxapram and midazolam).

f. There were no positive control data for the neurohistopathology... recommended stains were not used.

Positive control data for neurohistopathology data require that additional animals be euthanized. We normally do not do this in dogs because of animal use and welfare issues. An example of such as study in rats is 99199 (protocol enclosed). In the Schaefer study, the special stains were only to be used in the event that lesions were observed. Since none were observed, there was no justification for the use of special stains.

4. "In the motor activity test, there was no obvious treatment effects, but supplemental information is needed"

Please see study WIL-99211(enclosed). It can be seen that spontaneous locomotor activity was both increased by administering a central nervous system (CNS) stimulant and was decreased by administering a CNS depressant. A similar result was observed in WIL-99241 (also enclosed.)

· Table 2: There appear to be errors in some of the data entries for emesis. Please check for correct numbers.

Data have been re-checked by our QA personnel. No error was found. Please provide any additional information you consider relevant to a potential error.

Table 3: Please address Questions 1 and 2 as to "treatment related" effects at 5 ppm, and sufficient evidence to diagnose INFA.

With regard to lack of the proprioceptive placing response, the well-recognized veterinary medical text by Oliver and Lorenz (1983) states on page 30 that this response may be absent when dogs are accustomed to being held and are allowed to

see the table surface. It should also be noted that the response is not robust in the rodent FOB[13].

With regard to the diagnosis of beagle pain syndrome, two qualified veterinarians, with board certifications in laboratory animal medicine, surgery, toxicology and pathology, made the diagnosis based on: (1) clinical signs, (2) blood tests (3) autopsy findings, and (4) microscopic pathology.

Table 3: Question 3: Address why lack of proprioceptive placing response at 10 and 20 ppm is not treatment related.

The lack of proprioceptive placing was not considered test-article related because (1) the increase was not statistically significantly different from the control group, (2) did not increase with increases in dose, (3) was not consistent between the sexes, (4) did not persist throughout the course of the study, or increase with time on study and (5) was not corroborated by another neurological sign such as wheel-barrowing or hemiwalking/hemistanding.

Number of animals used: Address why most dog studies are conducted using 4 dogs/dose/gender

The number of dogs used per sex per group is dictated by governmental toxicity testing guidelines, in particular, the US EPA. In addition, the number of animals per group is based on generally accepted scientific principles dictating the fewest number of animals needed to detect a test article effect. The number of animals used in this protocol was reviewed by DPR. Furthermore, the United States Animal Welfare Act (1966 as amended), (7 USC 2131-2157) by way of the organization's federally-mandated Institutional Animal Care and Use Committee requires investigators to use the fewest animals possible that will yield scientifically valid data.

Neurotoxicity Evaluation: Address the question as to whether the FOB was sensitive enough to detect methyl bromide toxicity in dogs.

We have conducted several dog FOB studies with positive controls including doxapram and midazolam and the dogs do show test article-related effects. This stands in contrast to the Newton study in which the neurobehavioral results were based on anecdotal findings from a veterinarian.

Address why lack of proprioceptive placing was not a dose-response relationship.

A maximum of two out of eight dogs showed this response. This is less than half of the animals in any group. Although it is difficult to say, with certainty, when a dose response relationship is present, it would require more than that seen in this study.

Address why emesis, clear eye discharge, and feces related effects are not a "spectrum" of effects when considered with twitching/tremor in one dog.

We do not consider the findings of emesis, clear ocular discharge, and feces related effects to be a "spectrum" because it occurred in both control dogs as well as in the dogs exposed to methyl bromide. Furthermore, we observed these same effects in all dogs even before they were exposed to methyl bromide. In addition, if these were related to methyl bromide, we would anticipate changes in other signs, in particular, weight loss and/or decreases in food consumption. This did not occur.

Summary:

The Schaefer study was conducted as outlined in the protocol reviewed by DPR. The data produced were internally consistent. The interpretation offered by every qualified expert has also been consistent. The study successfully addressed the data gap identified by the NAS, and there is no rational reason to reject its conclusion.

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1 PG 2 PH 3 Andrews

March 11, 2003

Paul Helliker, Director
California Department of Pesticide Regulation
1001 I Street
Sacramento, CA 95814

Re: Methyl Bromide Field Fumigation Regulations

Dear Mr. Helliker:

Methyl bromide is one of the most important tools enabling California growers and processors to efficiently produce food for both domestic and export consumption. Its use is also essential in field and commodity fumigations in order to comply with many state, national and international requirements.

The methyl bromide phase-out mandated by the Montreal Protocol would eliminate the use of methyl bromide in 2005. However, the Parties to the Protocol, as well as the U.S. EPA recognized that certain methyl bromide uses are essential and must not be eliminated. Thus, the Protocol itself, as well as the U.S. Congress, created an exemption for "quarantine and preshipment" uses of methyl bromide. Moreover, the U.S. EPA has recently recommended to the parties of the Montreal Protocol that the production and use of 22,000,000 pounds of methyl bromide be declared "critical" for the year 2005. EPA made this recommendation after rigorous examination of the various uses of methyl bromide and the available alternatives. The EPA determined that certain of these uses were essential for agriculture throughout the United States. The extent of this recommendation indicates the importance of methyl bromide to agriculture.

We want to be sure that DPR understands the devastating effect that its methyl bromide regulations can have on significant segments of California agriculture. These segments depend on methyl bromide for survival. Therefore, regulatory decisions must be based upon the latest available data and the proper scientific evaluation of this data.

In its Risk Characterization Document (RCD) for Methyl Bromide, Volume 1, issued in August 2002, DPR established a Reference Concentration (RfC) for sub-chronic exposure to methyl bromide at 1ppb for children and 2 ppb for adults. These levels were

based on the so-called "Newton study" of inhaled methyl bromide in dogs. After the National Academy of Science (NAS) subcommittee reviewed the draft RCD and characterized the Newton study as "equivocal" and recommended a new study, the Alliance of the Methyl Bromide Industry (AMBI) conducted such a study (the "Schaefer study") and submitted it to DPR for review in June, 2002.

It is our understanding that the study director (Dr. Gerald Schaefer), Dr. Janice Chambers (a member of the NAS review committee), Dr. Nancy O'Malley (industry) and at least one DPR toxicologist agreed that the Schaefer study demonstrated a No Effect Level (NOEL) of 20 ppm which would lead to a RfC of 40 ppb in children. It appears that DPR, however, in its Addendum to Vol. 1 of the RCD, concluded that the NOEL for the Schaefer study is 5 ppm, leading to a RfC of 9 ppb for children. DPR's conclusion was apparently based upon some external discussions and on the opinion of two individuals from U.C. Davis. We are concerned because we believe that the Davis reviewers lack the same experience and expertise in the evaluation of the neurotoxicity studies as Doctors Schaefer, Chambers and O'Malley. We have been repeatedly assured that DPR will use sound science as the basis for its proposed new regulations. However, in this case we are concerned that the regulations may be inconsistent with the most accurate interpretation of the study results.

It is our understanding, early in the review process, a DPR reviewer raised some concerns about the Schaefer study which were made known to the laboratory which completed the study on February 24, 2003. We further understand that the laboratory is responding to the questions raised by the reviewer. It is unclear to what extent these concerns influenced DPR's derivation of the reference dose.

It is essential for fairness and sound science, that even at this late date, DPR fully consider the response of the performing laboratory to its questions and interpretation of the Schaefer study, and that DPR consider the views of other outside scientists who are qualified to comment on the interpretation of the neurotoxicity studies. We believe that the evidence will indicate that a methyl bromide reference concentration of 40ppb in children is fully protective of health.

California already has the most stringent rules governing the use of methyl bromide in the world. Despite the ingenuity and commitment of California's growers, the competitiveness of the state's agricultural industry has already been eroded by the overly stringent regulations on the use of methyl bromide. We are concerned that new regulations, if based on an unnecessarily low reference concentration, may further damage the agricultural industry so that California will no longer be the leader in the production and export of fresh fruit, vegetables, nuts, grains and other agricultural commodities.

We are eager to provide any additional information you need to make the regulatory decision that protects the health of California citizens. However, we believe that "over-regulating" in this instance would be crippling to the most economically significant industry in California.

We look forward to working with you to protect the food supply and health of Californians.

Robert P. Roy, President/General Counsel
Ventura County Agricultural Association

Jim Bogart, President/CEO
Grower-Shipper Association of Central California

David Gill, General Partner
Rio Farms

Thomas A. Nassif, President/CEO
Western Growers Association

Carol Chandler, President
California Women for Agriculture

Dennis A. Balint, CEO
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David Riggs
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George Gomes, Administrator
California Farm Bureau

Ed Camp, Chairman
Western Growers Association

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California Association of Nurseries & Garden Centers

Bob Klein, Director of Research
California Pistachio Commission

Ron Klamm, Managing Director
California Fig Institute

Rich Peterson, Executive Director
California Dried Plum Board

Rich Novy, President
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Earl P. Williams, President/CEO
California Cotton Ginners Association
California Cotton Growers Association

Steve Beckley, President
California Plant Health Association

Roger Loftus, President
Shasta Nursery, Inc.

Nick Bikakis
Castle Rock Vineyards

Jack J. Pandol, Owner
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Dean Storkan, President
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Lee Murphy, President
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Jeff Gilles
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Paul Paulin, General Manager
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Samuel Finkle, President
Nat Feinn & Son

George and Martin Rajkovich
Rajkovich Brothers

Don Gordon, President
Ag Council of California

Carol Fiscalini, President
CDK Agriculture, Inc.

Mark R. Goss, General Manager
Cal-Cel Marketing, Inc.

Ed Yates, Sr. Vice President
California League of Food Processors

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Tom Perez
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Lon McCracken, Controller
Philip Giba Farms

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Lucky Westwood, Vice President
California Giant, Inc.

Michael E. Boggiatto, President
Boggiatto Produce, Inc.

Russ Matthews, Executive Director
San Joaquin County Farm Bureau

Richard Smith, Owner/Operator
Paraiso Vineyards

Michael Turnipseed, Owner
Michael Turnipseed & Associates

Richard Mounts
Winegrape Grower

Lex McCorvey, Executive Director
Sonoma County Farm Bureau

Richard Taylor, President
Shasta County Farm Bureau

Stephen Albaugh, Owner/Partner
Fall River Nursery

Betsy K. Peterson
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California Bean Shippers Association
California Grain & Feed Association
California Warehouse Association
California Association of Wheat Growers

Miguel Cea, President
Ag-Fume Services, Inc.

Greg Augustine, President
Harbor Pest Control

Mike Sudduth, Owner
Mike Sudduth Farms

James K. Carter, Jr., General Manager
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Sig Christierson, President
Major Farms, Inc.

Bob Grimm
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Mark Perez
Perez Packing

D. F. Danna, President
Danna & Danna, Inc.

Edward Zuckerman, President
CA Sod Producers Association
Delta Blue Grass/Zuckerman Heritage, Inc.

Nish Noroian, Owner
Nish Noroian Farms

Lawrence Sambado, President
A. Sambado & Son

Paul Allen, President
Main Street Farms
Main Street Produce, Inc.

Tom Deardorff, II, President
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Darrell R. Ferreira
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Linda R. Jacobson, President
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Bryan Fiscalini
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Diego Celis
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Chris Freitas
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Hugh Miller, Executive Vice President
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Pat Ricchuiti
P-R Farms, Inc.

Butch Massa, Vice President
Comgro, Inc.

Mark Nickerson
Prime Time International

Tom Mazzzetti, President
Blue Banner Company

Clint Miller, President
Royal Oaks Farms

Sarah West, Executive Director
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O-G Packing Company

Del Gotelli
Joe Gotelli & Sons

Lance Leffler
Andiamo Ranch

Peter Barth
Gibralter Ranch

Guy Cotton
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Rod Peters
Cooper Farms

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Carrie Besumer
La Vina Ranch

Ruani Lavagnino
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Frank Maggiore
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Kevin Sanguinetti
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John Podesta
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Samuel Farms

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Schumacher Farms

Dave Vana
Vana Ranch

Mike Wassum
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Richard Salmon
Waterloo Orchards

Paul Gotelli
Tri G Farms

Steve Fortin
Sierra Cascade Nursery, Inc.

David Van Klaveren
Hollandia Nursery

Steve Miller
Sunsweet Growers

J. Miles Reiter, President/CEO
Driscoll Strawberry Associates, Inc.

Skip Larson
Sierra Cascade Nursery

Roger Wood, Director of Government Relations
J. R. Wood Inc.

Bill Warmerdam
Warmerdam Packing LLC/Excelsior Farms LLC

Glen Goto, CEO
Raisin Bargaining Association

Richard Nelson, President
Plant Sciences, Inc.

Cc: Governor Gray Davis
Secretary Winston Hickox
Secretary Bill Lyons
Secretary Hatamiya

Appendix B. Review from Dr. Virginia Moser

CALIFORNIA STRAWBERRY COMMISSION

1. RG March 14, 2003 3. Andrews

Paul Helliker, Director
California Department of Pesticide Regulation
1001 I Street
Sacramento, CA 95812

Re: Methyl Bromide Field Fumigation Regulations

Dear Mr. Helliker:

I am writing on to you on behalf of California's strawberry production industry regarding the workshop on Risk Management Considerations for Methyl Bromide Subchronic Toxicity, held on February 26, 2003, in Sacramento. Methyl bromide is a critical tool for California's strawberry growers. Its use is essential to producing the valuable, high quality strawberries necessary to compete in the national and international market.

The methyl bromide phase-out mandated by the Montreal Protocol would eliminate the use of methyl bromide in 2005. However, the Parties to the Protocol, as well as the U.S. EPA recognized that certain methyl bromide uses are essential and must not be eliminated. Thus, the Protocol itself, as well as the U.S. Congress, created an exemption for "quarantine and preshipment" uses of methyl bromide. Moreover, the U.S. EPA has recently applied to the parties of the Montreal Protocol for a Critical Use Exemption (CUE) for the consumption of 22,000,000 pounds of methyl bromide after the phase out in 2005. The EPA determined that certain of these uses, including pre-plant fumigation for strawberries, were essential for agriculture throughout the United States. The CUE application indicates the importance of methyl bromide to agriculture. Although we are aggressively seeking alternatives, the California strawberry industry still depends on methyl bromide for survival. For this reason, California's strawberry growers have been following closely the scientific discussion that will determine the content of the next amendments to the methyl bromide regulations.

It is our understanding that the Reference Concentration (RfC) for sub-chronic exposure to methyl bromide, established in DPR's Risk Characterization Document (RCD) for Methyl Bromide at 1ppb for children and 2 ppb for adults, is being reconsidered based on a new dog inhalation study (Schaeffer study). We also understand that highly qualified toxicologists, including Dr. Janice Chambers (a member of the NAS committee that reviewed the DPR RCD), agreed that the new study demonstrated a No Effect Level (NOEL) of 20 ppm which would lead to a RfC of 40 ppb in children. However, DPR, in its presentation at the methyl bromide workshop, proposed that the NOEL for the Schaefer study is 5 ppm, leading to an RfC of 9 ppb for children. DPR's conclusion was apparently based upon some external discussions and on the opinion of two individuals from U.C. Davis.

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During the workshop, it became evident that, early in the review process, a DPR reviewer raised some concerns about the Schaeffer study, which were made known to the study sponsors on February 24, 2003. We further understand that the laboratory that conducted the study is responding to the questions raised by the reviewer. It is unclear to what extent these concerns influenced DPR's derivation of the reference dose. However, we urge DPR to fully consider the response of the performing laboratory to its questions and interpretation of the new study and to consider the views of other outside scientists who are qualified to comment on the interpretation of the neurotoxicity studies. We believe that the evidence will indicate that a reference concentration for methyl bromide in children around 40 ppb is fully protective of health.

California already has the most stringent rules governing the use of methyl bromide in the world. Strawberry growers in California must compete with growers in other states and nations that don't face these regulatory requirements. We are concerned that new regulations, if based on an unnecessarily low reference concentration, may further erode the competiveness of the strawberry industry.

The California strawberry industry recognizes and supports the fact that DPR must make regulatory decisions that protect the health of California citizens. However, we ask the department to carefully consider all of the information available, and allow time for additional responses from the laboratory in question and other qualified experts before establishing an RfC that has the potential to significant negative impact on our industry.

Sincerely,

Rodger Wasson

Rodger Wasson
President, California Strawberry Commission

Cc: Governor Gray Davis
Secretary Winston Hickox
Secretary Bill Lyons
Secretary Lon Hatamiya
California Strawberry Commission Board of Directors Members and Alternates
Dr. Dan Legard, Director of Research and Education, CSC
Thomas Krugman, Director of Industry Services, CSC

Curriculum Vitae

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Toxicology Services
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Specializing in: non-clinical neurobehavioral, reproductive, developmental, and juvenile toxicology consultations; regulatory reporting; scientific writing

Educational Background

Western Michigan University Kalamazoo, MI	BA	Honors College Graduate History/German	1968
	MA	Experimental Psychology	1971
University of Michigan	—	Psychobiology	1970-1971

Previous Professional Employment

Lilly Research Laboratories — Developmental Toxicologist — 1985-Mar 1999
A Division of Eli Lilly and Company
Greenfield, IN

Study director for Segment I, II, and III studies conducted for global submission; Test plan development for DART and juvenile studies, neurotoxicity consultant for large animal (dog and primate) toxicity studies of new compounds; Toxicology liaison for special neurobehavioral, reproductive and developmental issues on selected marketed drugs and drugs under development, e.g. Prozac, Evista, Zyprexa, and several insulin and endocrine products.

National Center for Toxicological Research — Pharmacologist — 1976-85
Developmental Toxicology Division
FDA/PHS/DHHS, Jefferson, AR

Methods development for projects of interest to the FDA and EPA, including the distribution of uterine blood flow in pregnant rats, of particular value to physiologically-based kinetic modeling, and co-director of the 6-laboratory, collaborative behavioral teratology study.

Research Institute of Pharmaceutical Sciences — Research Associate — 1972-76
University of Mississippi, Oxford, MS

Head, Biological Screening Group. Whole animal and in vitro testing support for identifying pharmacologic and toxicologic activity of medicinal chemistry products, animal extracts, plant extracts. Co-investigator on NIDA contract evaluating toxicology profiles of a structural series of amphetamine analogs in mice, rats, dogs and primates.

Kalamazoo State Hospital — Research Associate — 1972
Kalamazoo, MI
Behavioral testing associate

University of Michigan — Rackham Graduate Fellowship — 1970-71
Ann Arbor, MI
Primate behavioral laboratory, psychophysical testing of primates exposed to ototoxic noise levels and/or compounds.

Western Michigan University — Research Assistant — 1969-70
Kalamazoo, MI
Graduate assistant in the physiological psychology laboratory, including projects concerning evoked potentials in the auditory and visual system of cats.

Professional Memberships

Society for Neuroscience
Neurobehavioral Teratology Society
Teratology Society
Midwest Teratology Association

Selected Professional Activities

Neurobehavioral Teratology Society: Secretary, 1979-1980; Nominations Committee, 1984-1985; Membership Committee, 1987-1988; President, 1988-1989; Constitution Committee, 1989-1994; Nominations Committee, 1995-1997; Publications Committee and Liaison Council Member, 2001- 2003.
Teratology Society: Constitution Committee, 1986-1988; Animal Use Committee, 1991-1993; Program Committee, 2002 and 2003Annual Meetings
"Neurotoxicology and Teratology": Editorial Advisory Board, 1981-1989, 2001-2003; reviewer, 1981- present
"Birth Defects Research, Part B": Behavioral/functional Teratology Section Editor, 2003-2005; reviewer, 1987-present.
"Reproductive Toxicology": Editorial Advisory Board, 2003-2007; reviewer, 1992-present.
Food and Drug Administration, Commissioner's Commendable Service Award, 1986
DRUSAFE, Pharmaceutical Manufacturers Association ad hoc Committees on Behavioral Toxicology, 1986-1988; Neurotoxicology, 1989-1993.
National Academy of Science/National Research Council. Panel on Reproductive and Neurodevelopmental Toxicology, Committee on Biological Markers, 1986-1989.
Proposal and Presentation to FDA Advisory Committee on Pregnancy Labeling for Pharmaceuticals, 1997.

Consultant Project Areas

Adult and developmental neurotoxicity advising, opinions, reviews and commentary.

Advisor for program development: use of the minipig/dog in juvenile toxicity studies to support pediatric drug development

Design and interpretation of nonclinical developmental and reproductive toxicity [DART] studies in the development of new pharmaceuticals.

Reproductive, developmental, juvenile and neurobehavioral toxicity program development for new pharmaceuticals.

Regulatory report writing for DART, pharmacokinetic and multi-generation studies

Advisor/study coordinator on design, conduct and interpretation issues for multi-generation and developmental neurotoxicity studies of chemicals and pesticides

Expert Panel Member, identifying most appropriate animal species for use in risk assessment for a pesticide; with J.F. Holson, J. DeSesso, R. Tyl, D. Mattison.

Peer Review of EPA animal studies overview and criteria documents

Scientific consultant, manufacturers of rodent and large animal behavior testing equipment

Selected Publications

Mole ML, Buelke J, Turner CE. 1974. Preliminary observations on cardiac activities of Cannabis sativa L. root extracts. J Pharm Sci 63(7):1169-1170.

Waller C, Denny J, Walz M, Buelke J, Turner CE. 1974. Annotated Bibliography of Marihuana (Cannabis sativa L) 1972 Supplement. University of Mississippi Press.

Waller C, Denny J, Walz M, Buelke J, Guinn M. 1974. Annotated Bibliography of Marihuana (Cannabis sativa L.). 1973 Supplement. University of Mississippi Press.

Waller CW, Johnson JJ, Buelke J, Turner CE. 1976. Marihuana: An Annotated Bibliography. New York: Macmillan Information.

Wilson MC, Bedford JA, Buelke J, Kibbe AH. 1976. Acute pharmacological activity of intravenous cocaine in the rhesus monkey. Psychopharmacol Commun 2(3):251-261.

Borne RF, Bedford JA, Buelke JL, Craig CB, Hardin TC, Kibbe AH, Wilson MC. 1977. Biological effects of cocaine derivatives. I. Improved synthesis and pharmacological evaluation of norcocaine. J Pharm Sci 66(1):119-120.

Davis WM, Waters IW, Hatoum HT, Buelke JL, Braude MC. 1977. Triphasic dose-lethality relationships for amphetamine and certain ring substituted amphetamines in isolated or aggregated mice. Res. Commun. Chem Path Pharmacol 17(4):575-582.

Wilson MC, Buelke J. 1978. Discriminative properties of l-amphetamine: stimulus generalization. In: Drug Discrimination and State Dependent Learning, Ho BT, Richards DW, Chute DL. eds. New York: Academic Press. p 47-66.

Buelke-Sam J, Holson Jr JF, Bazare JJ, Young JF. 1978. Comparative stability of physiological parameters during sustained anesthesia in rats. Lab Ani Sci 28(2):157-162.

Davis WM, Bedford JA, Buelke JL, Guinn MM, Hatoum HT, Waters IW, Wilson MC, Braude MC. 1978. Acute toxicity and gross behavioral effects of d-amphetamine and four methoxyamphetamines in rodents, dogs and monkeys. Toxicol Appl Pharmacol 45:49-62.

Buelke-Sam J, Kimmel CA. 1979. Development and standardization of screening methods for behavioral teratology. Teratology 20:17-30.

Buelke-Sam J. 1980. Commentary. Standardization is not an ugly word. Neurobehav Toxicol 2:289-290.

Buelke-Sam J. 1981. Book Review. Advances in the Study of Birth Defects: Neural and Behavioral Teratology. Vol. 4, T.V.N. Persuad (ed.). 1980 Baltimore: University Park Press. In Teratology 23:413-414.

Adams J, Buelke-Sam J. 1981. Behavioral assessment of the postnatal animal: testing and methods development. In: Developmental Toxicology. Kimmel CA, Buelke-Sam J. eds. New York: Raven Press. p 233-257.

Kimmel CA, Buelke-Sam J. eds. 1981. Developmental Toxicology. New York: Raven Press.

Adams J, Buelke-Sam J, Kimmel CA, LaBorde JB. 1982. Behavioral alterations in rats prenatally exposed to low doses of d-amphetamine. Neurobehav Toxicol Teratol 4:63-70.

Buelke-Sam J, Nelson CJ, Byrd RA, Holson JF. 1982. Blood flow during pregnancy in the rat: I. Flow patterns to maternal organs. Teratology 26:269-277.

Buelke-Sam J, Holson JF, Nelson CJ. 1982. Blood flow during pregnancy in the rat: II. Dynamics of and litter variability in uterine flow. Teratology 26:279-288.

Ozemek HS, Adams J, Oglesby DM, Rath J, Buelke-Sam J, Kimmel CA. 1982. A microprocessor-controlled laboratory for the measurement of visual discrimination learning in rodents. Proceedings of the 10th Annual NE Bioengineering Conference. p 56-60.

Buelke-Sam J, Byrd RA, Nelson CJ. 1983. Blood flow during pregnancy in the rat. III. Alterations following mirex treatment. Teratology 27(3):401-409.

Buelke-Sam J, Kimmel CA, Nelson CJ, Sullivan PA. 1984. Sex and strain differences in the developmental activity profile of rats prenatally exposed to sodium salicylate. Neurobehav Toxicol Teratol 6:171-175.

Buelke-Sam J, Kimmel GL, Webb PJ, Slikker Jr W, Newport GD, Nelson CJ, Kimmel CA. 1984. Postnatal toxicity following prenatal reserpine: effects of dose and dosing schedule. Fund Appl Toxicol 4:983-991.

Buelke-Sam J, Sullivan PA, Kimmel CA, Nelson CJ. 1984. Sex and strain differences in the developmental activity profile of the rat tested over clean vs. home cage bedding. Dev Psychobiol 17(1):67-77.

Buelke-Sam J, Kimmel CA, Adams J. eds. 1985. Design considerations in screening for behavioral teratogens: results of the Collaborative Behavioral Teratology Study. Neurobehav Toxicol Teratol 7(6):537-790.

Adams J, Buelke-Sam J, Kimmel CA, Nelson CJ, Miller DR. 1985. Collaborative behavioral teratology study: preliminary research. Neurobehav Toxicol Teratol 7(6):579-586.

Adams, J, Buelke-Sam J, Kimmel CA, Nelson CJ, Reiter LW, Sobotka TJ, Tilson HA, Nelson BK. 1985. Collaborative behavioral teratology study: protocol design and testing procedures. Neurobehav Toxicol Teratol 7(6):579-586.

Adams J, Oglesby DM, Ozemek HS, Rath J, Kimmel CA, Buelke-Sam J. 1985. Collaborative behavioral teratology study: programmed data entry and automated test systems. Neurobehav Toxicol Teratol 7(6):547-554.

Buelke-Sam J, Kimmel CA, Adams J, Nelson CJ, Vorhees CV, Wright DC, St. Omer V, Korol BA, Butcher RE, Geyer MA, Holson JF, Kutscher C, Wayner MJ. 1985. Collaborative behavioral teratology study: Results. Neurobehav Toxicol Teratol 7(6):591-624.

Holson RR, Adams J, Buelke-Sam J, Gough B, Kimmel CA 1985. d-Amphetamine as a behavioral teratogen: effects depend on dose, sex, age and task. Neurobehav Toxicol Teratol 7(6):753-758.

Kimmel CA, Buelke-Sam J. 1985. Collaborative behavioral teratology study: Background and overview. Neurobehav Toxicol Teratol 7(6):541-545.

Kimmel CA, Buelke-Sam J, Adams J. 1985. Collaborative behavioral teratology study: Implications, current applications and future directions. Neurobehav Toxicol Teratol 7(6):669-673.

Nelson CJ, Felton RP, Kimmel CA, Buelke-Sam J, Adams J. 1985. Collaborative behavioral teratology study: Statistical approach. Neurobehav Toxicol Teratol 7(6):587-590.

Buelke-Sam J. 1986. Postnatal functional assessment following CNS stimulant exposure: amphetamine and caffeine. In: Handbook of Behavioral Teratology. Riley EP, Vorhees CV. eds. New York: Plenum Press. p 161-172.

Ali SF, Buelke-Sam J, Newport GD, Slikker Jr W. 1986. Early neurobehavioral and neurochemical alterations in rats prenatally exposed to imipramine. Neurotoxicology 7:371-386.

Ali SF, Buelke-Sam J, Slikker Jr W. 1986. Prenatal reserpine exposure in rats decreases caudate nucleus dopamine receptor binding in female offspring. Toxicology Letters 31:195-201.

Buelke-Sam J. 1987. Practical considerations in establishing reliable and sensitive neurobehavioral test methods. International Journal of Microbiology and Hygiene, 185:4-9.

Buelke-Sam J. 1987. Behavioral and physiological effects following prenatal exposures: relationships among human and animal findings. In: Functional Teratogenesis: Functional Effects on the Offspring After Parental Drug Exposure. Fujii T, Adams PM. eds. Teikyo Tokyo: University Press. p 217-231.

Buelke-Sam J. 1987. Results of the NCTR Collaborative Behavioral Teratology Study. Congenital Anomalies 27:125-138.

Slikker W, Scallet A, Buelke-Sam J, Paule MG, Ali SF, Cunny H, Bailey J. 1987. Improving risk assessment for chemicals affecting the developing central nervous system. Proceedings of the 2nd Conference on Current Concerns of Toxicity. p 1-20.

Subcommittee on Reproductive and Neurodevelopmental Toxicology. 1989. Biological Markers: Use in Reproductive and Developmental Toxicology. Washington D.C.: National Academy of Sciences Press

Buelke-Sam J, Ali SF, Kimmel GL, Slikker Jr W, Newport GD, Harmon JR. 1989. Postnatal function following prenatal reserpine exposure in rats: neurobehavioral toxicity. Neurotoxicol Teratol 11:515-522.

Buelke-Sam J, Tizzano J, Probst KS, Fisher LF, Matsuda K. 1989. Effects of nizatidine administered orally to CD rats during the perinatal and postnatal periods. Jap Pharmacol Thera 17:223-241 (in Japanese).

Buelke-Sam J, Hagopian GS, Probst KS, Fisher LF, Matsuda K. 1989. A developmental toxicology study of nizatidine administered orally to CD rats during gestation. Jap Pharmacol Thera 17:199-222 (in Japanese).

Buelke-Sam J, Kimmel CA, Nelson CJ, Adams J. 1990. Letter to the Editor. Comments on "Behavioral teratogenic effect of methylmercury and d-amphetamine: Meta-analysis and power analysis of data from the collaborative behavioral teratology study of the NCTR." Teratology 41:743-745.

Buelke-Sam J, Mactutus C. 1990. Workshop on the qualitative and quantitative comparability of human and animal developmental neurotoxicity: testing methods in developmental neurotoxicity for use in human risk assessment. Neurotoxicol Teratol 12:269-274.

Buelke-Sam J, Byrd RA, Johnson JA, Tizzano J, Owen NV. 1991. Developmental toxicity of the dopamine agonist pergolide mesylate in CD-1 mice I: Gestational exposure. Neurotoxicol Teratol 13:283-295.

Buelke-Sam J, Cohen IR, Tizzano J, Owen NV. 1991. Developmental toxicity of the dopamine agonist pergolide mesylate in CD-1 mice: Perinatal and postnatal exposure. Neurotoxicol Teratol 13:297-306.

Tamura R, Buelke-Sam J. 1992. The use of repeated measures analyses in developmental toxicity studies. Neurotoxicol Teratol 14:205-210.

Holson RR, Buelke-Sam J. 1992. Design and analysis issues in developmental neurotoxicology. Neurotoxicol Teratol 14:197.

Kimmel CA, Buelke-Sam J, eds. 1994. Developmental Toxicology, 2nd edition. New York: Raven Press.

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Vorhees CV, Acuff-Smith KD, Schilling MA, Fisher JE, Moran MS, Buelke-Sam J. 1994. A developmental neurotoxicity evaluation of the effects of prenatal exposure to fluoxetine in rats. Fund Appl Toxicol 23:194-205.

Buelke-Sam J, Byrd RA, Hoyt JA, Zimmermann JL. 1994. A reproductive and developmental toxicity study in CD rats of LY275585, [Lys(B28),Pro(B29)]-human insulin analog. J Amer College Toxicol 13:247-260.

Bymaster F, Whitesitt C, Shannon H, DeLapp N, Ward J, Calligaro D, Shipley L, Buelke-Sam J, et al. 1997. Xanomeline: a selective muscarinic agonist for the treatment of Alzheimer's disease. Invited paper for Drug Development Research, 40:158-170.

Hoyt JA, Fisher LF, Buelke-Sam J, Francis PC. 1998. The selective estrogen receptor modulator raloxifene: Reproductive assessments following premating exposure in female rats. Reprod Toxicol. 12(3):233-245.

Clarke DO, Griffey KI, Buelke-Sam J, Francis PC. 1998. The selective estrogen receptor modulator raloxifene: Reproductive assessments following preimplantation exposure in mated female rats. Reprod Toxicol. 12(3):247-259.

Buelke-Sam J, Bryant HU, Francis PC. 1998. The selective estrogen receptor modulator raloxifene: An overview of nonclinical pharmacology and reproductive and developmental testing. Reprod Toxicol. 12(3): 217-221.

Buelke-Sam J, Cohen IR, Wierda D, Griffey KI, Fisher LF, Francis PC. 1998. The selective estrogen receptor modulator raloxifene: A Segment II/III delivery study in rats. Reprod Toxicol. 12(3): 271-288.

Kimmel CA and Buelke-Sam J. 2000. Reproductive and Developmental Toxicology. In: Patty's Toxicology, Fifth Edition, Volume I (E Bingham, B Cohrssen, D Powell, eds.). New York: John Wiley & Sons, Inc., pp 53-115.

Selected Presentations, Invited Addresses, Abstracts

Edmund D, Buelke J. Hippocampal seizures and memory. 1969; Detroit (MI): Michigan Academy of Arts, Sciences and Letters.

Buelke J. Auditory evoked potentials and noise exposure. 1970; Kalamazoo (MI): Michigan Academy of Arts, Sciences and Letters.

Turner CE, Mole ML, Buelke J. Cardiac toxins of non-polar extracts of Cannabis sativa L. roots of Mexican origin. 1973; Sao Paulo (Brazil): First Annual Latin American Congress of Psychobiology.

Waters IW, Davis WM, Buelke J. 1975. Acute behavioral and toxic effects of d-amphetamine and three methoxy derivatives in mice. Fed Proc 34:780.

Waters IW, Davis WM, Guinn MM, Hatoum HT, Buelke JL, Braude MC. 1976. Acute toxicology and behavioral effects of several methoxyamphetamines in rodents and dogs. Pharmacologist 18:142.

Wilson MC, Bedford JA, Buelke JL, Davis WM. 1976. Acute behavioral and pharmacological effects of several methoxyamphetamines in primates. Pharmacologist 18:142.

Buelke-Sam J, Kimmel CA. 1978. Screening methods for behavioral teratology. Meridian (NH): Gordon Conference on Toxicology and Safety Evaluation.

Buelke-Sam J, Holson JF. 1979. Dynamics of uterine blood flow during organogenesis in the rat. Teratology 19:21A.

Adams J, Buelke-Sam J, Kimmel CA. 1980. Postnatal behavioral alterations in rats exposed prenatally to low doses of d-amphetamine. Proc Inter Soc Develop Psychobiol.

Buelke-Sam J, Holson JF. 1980. Distribution of maternal blood flow throughout gestation in the rat. Teratology 21:31A.

Buelke-Sam J, Kimmel CA. 1980. Developmental locomotor activity in rats tested over clean vs. home cage bedding. Neurosci Abst 6:631.

Kimmel CA, Buelke-Sam J. 1980. Cardiovascular function following prenatal salicylate exposure to rats Teratology 21:49A.

Phillips M, Adams J, Buelke-Sam J. 1980. Righting vs. negative geotaxis: a methodological evaluation. Teratology 21:60-61A.

Adams J, Miller D, Buelke-Sam J. 1981. Righting vs. negative geotaxis: an examination of methods reliability and sensitivity in the detection of behavioral teratogenic effects. Teratology 24:52A.

Buelke-Sam J. 1981. Postnatal functional assessment: sodium salicylate as an example. Invited address, Milwaukee (WI): Midwest Teratology Association.

Kimmel CA, Buelke-Sam J. 1981. Dose-related increase in blood pressure and vascular responsiveness following prenatal salicylate treatment in rats. Toxicologist 1(1):11-12.

Adams J, Kimmel CA, Buelke-Sam J, Miller DR, Nelson CJ. 1982. Behavioral assessment of rats treated prenatally with low doses of d-amphetamine. I. Physical and early behavioral characteristics. Teratology 25(2):26A.

Buelke-Sam J, Kimmel CA, Adams J, Miller DR, Nelson CJ. 1982. Behavioral assessment of rats treated prenatally with low doses of d-amphetamine. II. Activity and pharmacological challenge testing. Teratology 25(2):30A-31A.

Byrd RA, Buelke-Sam J, Nelson CJ. 1982. Stage-dependent changes in maternal blood flow in mirex-treated rats. Teratology 25(2):32A.

Adams, J, Kimmel CA, Buelke-Sam J, Miller DR, Nelson CJ. 1983. Behavioral assessment of rats treated prenatally with methylmercuric chloride (M): I. Physical and early behavioral characteristics. Teratology 27(2):27A.

Buelke-Sam J, Adams J, Kimmel CA, Miller DR, Nelson CJ. 1983. Behavioral assessment of rats treated prenatally with methylmercuric chloride (M): II. Activity, pharmacological challenge and discrimination testing. Teratology 27(2):35A.

Buelke-Sam J, Kimmel CA, Nelson CJ, Sullivan PA. 1983. Sex and strain differences in the developmental activity profile of rats prenatally exposed to sodium salicylate. Neurosci Abstr 9:521.

Buelke-Sam J, Kimmel GL, Slikker Jr W, Kimmel CA. 1983. Evaluation of postnatal toxicity following prenatal reserpine exposure: effect of dose and dosing schedule. Teratology 27(2):35A.

Buelke-Sam J, Slikker Jr W, Newport GD, Miller DR, Adams J, Kimmel CA. 1983. Neurochemical and behavioral responses to d-amphetamine in the periadolescent rat. Proc Int Soc Develop Psychobiol.

Kimmel CA, Buelke-Sam J, Adams J, Reiter LW, Sobotka TJ, Tilson HA. 1983. An interlaboratory comparison of selected methods in a behavioral teratology protocol. Teratology 27(2):57A-58A.

Slikker Jr W, Buelke-Sam J, Newport GD, Adams J, Kimmel CA. 1983. Neurotransmitter ontogeny in the rat: effects of prenatal methylmercury. Am Soc Neurochem 14(1):235.

Adams J, Buelke-Sam J, Holson R, Gough BJ, Kerr L. 1984. Effects of prenatal amphetamine exposure on auditory startle habituation and activity in CD rats. Proc Int Soc Develop Psychobiol.

Adams J, Kimmel CA, Buelke-Sam J. 1984. Intralaboratory data from a standardized behavioral teratology test battery. 1983; Paris: European Teratology Society. Teratology 29(2):8A.

Buelke-Sam J, Kimmel GL. 1984. Early behavioral alterations in rats prenatally exposed to reserpine. Neurosci. Abstract 10 249.

Buelke-Sam J, Slikker Jr W, Nelson CJ, Newport G, Adams J, Kimmel C. 1984. Neurochemical responses to d-amphetamine in the periadolescent rat. Proc Int Soc Develop Psychobiol.

Ali SF, Buelke-Sam J, Slikker Jr W, Newport GD, Kimmel GL. 1985. Prenatal reserpine exposure induces changes in dopamine receptor binding in postnatal rats. Little Rock (AR): Neurotoxicology in the Fetus and Child.

Ali SF, Buelke-Sam J, Newport GD, Slikker Jr W, Harmon JR. 1985. Neurochemical alterations in rats prenatally exposed to imipramine. Teratology 31(3):11B.

Ali SF, Buelke-Sam J, Slikker Jr W, Newport GD, Kimmel GL. 1985. Early neurochemical alterations in rats prenatally exposed to reserpine. The Toxicologist 5:199.

Buelke-Sam J, Felton RP, Harmon JR, Webb P. 1985. Early behavioral alterations in rats following prenatal imipramine exposure. Teratology 31(3):11B.

Buelke-Sam J. Collaborative behavioral teratology study: results. 1985. Cincinnati (OH): Design Considerations in Screening for Behavioral Teratogens: Results of the Collaborative Behavioral Teratology Study".

Buelke-Sam J. 1985. Practical considerations in establishing reliable and sensitive neurobehavioral test methods. Invited address, Dusseldorf (FRG): Neurobehavioral methods in safety assessment of chemicals and drugs.

Slikker Jr W, Buelke-Sam J, Ali SF, Kimmel GL, Newport GD. 1985. The correlation of early postnatal behavioral and neurochemical alterations in rats prenatally exposed to reserpine. Rostock-Warnemunde (GDR): European Teratology Society.

Buelke-Sam J. 1986. Behavioral and physiological effects following prenatal exposures: relationships among human and animal findings. Invited address, Tokyo (Japan): Functional Effects on the Offspring after Parental Drug Exposure: Functional Teratogenesis.

Buelke-Sam J. 1986. Results of the NCTR Collaborative Behavioral Teratology Study. Invited address, Tokyo (Japan): Japanese Behavioral Teratology Meeting.

Buelke-Sam J, Bailey RL. 1987. Auditory startle habituation: response amplitude following acute d-amphetamine, PCA or pentobarbital challenge. Neurosci. Abstract 13:962.

Buelke-Sam J. 1987 September; Little Rock (AR): Workshop on Risk Assessment in Reproductive and Developmental Toxicology. Invited expert participant--THC panel.

Buelke-Sam J, Berger E, Bick P, Byrd T, Cocke K, Long G, Pohland R. 1988. Pharmacodynamics and immunological effects in rats following perinatal/postnatal exposure to diphenylhydantoin (DPH). Teratology 37:514.

Tizzano J, Bailey R, Buelke-Sam J. 1988. Behavioral effects in rats following perinatal/postnatal exposure to diphenylhydantoin (DPH). Teratology 37:520-521.

McGuire P, Tizzano J, Johnson JA, Martin BS, Buelke-Sam J. 1988. Effects of the B-carboline, noreleagnine, on activity and startle habituation in preweanling rats. Neurosci. Abstract 14:349.

Tizzano J, Tamura R, Bailey R, Buelke-Sam J. 1988. A dose-response study of p-chloroamphetamine effects on auditory and tactile startle habituation. Neurosci. Abstract 14:559.

Helton D, Tizzano J, Buelke-Sam J, Tamura R, Williams P. 1988. Effects of NMDA, l-glutamic acid, and l-aspartic acid on auditory and tactile startle habituation in mice. Neurosci. Abstract 14:940.

Buelke-Sam J. 1989. EPA-NIDA Workshop Williamsburg (VA): Qualitative and quantitative comparability of human and animal developmental neurotoxicity. Invited Participant and Session Chairman.

Buelke-Sam J. 1989. Selecting behavioral methods for use in toxicity studies. Invited address, Chicago (IL): Midwest Teratology Association

Buelke-Sam J. 1989. A perinatal/postnatal study of diphenylhydantoin in rats: exposure and immunological effects. Invited address, Greenfield (IN): Midwest Teratology Association.

Tizzano J, Calligaro D, McGuire P, Bailey R, Buelke-Sam J. 1989. Effects of noreleagnine on motor activity and BZ/GABA-receptor binding in the preweaning rat. Teratology 39:505-506.

Tizzano J, Helton D, Tamura R, Buelke-Sam J. 1989. Selective antagonism of excitatory amino acid effects on startle and Figure-8 maze activity in mice. Neurosci. Abstract 15:770.

Buelke-Sam J, Johnson JA, Shannon HE, Tizzano J, White JF. 1989. Cholinergic modulation of startle and Figure-8 maze activity in female mice. Neurosci. Abstract 15:556.

Tizzano J, Buelke-Sam J. 1989. Using the mouse in behavioral toxicology: auditory startle. Invited participants, Little Rock (AR): Workshop on Methods in Behavioral Toxicology/Teratology.

Buelke-Sam J. 1990. Behavioral testing in developmental toxicity studies of pharmaceuticals: repeated measures analyses. Invited address, Muncie (IN): Midwest Association of Pharmaceutical Statisticians.

Buelke-Sam J. 1990. Neurobehavioral testing in the pharmaceutical industry. Invited address, Kalamazoo (MI): 10th Annual IRDC Symposium.

Buelke-Sam J, Byrd RA, Johnson JA, Tizzano J, Owen NV. 1990. Developmental toxicology of the dopamine agonist pergolide mesylate in CD-1 mice. Teratology 41:619-620.

Buelke-Sam J, Tanimura T, Pizzi WJ. 1991. Improving approaches to the characterization of developmental neurotoxicity. Symposium organizer and co-chairperson. Boca Raton (FL): International Federation of Teratology Societies.

Buelke-Sam J, Holson RR. 1991. Design and analysis issues in developmental neurotoxicology. Symposium co-organizer and chairperson. Boca Raton (FL): Neurobehavioral Teratology Society.

Kaster J, Cohen IR, Buelke-Sam J. 1991. Circadian activity and startle amplitude in rats exposed to constant light: effects of ovariectomy and E_2 replacement. Neurosci. Abstracts 17:1412.

Buelke-Sam J. 1992. The neurotoxicity profile. Invited address, Greenfield (IN): Lilly/Purdue Neurotoxicology Symposium.

Buelke-Sam J, Bates H. 1992. Interpretation of developmental neurotoxicology data. Workshop co-chairperson. Boca Raton (FL): Teratology Society.

Vorhees CV, Acuff-Smith KD, Schilling MA, Fisher E, Buelke-Sam J. 1992. Evaluation of the behavioral teratogenic potential of fluoxetine (F) in rats. Teratology 45:526-527.

Tizzano JP, Johnson JA, Griffey KI, Hoover DM, Buelke-Sam J. 1993. Behavioral evaluation in rats following peri/postnatal exposure to the 5-HT_3 receptor antagonist, zatosetron maleate. Teratology 47:464-465.

Buelke-Sam J, Fix AS, Griffey KI, Smalley TL, Novilla MN. 1993. Onset and recovery of neuromotor dysfunction in F344 rats fed diets containing the anthelmintic (LY274537). Neurosci. Abstract 23:1892.

Buelke-Sam J. 1993. Growth as a manifestation of developmental neurotoxicity. Symposium organizer and chairperson. Tuscon (AZ): Neurobehavioral Teratology Society.

Buelke-Sam J, Byrd RA, Clarke DO, Hoyt JA, Pohland RC, Seyler DE, Vodicnik MJ. 1994. Implementing the ICH guidelines: one approach to tiered evaluation of reproductive and developmental toxicity. Teratology 49:399.

Buelke-Sam J, Byrd RA, Clarke DO, Rippy MK, Swanson SS, Swisher DK. 1994. Implementing the ICH guidelines: a rat segment I/II study and maternal kinetics evaluation (LY300046) a new antiviral agent. Teratology 49:400.

Buelke-Sam J, Byrd RA, Hoyt JA, Zimmermann JL. 1994. Implementing the ICH guidelines: a combined Segment I/II/III study in CD rats (LY275585), [Lys(B28),Pro(B29)]-human insulin analog. Teratology 49:400.

Kimmel CA, Buelke-Sam J. 1995. Neurobehavioral testing: regulatory update. Symposium co-organizer and co-chairperson. Newport Beach (CA): Joint Teratology/Neurobehavioral Teratology Societies.

Buelke-Sam J. 1996. Toxicology testing endpoints sensitive to estrogenic/anti-estrogenic materials in developing animals. Invited address, Arlington (VA): Endocrine Issue Coalition.

Buelke-Sam J, Schwier PW, Griffey KI, Pohland RC. 1996. Behavioral alterations in rats developmentally exposed to duloxetine, a mixed 5-HT/NE-reuptake inhibitor. Neurotoxicology and Teratology 18:334.

Hoyt JA, Fisher FL, Buelke-Sam JL, Hoffman WP, Francis PC. 1996. The selective estrogen receptor modulator, raloxifene: reproductive assessment following premating exposure in female rats. Teratology 53:103.

Clarke DO, Griffey KI, Buelke-Sam JL, Francis PC. 1996. The selective estrogen receptor modulator, raloxifene: reproductive assessments following preimplantation exposure in mated female rats. Teratology 53:103-104.

Buelke-Sam J, Griffey KI, Schwier PW, Francis PC. 1996. The selective estrogen receptor modulator, raloxifene: A Segment II/III delivery study in rats. I - maternal and preweaning offspring assessments. Teratology 53:104.

Buelke-Sam J, Cohen I, Wierda D, Griffey KI, Schwier PW, Fisher III L, Francis PC. 1996. The selective estrogen receptor modulator, raloxifene: A Segment II/III delivery study in rats. II - postweaning offspring assessments. Teratology 53:104.

Buelke-Sam, J. 1997. Preclinical reproductive and developmental toxicity testing of raloxifene. Invited address, Indianapolis (IN): Grand Rounds presentation.

Buelke-Sam J. 1998. ICH Update: Reproductive and Developmental Testing. Invited address, Indianapolis (IN): ICH Workshop.

Buelke-Sam J. 1998. Pregnancy Labeling Update. Invited address, Chicago (IL): Midwest Teratology Association.

Buelke-Sam J. 1999. Preclinical Testing to Support Pediatric Clinical Trials. Invited Seminar, G.D. Searle, Chicago, IL.

Buelke-Sam J. 2000. Design Issues in Studies of Postnatal Assessment Conducted for the EPA and FDA. Invited Seminar, WIL Research Laboratories, Ashland, OH.

Buelke-Sam J. 2000. Postnatal Evaluation in Developmental and Neonatal Toxicity Studies. Henry Stewart conference on Understanding the Regulator's Approach to Reproductive Toxicology Data. Washington, DC.

Buelke-Sam J. 2000. The role of sensory and motor assessments in developmental neurotoxicity testing. Invited speaker, Symposium: Revisiting the Developmental Neurotoxicity Test Guideline. Neurobehavioral Teratology Society Annual Meeting, Neurotoxicology and Teratology, 22:454.

Buelke-Sam, J, DeSesso, J., Holson, J., Mattison, D., Tyl, R. 2000. Mesotrione: the mechanistic basis for the species difference in reproductive and developmental toxicity and its relevance to humans. Expert Panel Member, Special Session, Teratology Society Annual Meeting, West Palm Beach, FL.

Buelke-Sam J. 2001. Postnatal Evaluation in Developmental and Juvenile Toxicity Studies. Henry Stewart Conference on Understanding the Regulator's Approach to Reproductive Toxicology Data. Washington, DC.

Beck, M.J., M.D. Nemec, G.J. Schaeffer, D.G. Stump, J. Buelke-Sam. 2002. Validation of peripheral tissue cholinesterase activity assessment in rats administered chlorpyrifos by gavage. Teratology, 65, 327.

Buelke-Sam J. 2002. Postnatal Evaluation in Developmental and Juvenile Toxicity Studies. Invited presenter, Henry Stewart Conference on Understanding the Regulator's Approach to Reproductive Toxicology Data. Washington, DC.

Buelke-Sam J. 2003. Comparative schedules of development in rats and humans: implications for developmental neurotoxicity testing. Invited speaker and discussant – Workshop on challenges of the developmental neurotoxicity study. Society of Toxicology, Annual Meeting, Salt Lake City, March 2003.

Buelke-Sam J and J.E. Fisher, symposium co-organizers. 2003. An update on animal juvenile toxicity testing: pharmaceutical use and environmental exposures in children. Co-sponsored by the Neurobehavioral Teratology Society and Teratology Society, Philadelphia. June, 2003.

Buelke-Sam J. 2003. Design considerations in juvenile toxicity testing. Invited symposium speaker, Co-sponsored by the Neurobehavioral Teratology Society and Teratology Society, Philadelphia, June, 2003.

Buelke-Sam J. C. Chambers, J. Friedman, C.A. Kimmel, J. Polifika, A. Scialli, M. Tassanari, Co-organizers. 2003. Teratology Society's Public Affairs Committee, COMMUNICATING RISKS FOR PREGNANCY EXPOSURES: A One-day Workshop on Appropriate Incorporation Of Animal Developmental Toxicity Data in Drug Labels. Philadelphia, June 2003.

Beck, M.J., D.G. Stump, M.D. Nemec, J. Holson, J.P. Tizzano and J. Buelke-Sam. 2003. Developmental toxicity studies in rats and rabbits with DOV 21,947: a triple reuptake inhibitor. Abstract for poster presentation at the Teratology Society Annual Meeting, Philadelphia, June 2003.

Buelke-Sam J. 2003. Postnatal Evaluation in Developmental and Juvenile Toxicity Studies. Invited presenter, Henry Stewart Conference on Understanding the Regulator's Approach to Reproductive Toxicology Data. April, Washington, DC.