UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF PREVENTION, PESTICIDES, AND TOXIC SUBSTANCES
WASHINGTON, D.C. 20460

THIS DOCUMENT SUPERSEDES THE PREVIOUS HIARC DOCUMENT DATED JUNE 20, 2001 (TXR No. 014599).

HED DOC. NO. 0051439

DATE: January 6, 2003

MEMORANDUM

SUBJECT: ***METHYL BROMIDE*** - 2ND Report of the Hazard Identification Assessment Review Committee.

FROM: Paul Chin
Reregistration Branch I
Health Effects Division (7509C)

THROUGH: Jess Rowland, Co-Chair
and
Elizabeth Doyle, Co-Chair
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: Christine Olinger, Risk Assessor
Reregistration Branch I
Health Effects Division (7509C)

PC Code: 053201

On November 19, 2002, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) re-evaluated the toxicology data because the registrant recently submitted a new subchronic (6-week) inhalation toxicity study in dog (MRID 45722801). The HIARC considered the results of this study in determining the endpoints for use in inhalation exposure risk assessments. The HIARC also re-affirmed the acute and chronic Reference Doses (RfDs) established at the previous HIARC meeting (June 20, 2001). In addition, HIARC re-evaluated the increased susceptibility of infants and children from exposure to Methyl Bromide as required by the Food Quality Protection Act (FQPA) of 1996 according to the 2002 OPP 10X Guidance document. The conclusions drawn at this meeting are presented in this report.

Committee Members in Attendance

Members present were: William Burnam, Elizabeth Doyle, Pam Hurley, Elizabeth Mendez, David Nixon, Jess Rowland, Ayaad Assaad, Jonathan Chen, Steve Knizner, John Liccione and Brenda Tarplee.

Member(s) in absentia: Paula Deschamp and Susan Makris

Also in attendance were: Whang Phang, Michael Metzger, Christine Olinger, Susan Hanley (Reregistration Branch 1)

Data Evaluation / Report Presentation

Paul Chin
Toxicologist
Reregistration Branch I

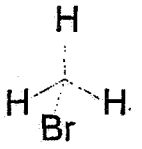
I. INTRODUCTION

Methyl bromide (MeBr) is a fumigant used to control insects, mites, rodents, plant pathogens, nematodes, termites and weeds. The registered uses are preplant, soil fumigation; stored commodities (both raw agricultural commodities and processed foods/feeds); greenhouses; termite control; grain elevators; mills, ships and transportation vehicles.

MeBr is a colorless and odorless gas at room temperature and atmospheric pressure.

The residue of concern is methyl bromide *per se* (R. Perfetti, CBRS No. 8601, 9/24/91). Tolerances for residues of methyl bromide in/on food and feed commodities are currently expressed in terms of inorganic bromide [40 CFR §180.123, §180.199 and §185.3480]. However, the Agency has determined that inorganic bromide is not of toxicological concern based on the currently available data and is requiring registrants to propose tolerances for methyl bromide to replace the inorganic bromide tolerances.

Chemical structure:



On April 29, 1999, under the request of the U.S. Department of Agriculture's Animal and Plant Health Inspection Service, Plant Protection and Quarantine (APHIS/PPQ), HED's Hazard Identification Assessment Review Committee (HIARC) met and made an expedited finding regarding the toxicological endpoints for methyl bromide for Section 18 for use on imported commodities [HED DOC. NO. 013340].

On April 12 and May 22, 2001, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) conducted a thorough evaluation of the toxicology data base of methyl bromide and of the proposed toxicity endpoints for use in risk assessments. The HIARC also evaluated the potential for increased susceptibility of infants and children from exposure to methyl bromide as required by the Food Quality Protection Act (FQPA) of 1996.

On November 19, 2002, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) re-evaluated the toxicology data because the registrant recently submitted a new subchronic (6-week) inhalation toxicity study in dog (MRID 45722801). The HIARC considered the results of this study in determining the endpoints for use in inhalation exposure risk assessments. The HIARC also re-affirmed the acute and chronic Reference Doses (RfDs) established at the previous HIARC meeting (June 20, 2001). In addition, HIARC re-evaluated the increased susceptibility of infants and children from exposure to Methyl Bromide as required by the Food Quality Protection Act (FQPA) of 1996 according to the 2002 OPP 10X Guidance document.

II FQPA - HAZARD CONSIDERATIONS

1. Adequacy of the Data Base for FQPA

The HIARC concluded that the toxicology data base for methyl bromide is adequate for an FQPA assessment based on the availability of the following studies:

- Developmental toxicity studies in rats and rabbits

- A two-generation reproduction toxicity in rats

- Acute and subchronic neurotoxicity studies in rats

- Acute and subchronic toxicity studies in dogs

- Studies from the open literature on neurotoxicity

2. Evidence of Neurotoxicity

HIARC concluded that there were concerns for neurotoxicity based on the following considerations:

Acute Neurotoxicity– See **Acute Reference Dose (RfD)–General Population**

Subchronic Neurotoxicity

In a 13-week neurotoxicity study (MRID No. 42964301; 43077401), CD rats (15 rats/sex/dose) were exposed by whole body inhalation to methyl bromide vapor (>99% a.i.) at levels of 0, 30, 70 or 140 ppm for 6 hr/day, 5 days/week (equivalent to male: 0, 19, 45, or 95 mg/kg/day; females: 0, 22, 51, or 101 mg/kg/day). Functional observation battery (FOB) and motor activity measurements were conducted at pre-test and weeks 4, 8 and 13 of the study.

Males and females showed different responses to methyl bromide in this study. In females at 30 ppm, methyl bromide did not produce treatment-related effects on mortality, body weight, FOB or motor activity. At 70 ppm, females had significantly decreased body weight/body weight gain (-7%/-23%), decreased total motor activity (-37%) and slightly reduced absolute brain weight (-5%). At 140 ppm, females had further decreases in mean body weight/body weight gain (-13%/-44%) and absolute brain weight (-10%). Motor activity decrease (-34%) was comparable to 70 ppm females. Number of rears was decreased (30% of controls) and ataxia was observed in 1-3 animals during FOB sessions. Increased inactivity was also noted. Slight nasal cavity epithelium dysplasia was observed in 3/6 females at 140 ppm.

In males at 30 and 70 ppm, methyl bromide did not produce treatment-related effects on mortality, body weight, FOB or motor activity. However, at 140 ppm, males had decreased body weight/body weight gain (-13%/-36%), mortality (2 animals), convulsions (2 animals), increased landing foot splay (+48%), increased incidence of uncoordinated air righting (8 vs. 4 control animals), possible slight decrease in fore- and hindlimb grip strength (-20%) were observed. Brain histopathology (2/6 males) was observed in animals that developed convulsions (one survived, one died during study). Slight nasal cavity epithelium dysplasia was also observed in 3/6 males at 140 ppm.

For females, the NOAEL is 30 ppm (22 mg/kg/day) and the LOAEL is 70 ppm (51 mg/kg/day) based on decreased body weight and motor activity.

For males, the NOAEL is 70 ppm (45 mg/kg/day). The LOAEL is 140 ppm (90 mg/kg/day) in males based on decreased body weight, increased mortality (2 animals), convulsions (2 animals affected), effects on several FOB parameters and brain histopathology in males.

The results of **developmental toxicity in rabbits (inhalation)** with methyl bromide showed lethargy, right side head tilt and ataxia at 80 ppm (MRID 41580401).

The results of **chronic toxicity/carcinogenicity study in mice (inhalation)** with methyl bromide showed ataxia, limb paralysis, and degenerative changes in cerebellum and celebrum at 100 ppm (MRID 42504101).

The results of **subchronic (5- to 7-week) toxicity study in dogs (inhalation)** with methyl bromide showed decreased responsiveness at 5 ppm, the lowest dose tested (MRID 43386802).

3. Developmental Toxicity Conclusions

Developmental Toxicity Study, Rabbit (inhalation)

In a developmental toxicity study (MRID No. 41580401), pregnant New Zealand White rabbits (26 animals/dose) were exposed by whole body inhalation to 0, 20, 40 or 80 ppm methyl bromide vapor for 6 hr/day on Days 6-16 of gestation. Mating was conducted using artificial insemination. Based on the insemination record the females were inseminated with sperm pooled from several bucks.

Maternal Toxicity

At 80 ppm, clinical signs of maternal toxicity including decreased appetite, lethargy, right side head tilt, slight ataxia and slight lateral recumbency were observed. These signs were mostly observed in three rabbits: #5427, #5428 and #5431. One doe (#5428) in this treatment group delivered on gestation day 27 and it was determined that this early

delivery may have been related to the toxicity that this animal was experiencing. In addition, a treatment-related, but not dose-related, decrease in body weight was observed in the maternal animals in the high dose group. Three animals (# 5427, 5428, and 5431) caused decrease in the mean body weights of the high dose group. The body weight loss of these animals prior to delivering their litters were 604, 464, and 136 g, respectively. No clinical signs of toxicity were present in the lower treatment groups.

Developmental Toxicity

The fetal data indicate an increase in the incidence of agenesis (absence) of the gall bladder in the fetuses of the high dose group (13/159) (8.2%) relative to the control group (2/190) (1.1%). The litter incidences of agenesis of the gall bladder were 5/19 (26.3%) in the high dose group and 1/21 (4.8%) in the control group. The litter incidences of agenesis of the gall bladder in the low- and mid-dose groups were 1/15 (6.7%) and 1/19 (5.3%), respectively. The individual animal data indicate 9 fetuses with missing gall bladder were from 4 dose with maternal toxicity in the high dose group. The litter incidences of agenesis was seen in 6 fetuses from one litter (animal # 5427) and 1 fetus each from 3 litters [animal # 5428, 5431 and 5430]. One dose (animal # 5432) with no maternal toxicity had 4 fetuses with missing gall bladder. Two dose (animal # 5426 and 5433) with maternal toxicity (lethargy only) had normal fetuses.

In a repeated study, it was confirmed that the observed finding of agenesis of the gall bladder was related to treatment and was not attributed to a particular male used for artificial insemination. The incidence of agenesis of the gall bladder found in this repeat study is similar to the incidence in the main study. The incidence of agenesis of the gall bladder in the fetuses were 4/92 (4.3%) in the high dose group and 1/114 (0.9%) in the control group. The incidence of agenesis of the gall bladder in the litters were 4/14 (28.6%) in the high dose group and 1/16 (6.3%) in the control group. At 80 ppm, the signs of severe maternal toxicity (lethargy, right side head tilt, slight ataxia and slight lateral recumbency) were not observed in this repeat study.

At 80 ppm, the number of fused sternebrae were increased in the high dose group (12.6%) when compared to the control group (0%). In addition, mean fetal body weight was slightly lower (4.4%; non-statistically significant) compared to the control group. Although the nominal fetal weight decrement was not statistically significant, the decrease is consistent with other effects occurring at the high dose.

The data seemed to indicate that the failure of gall bladder development was due to the direct effects of methyl bromide and it might not be caused by the parental influence.

The maternal NOAEL is 40 ppm and the LOAEL is 80 ppm based on decreased appetite, lethargy, right side head tilt, ataxia and lateral recumbency.

The developmental toxicity NOAEL is 40 ppm and the LOAEL is 80 ppm based on

agenesis of the gall bladder and increased incidence of fused sternebrae which was supported by decreased fetal body weight (statistically not significant).

This study is classified as acceptable/guideline and satisfies the guideline requirement (§83-3) for a developmental toxicity study in rabbits.

Developmental Toxicity Study, Rat (inhalation)

In a developmental toxicity study (MRID No. 00102990), methyl bromide vapor (99.5%) was administered to female Wistar rats by whole body exposure at concentrations of 0, 20 and 70 ppm
(1) during entire gestation period (Days 1 - 19) only,
(2) for 3 weeks prior to insemination and
(3) for 3 weeks prior to insemination through gestation period; exposure for 7 hr/day, 5 days/week.

Dams treated at high dose during gestation showed a non-statistically significant decrease in body weight at day 14 of gestation and at termination.

Among dams treated at high dose both before and during gestation, statistically significant but small (3.5%) decreases in body weight were observed between days 1-14 of gestation. These body weights were low primarily because of decreased weight gain that occurred between days 17-21 of pre-gestational treatment. Weight gain as % of gestation day 1 weight was similar to that of controls during gestation. In addition, slightly increased incidence of interstitial nephritis at 70 ppm during gestation is not considered significant enough to determine an LOAEL but is considered a possible threshold effect.

NOTE: A preliminary range-finding development toxicity study was not performed for this study. However, the rationale for dosing was based on the previous testing of methyl bromide at 66 or 100 ppm (7 hours/day, 5 days/week) in rats. This study showed that 6 months exposure to 66 ppm was tolerated and that exposure to 100 ppm produced severe pneumonia in some rats but no effects in others. In addition, decreased body weight was observed at 70 and 90 ppm with methyl bromide in a subchronic neurotoxicity study (MRID No. 43077401; 42964301) and a 2-generation reproduction study in rats (MRID 00160477), respectively.

The NOAEL for maternal toxicity is 70 ppm (HDT). Slightly increased incidence of interstitial nephritis at 70 ppm during gestation is not considered significant enough to determine an LOAEL but is considered a possible threshold effect.

No compound related developmental toxicity was found in this study. The NOAEL is 70 ppm (HDT).

This study is classified as acceptable/guideline and satisfies the requirements (§83-3) for a developmental toxicity study in rats.

4. Reproductive Toxicity Conclusions

A Two-Generation Reproduction Study, Rat

In a two-generation reproduction study (MRID 00160477; Accession No. 261736-261742), methyl bromide as vapor was administered to male and female CD Sprague-Dawley rats by whole body exposure at concentrations of 0, 3.0, 30 or 90 ppm (Males - 0, 2.4, 24 or 73 mg/kg/day; Females - 0, 2.8, 28 or 85 mg/kg/day) for two successive generations (6 hrs/day, 5 days/week). F0 males and females were exposed for 8 weeks prior to mating. Exposure of the F1 and F2 generations was initiated at 29-33 days of age and was continued for 11 weeks. Females were not exposed from Day 21 of gestation to Day 4 of lactation.

At 3 ppm, no maternal or reproductive effects were seen. At 30 ppm, decreased pregnancy rate was observed for the F2b generation ranging 23-25% and decreased pup weights on post-natal day 21 (F1a, F2a, F2b generations) ranging from 10-20%. However, at 30 ppm the reproductive effects were considered marginal.

At 90 ppm, F0 males showed significantly reduced body weight when compared to controls after the third week of the study. At this dose, significantly reduced absolute brain weights were observed in F0 males and F1 males and females. Significantly increased relative liver weights were evident in high-dose F0 males and females. In addition, decreased pregnancy rate was observed for the F2b generation and decreased pup weights on post-natal day 21 (F1a, F2a, F2b) ranging from 10-20%. Also at 90 ppm, decreased pup survival was observed in the F1b and F2a litters (12-16%).

The NOAEL for parental/systemic toxicity is 30 ppm (24 mg/kg/day) and the LOAEL is 90 ppm (73 mg/kg/day) based on reduced body weight during gestation.

The NOAEL for reproductive toxicity is 3 ppm (2.8 mg/kg/day) and the LOAEL is 30 ppm (24 mg/kg/day) based on reduced pregnancy rates (F2b generation).

The NOAEL for offspring toxicity is 3 ppm (2.8 mg/kg/day) and the LOAEL is 30 ppm (24 mg/kg/day) based on reduced pup weight on post-natal day 21 (F1a, F2a, F2b generations) ranging from 10-20%.

This study is classified as Acceptable/Guideline and satisfies the guideline requirements for a multi-generation reproduction study (83-4) in rats.

5. Additional Information from Literature Sources (if available)

A literature search on Medline and Toxline was conducted. The following relevant information is valuable in considering the toxicity of methyl bromide.

Severe methyl bromide poisoning in humans, some of them fatal, were reported. "For example, von Oettingen recorded 47 fatal and 174 nonfatal cases of methyl bromide intoxication between 1899 and 1952. Acute poisoning was characterized by lung irritation. The toxicity was manifested as paralysis of extremities, delirium, convulsions, and even typical epileptiform attacks. Some of these symptoms were persistent, and recovery occurred in a matter of months, sometimes incompletely with permanent disability. In all cases, the conditions of exposure are inadequately described, neither the methyl bromide concentration nor the exposure duration are exactly known." [Citation from Supplement: Methyl Bromide, American Conference of Governmental Industrial Hygienists (ACGIH) (1997) TLVs. Threshold Limit Values and Biological Exposure Indices for 1985-1986, 2nd ed., Cincinnati, OH]

6. Pre- and/or Post-natal Toxicity

Based on the weight-of -the-evidence considerations, HIARC determined that there is a low concern for pre-and/or post-natal toxicity resulting from exposure to methyl bromide.

A. Determination of Susceptibility

The HIARC concluded that there was no indication of increased susceptibility of rat fetuses following *in utero* exposure to Methyl Bromide in the prenatal developmental study in rats. However, there is qualitative evidence of increased susceptibility in the prenatal developmental study in rabbits since developmental effects were seen in the presence of lesser maternal toxicity. There was also quantitative evidence of increased susceptibility in the 2-generation reproduction study in rats since offspring effects were observed at a dose lower than that eliciting parental effects.

B. Degree of Concern Analysis and Residual Uncertainties

Since there is evidence of increased susceptibility of the young following exposure to Methyl Bromide in the rabbit developmental study and in 2-generation rat reproduction study, HIARC performed a Degree of Concern Analysis to: 1) determine the level of concern for the effects observed when considered in the context of all available toxicity data; and 2) identify any residual uncertainties after establishing toxicity endpoints and traditional uncertainty factors to be used in the risk assessment of this chemical. If residual uncertainties are identified, HIARC examines whether these residual uncertainties can be

addressed by a special FQPA safety factor and, if so, the size of the factor needed. The results of the HIARC Degree of Concern analysis for Methyl Bromide are presented as follows.

In the rabbit developmental toxicity study, the HIARC concluded that qualitative susceptibility was demonstrated because increased incidence of fused sternebrae and agenesis of the gall bladder were observed in pups whereas the maternal toxicity reported in this study (decreased appetite, lethargy, right side head tilt, ataxia, and lateral recumbency) was not seen in the repeat study. However, considering the overall toxicity profile and the doses and endpoints selected for risk assessment for Methyl Bromide, the HIARC characterized the degree of concern for the effects observed in this study as low, noting that the study was well-conducted, clear NOAELs/LOAELs were established, and the dose response for the observed effects are well characterized. In addition, the developmental NOAEL of 14 mg/kg/day identified in this study is used to establish the acute Reference Dose (aRfD) for the Females 13-50 population subgroup. Therefore, no residual uncertainties were identified for prenatal toxicity.

In the 2-generation reproduction study, quantitative susceptibility was demonstrated by reduced pregnancy rates in the F_2b generation and reduced pup body weight on post-natal day 21 (10-20%) at a dose lower than that for parental effects (reduced body weight during gestation). Considering the overall toxicity profile and the doses and endpoints selected for risk assessment for Methyl Bromide, the HIARC characterized the degree of concern for the effects observed in this study as low, noting that the study was well-conducted, clear NOAELs/LOAELs were established, and the dose response for the observed effects are well characterized. In addition, the NOAEL of 2.2 mg/kg/day identified to established the chronic RfD is comparable to the NOAEL of 2.8 mg/kg/day for offspring toxicity. Therefore, no residual uncertainties were identified for pre- and/or postnatal toxicity.

C. Special FQPA Safety Factor(s):

The HIARC determined that the special FQPA Safety Factor can be removed (**1X**) because: 1) acceptable developmental and reproduction studies have been submitted and reviewed; 2) there is no evidence (quantitative or qualitative) of susceptibility following *in utero* exposure to rats; 3) there is low level of concern and no residual uncertainties for the effects seen in the developmental toxicity study in rabbits and in the 2-generation reproduction studies after establishing toxicity endpoints and traditional uncertainty factors to be used in the risk assessment.

NOTE: The Special FQPA Safety Factor recommended by the HIARC **assumes**

that the exposure databases (dietary food, drinking water, and residential) are complete and that the risk assessment for each potential exposure scenario includes all metabolites and/or degradates of concern and does not underestimate the potential risk for infants and children.

7.Recommendation for a Developmental Neurotoxicity Study

The HIARC concluded that there is a concern for developmental neurotoxicity resulting from exposure to Methyl Bromide.

A. Evidence that suggest requiring a Developmental Neurotoxicity study:

The results of both **acute and subchronic neurotoxicity studies (inhalation) in rats** with methyl bromide showed decreased activity, alertness, decreased grip strength, and increased landing foot splay at 350 and 70 ppm, respectively.

The results of **developmental toxicity study in rabbits (inhalation)** with methyl bromide showed lethargy, right side head tilt and ataxia at 80 ppm.

The results of **chronic toxicity/carcinogenicity study in mice (inhalation)** with methyl bromide showed ataxia, limb paralysis, and degenerative changes in cerebellum and celebrum at 100 ppm.

The results of **subchronic (5- to 7-week) toxicity study in dogs (inhalation)** methyl bromide showed decreased responsiveness at 5 ppm, the lowest dose tested.

B. Evidence that do not support a need for a Developmental Neurotoxicity study:

None.

Based on the weight of evidence presented, the HIARC concluded that a developmental neurotoxicity study conducted in rats via the inhalation route of administration is required for Methyl Bromide.

In accordance with the 2002 *OPP Guidance Document on Determination of the Appropriate FQPA Safety Factor(s) in Tolerance Assessment*, since there is not sufficient reliable data to assign a different factor than the 10X default factor, the HIARC concluded that a Database Uncertainty Factor (UF_{DB}) of 10X is required until the data from the DNT are received and evaluated.

III. HAZARD IDENTIFICATION

1. Acute Reference Dose (RfD)–Females 13-50

Study Selected: Developmental Toxicity Study in Rabbits (Inhalation)

Guideline #: 870.3700b

MRID No.: 41580401

Executive Summary:

In a developmental toxicity study (MRID No. 41580401), pregnant New Zealand White rabbits (26 animals/dose) were exposed by whole body inhalation to 0, 20, 40 or 80 ppm methyl bromide vapor for 6 hr/day on Days 6-16 of gestation. Mating was conducted using artificial insemination. Based on the insemination record the females were inseminated with sperm pooled from several bucks.

Maternal Toxicity
At 80 ppm, clinical signs of maternal toxicity including decreased appetite, lethargy, right side head tilt, slight ataxia and slight lateral recumbency were observed. These signs were mostly observed in three rabbits: #5427, #5428 and #5431. One doe (#5428) in this treatment group delivered on gestation day 27 and it was determined that this early delivery may have been related to the toxicity that this animal was experiencing. In addition, a treatment-related, but not dose-related, decrease in body weight was observed in the maternal animals in the high dose group. Three animals (# 5427, 5428, and 5431) caused decrease in the mean body weights of the high dose group. The body weight loss of these animals prior to delivering their litters were 604, 464, and 136 g, respectively. No clinical signs of toxicity were present in the lower treatment groups.

Developmental Toxicity
The fetal data indicate an increase in the incidence of agenesis (absence) of the gall bladder in the fetuses of the high dose group (13/159) (8.2%) relative to the control group (2/190) (1.1%). The litter incidences of agenesis of the gall bladder were 5/19 (26.3%) in the high dose group and 1/21 (4.8%) in the control group. The litter incidences of agenesis of the gall bladder in the low- and mid-dose groups were 1/15 (6.7%) and 1/19 (5.3%), respectively. The individual animal data indicate 9 fetuses with missing gall bladder were from 4 does with maternal toxicity in the high dose group. The litter incidences of agenesis was seen in 6 fetuses from one litter (animal # 5427) and 1 fetus each from 3 litters [animal # 5428, 5431 and 5430]. One doe (animal # 5432) with no maternal toxicity had 4 fetuses with missing gall bladder. Two does (animal # 5426 and 5433) with maternal toxicity (lethargy only) had normal fetuses.

In a repeated study, it was confirmed that the observed finding of agenesis of the gall bladder was related to treatment and was not attributed to a particular male used for artificial insemination. The incidence of agenesis of the gall bladder found in this repeat study is similar to the incidence in the main study. The incidence of agenesis of the gall bladder in the fetuses were 4/92 (4.3%) in the high dose group and 1/114 (0.9%) in the control group. The incidence of agenesis of the gall bladder in the litters were 4/14 (28.6%) in the high dose group and 1/16 (6.3%) in the control group. At 80 ppm, the signs of severe maternal toxicity (lethargy, right side head tilt, slight ataxia and slight lateral recumbency) were not observed in this repeat study.

At 80 ppm, the number of fused sternebrae were increased in the high dose group (12.6%) when compared to the control group (0%). In addition, mean fetal body weight was slightly lower (4.4%; non-statistically significant) compared to the control group. Although the nominal fetal weight decrement was not statistically significant, the decrease is consistent with other effects occurring at the high dose.

The data seemed to indicate that the failure of gall bladder development was due to the direct effects of methyl bromide and it might not be caused by the parental influence.

The maternal NOAEL is 40 ppm and the LOAEL is 80 ppm based on decreased appetite, lethargy, right side head tilt, ataxia and lateral recumbency.

The developmental toxicity NOAEL is 40 ppm and the LOAEL is 80 ppm based on agenesis of the gall bladder and increased incidence of fused sternebrae which was supported by decreased fetal body weight (statistically not significant).

This study is classified as acceptable/guideline and satisfies the guideline requirement (§83-3) for a developmental toxicity study in rabbits.

Dose and Endpoint for Establishing RfD: The NOAEL for developmental toxicity is 40 ppm (equivalent to 14 mg/kg/day) based on agenesis of the gall bladder and increased incidence of fused sternebrae which was supported by decreased fetal body weight at 80 ppm (28 mg/kg/day).

Uncertainty Factor (UF): 1000X (**UF_{DB} of 10X** for lack of rat developmental neurotoxicity study, 10X for interspecies extrapolation and 10X for intraspecies variation).

Comments about Study/Endpoint/Uncertainty Factor: This endpoint is appropriate for females 13-50 subpopulation only since the end point is an in utero affect. The HIARC noted that in the absence of oral toxicity studies with this material, the use of an endpoint via the inhalation route is a conservative approach and would not underestimate the risk from dietary exposure.

Acute RfD (Females 13-50) = $\frac{\text{14 mg/kg (NOAEL)}}{\text{1000 (UF)}}$ = 0.014 mg/kg

Acute Population Adjusted Dose (aPAD) = $\frac{\text{0.014 mg/kg (RfD)}}{\text{1X (Special FQPA SF)}}$ = **0.014 mg/kg**

2. Acute Reference Dose (RfD)–General Population

Study Selected: Acute Neurotoxicity Study in Rats (Inhalation)

Guideline #: 870.6200

MRID No.: 42793601

Executive Summary:

In an acute neurotoxicity study (MRID No. 42793601), CD rats (15 rats/sex/dose) were exposed by whole body inhalation to 0, 30, 100 or 350 ppm methyl bromide vapor for 6 hours (equivalent to males: 0, 27, 90 or 314 mg/kg/day and females: 0, 30, 101, or 354 mg/kg/day). Test animals were observed for 16 days. Functional observation battery (FOB) was conducted at pre-test and days 1, 2, 8 and 15 post-treatment. Motor activity measurements was conducted at pre-test and days 1, 8 and 15 post-treatment.

Under the conditions of this study, methyl bromide did not produce any mortality, body weight loss, gross or microscopic changes at all dose levels. However, at 350 ppm, decreased activity, increase in number of animals with drooping/half-closed eyelids and alertness as measured in a FOB examination, decreased rears, decreased motor activity, increased piloerection and decreased body temperature in males and females were observed. A slight decrease in hind-limb grip strength in males may have been treatment-related. Effects were transient and all animals were assessed to be normal by 1 week post-exposure. At 30 or 100 ppm, no treatment-related effects on FOB or motor activity were observed.

The NOAEL is 100 ppm and the LOAEL is 350 ppm decreased activity, increase in number of animals with drooping/half-closed eyelids and alertness as measured in a FOB examination, decreased rears, decreased motor activity, increased piloerection and decreased body temperature in males and females after dosing.

This study is classified as acceptable/guideline and satisfies the guideline requirement (§81-81-8) for an acute neurotoxicity study in rats.

Dose and Endpoint for Establishing RfD: **The NOAEL is 100 ppm (equivalent to 90 mg/kg/day)** based on decreased activity, increase in number of animals with drooping/half-closed eyelids and alertness as measured in a FOB examination, decreased rears, decreased motor activity, increased piloerection and decreased body temperature at 350 ppm (314 mg/kg/day).

Uncertainty Factor (UF): 1000X (**UF_{DB} of 10X** for lack of rat developmental neurotoxicity study, 10X for interspecies extrapolation and 10X for intraspecies variation).

Comments about Study/Endpoint/Uncertainty Factor: Effects were seen after a single exposure, and thus appropriate for this scenario. The HIARC noted that in the absence of oral toxicity studies with this material, the use of an endpoint via the inhalation route is a conservative approach and would not underestimate the risk from dietary exposure.

Acute RfD (General population) = $\frac{\text{90 mg/kg (NOAEL)}}{\text{1000 (UF)}}$ = 0.09 mg/kg

Acute Population Adjusted Dose (aPAD) = $\frac{\text{0.09 mg/kg (RfD)}}{\text{1X (Special FQPA SF)}}$ = **0.09 mg/kg**

3. **Chronic Reference Dose (RfD)**

Study Selected: Chronic feeding/carcinogenicity in rats (microcapsulated)

Guideline #: 870.4300

MRID No.: 44462501

Executive Summary:

In a combined chronic toxicity/carcinogenicity study (MRID 44462501),

microencapsulated methyl bromide was administered to 4 groups of male and female Crl:CD®(SD)BR rats for a period of 12 or 24 months (interim and main study, respectively) in the diet at concentrations of 0 (diet control), 0 (placebo control), 0.5, 2.5, 50, or 250 ppm. These concentrations were equivalent to 0, 0.02, 0.11, 2.20 and 11.10 mg/kg/day in males and 0, 0.03, 0.15, 2.92 and 15.12 mg/kg/day in females. Groups of 50 males and 50 females were designated for the **main study** and were maintained on the treated food for up to 104 weeks. Groups of 20 males and 20 females were sacrificed at 52 weeks in the diet control, placebo control, 50 ppm group and the 250 ppm group.

Survival was not affected by the test substance in any of the treated groups compared to either of the control groups. No treatment-related clinical signs or effects on hematology, serum chemistry, urinalysis, or organ weight data were observed. The test article did not produce changes in ophthalmoscopic examinations for the treated groups compared to the controls. Macroscopic and microscopic evaluations of organs and tissues at the interim and final sacrifices revealed only normal age-related changes, changes that were observed with equal frequency in the controls. **No treatment-related increase in tumor incidence was found in this carcinogenicity study.**

Statistically significant treatment-related effects were observed on body weights, body weight gains and food consumption in males and females treated with 250 ppm of the test substance during the first 12 to 18 months of the study. Males in the 250 ppm group had decreases of 5.5% in mean body weight compared to the diet control at week 2, by week 14 this decrease was 10% and remained consistently lower through week 70. During the second year of the study these animals gradually regained the weight and were comparable to controls at the end of the study. Females in the 250 ppm group had a decrease of 3.7% in mean body weight compared to the diet control at week 2, by week 14 this decrease was 8.3% and also remained consistently lower through week 57. After week 57 females in the 250 ppm group gained weight gradually and the decreases disappeared by the end of the study (week 104) at which time this group had mean body weight values that were similar to controls. Mean body weight gain was markedly decreased during the first 18-months of the study for animals treated with 250 ppm methyl bromide; decreases of 9-18% and 12-21% were observed for males, and 7-22% and 11-19% were observed for females when compared to the basal diet and placebo control groups, respectively. Males receiving 250 ppm had decreased food consumption that ranged from 3.7 - 11.5 % for week 71-72, and females at this concentration had decreases of 4.8 - 10.5% for week 54-55 compared to their respective control groups.

The NOAEL is 50 ppm (2.20 mg/kg/day for males and 2.92 mg/kg/day for females). The LOAEL is 250 ppm (11.10 mg/kg/day for males and 15.12mg/kg/day for females), based on decreased body weight, body weight gain and food consumption in males and females during the first 18 months of the study.

No evidence of carcinogenicity was observed in male or female rats fed methyl

bromide at dietary concentrations of 0.5, 2.50, 50 or 250 ppm for 104 weeks. Dosing was adequate based on decreases in body weight, body weight gain and food consumption in males and females at 250 ppm (HDT).

This chronic toxicity/carcinogenicity study in the rat is **Acceptable/guideline** and satisfies the guideline requirements for a combined chronic toxicity/carcinogenicity oral study (§83-5) in rats.

Dose and Endpoint for Establishing RfD: The NOAEL is 50 ppm (equivalent to 2.2 mg/kg/day) based on decreased body weight, body weight gain and food consumption at 250 ppm (11.10 mg/kg/day).

Uncertainty Factor(s): 1000X (**UF_{DB} of 10X** for lack of rat developmental neurotoxicity study, 10X for interspecies extrapolation and 10X for intraspecies variation).

Comments about Study/Endpoint/Uncertainty Factor:
At the previous HIARC meeting (April 12, 2001) for this chemical the NOAEL of 250 ppm (11.1 mg/kg/day for males; HDT) was chosen because there were no biochemical or morphological effects at any dose tested **at the end of the study**. In addition, treatment with methyl bromide did not cause decreases in body weight and food consumption at 250 ppm at the end of the study.

However, consistent and statistically significant decreases were observed on body weights, body weight gains and food consumption in rats treated with 250 ppm of the test substance **during the first 12 to 18 months of the study**. Therefore, **conservatively**, the **NOAEL of 50 ppm** (2.2 mg/kg/day) is selected.

Two subchronic (4-week and 90-day feeding) studies in rats were available for consideration, however, use of the endpoints from these studies were considered not appropriate for the following reasons: In the 4-week feeding study (MRID No. 43776401), the NOAEL is 0.835 mg/kg/day and the effect seen at the LOAEL (7.99 mg/kg/day; HDT) is the marginal decrease in body weight gain seen in conjunction with decreased food consumption and also the duration of exposure (4-week) from this study was considered not appropriate for deriving the chronic RfD.

In the 90-day feeding study (MRID No. 00154564), the NOAEL is 2 mg/kg/day and the effects seen at the LOAEL (10 mg/kg/day) are due to irritation of the stomach lining (hyperplasia of the squamous epithelium) and not systemic toxicity and were not seen in the 2-year study. Therefore, this study was deemed not appropriate for establishing the RfD.

Chronic RfD = $\frac{\text{2.2 mg/kg/day (NOAEL)}}{\text{1000 (UF)}}$ = **0.002 mg/kg/day**

Chronic Population Adjusted Dose (cPAD) = $\frac{\text{0.002 mg/kg (RfD)}}{\text{1X (Special FQPA SF)}}$ = **0.002 mg/kg**

4. **Incidental Oral Exposure: Short-Term (1 - 30 days)**

The chemical is applied by a certified applicator. Use pattern and physical properties (methyl bromide is a gas at room temperature and atmospheric pressure) indicates no potential exposure via this route. Therefore, no hazard was identified and quantification of risk is not required.

5. **Incidental Oral Exposure: Intermediate-Term (1 - 6 Months)**

The chemical is applied by a certified applicator. Use pattern and physical properties (methyl bromide is a gas at room temperature and atmospheric pressure) indicates no potential exposure via this route. Therefore, no hazard was identified and quantification of risk is not required.

6. **Dermal Absorption**

The use pattern for methyl bromide (fumigation) does not present a concern for dermal exposure.

7. **Dermal Exposure (All Durations)**

The use pattern for methyl bromide (fumigation) does not present a concern for dermal exposure and therefore. Therefore, no hazard was identified and quantification of risk is not required.

8. **Inhalation Exposure: ALL DURATIONS [Short (1-30 days), intermediate (1-6 months), and long-term (> 6 months)]**

Selected Study: Subchronic (5- to 7-week) Inhalation Toxicity - Dog
Subchronic (6-week) Inhalation Toxicity - Dog

Guideline #: 870.3465

MRID No.: 43386802 (5-7 week); 45722801 (6-week)

Executive Summary (5-7 week):

In a subchronic (5- to 7-week) inhalation toxicity study (MRID 43386802), methyl bromide (tech., 100% a.i.) was administered 7 hours/day, 5 days/week to 4 beagle dogs/sex/dose by whole body exposure at target concentrations of 0, 5, 10/150, 25, 50 or 100 ppm (actual mean concentrations 0, 5.3, 11.0/158.0, 26.0, 53.1 or 102.7 ppm; equivalent to 0, 0.021, 0.043/0.614, 0.101, 0.206 or 0.399 mg/L), as follows:

5 Week sacrifice - 2 dogs/sex, 0 ppm group and all dogs, 25, 50 and 100 ppm groups, for 5 weeks (total 24 exposures);

7 Week sacrifice - 2 dogs/sex, 0 ppm group and all dogs, 5 ppm group for 7 weeks (total 34 exposures); and all dogs, 10/150 ppm group for 5 weeks at 10 ppm (24 exposures), then at 150 ppm for 6 additional exposures and terminated. In addition to standard evaluations performed in a guideline subchronic study, a neurological examination was performed by a veterinarian after termination of exposures and serum bromide levels were measured weekly.

5 Week sacrifice:

At **5.3, 11, or 26 ppm**, there were no treatment-related effects on food consumption, ophthalmological findings, hematology parameters, organ weights or gross findings (Table 2). However, at **53.1 ppm**, 2/8 dogs showed decreased activity during exposure beginning day 14. And, at **102.7 ppm**, 3/8 dogs showed decreased activity beginning exposure day 9, and by exposure day 12 and continued until sacrifice all dogs showed decreased activity. One male developed tremors on day 10. In addition, these dogs at 102.7 ppm lost body weight (9% less than controls). Cumulative weight loss of males and females were 0.6 kg and 1.0 kg, respectively. **The systemic toxicity NOAEL for 5 weeks (24 exposures) is 26 ppm. The LOAEL is 53.1 ppm based on decreased activity.**

7 Week sacrifice:

At 5.3 ppm, 2/8 dogs (both females) showed clinical signs of toxicity on exposure day 34 (Table 2). One female showed unresponsiveness and the other female showed unresponsiveness and depressed appearance. Since no treatment-related findings were reported in the animals exposed to 11 ppm for 5 weeks (24th exposure), exposure concentration of methyl bromide was increased from 11 to 158 ppm for 6 additional exposures. However, **on exposure day 2 at 158 ppm,** all dogs showed decreased activity. On exposure day 6, all dogs appeared lethargic and 1 male showed tremors and prostration. Two days after the 6th and last exposure, ataxia, intentional tremor,

nystagmus, marked depression and inability to perform postural responses were seen in all dogs. Three males were sacrificed due to opisthotonos, paddling gait of all limbs, opening/closing of jaws and convulsions. In addition, all dogs at 158 ppm lost body weight (males loss of 1.2 kg; females loss of 0.7 kg). Also at this dose, there were increased urinary bilirubin and protein; vacuolization of the cerebellar granular layer (8/8); olfactory epithelial degeneration in the nasoturbinal tissues (8/8) and intracytoplasmic vacuolization of the adrenal gland *zona fasciculata* (4/4 males). **The results of this study indicate that the effects of methyl bromide by inhalation exposure are cumulative and dose-related. At the lowest concentration no effect was seen until exposure day 34 whereas as the exposure concentration increased, the effects were seen at fewer exposure and severity was increased.**

The systemic LOAEL for a 7 weeks (34 exposures) is 5.3 ppm (1.43 mg/kg/day) based on decreased responsiveness in females; a NOAEL was not established for this exposure (7-week) period.

This subchronic toxicity study is classified **Acceptable/Non-Guideline** (§82-4). A subchronic inhalation study in the dog was not required by the US EPA for reregistration of methyl bromide; this study was conducted as a range-finding study for a chronic inhalation study in dogs to satisfy data requirements of California Department of Pesticide Regulation.

Executive Summary (6 week):

In a six-week nonguideline inhalation toxicity study (MRID 45722801), four groups of beagle dogs consisting of 4 males and 4 females/group were administered methyl bromide (Lot No: 1010PK15A; purity: 100% a.i.) by whole body exposure at concentrations of 0, 5.3, 10, and 20 ppm (**equivalent to 0, 1.8, 3.4 and 6.9 mg/kg/day**). The exposures were for seven hours/day, five days/week for six weeks (total of 30 exposures). There were no compound related effects on mortality, clinical signs, body weight, food consumption, spleen weights, or gross or histological pathology. Functional observational battery and locomotor activity tests showed no abnormalities relative to controls with one exception. One male and one female at the 20 ppm dose and one male at the 10 ppm dose demonstrated an absence of proprioceptive placing, although no evidence of weakness in motor strength or other signs of neurotoxicity was found.

The LOAEL for methyl bromide was 10 ppm for male dogs and 20 ppm for female dogs based on the absence of proprioceptive placing. The NOAELs was 5.3 ppm for male dogs and 10.0 ppm for female dogs. This six-week inhalation toxicity study in beagle dogs is **Acceptable/Nonguideline** and fulfills the intent of the study.

Dose/Endpoint for Risk Assessment: **The systemic LOAEL is 5.3 ppm (1.43**

mg/kg/day) based on decreased responsiveness in females following 7 weeks of exposure.

Comments about Study/Endpoint:

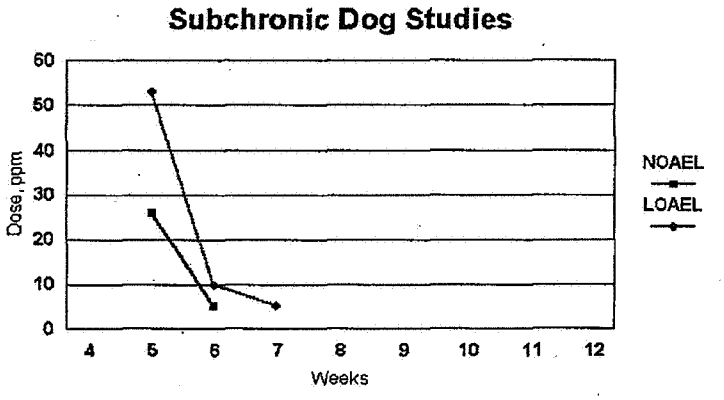
Two subchronic inhalation studies conducted in dogs with Methyl Bromide (MRID #43386802, 45722801) were considered together. In these subchronic studies, the test animals were exposed for 7 hours/day, 5 days/week, which simulates worker exposure. However, homeowners living near treated fields would be exposed a minimum of 16 hours/day (assuming workplace is not near the treated field) and 24 hours/day on weekends. If school and home is near a treated field, a bystander (i.e. child) would be continually exposed without a break. Although risk calculations take into account the differing exposure amounts, the endpoints do not reflect continuous exposure, a highly probable scenario for bystanders (i.e. children).

Analysis of the relationship between effects, duration of exposure, and dosages of the subchronic inhalation toxicity studies in dogs showed that toxicity of methyl bromide appeared to show **a cumulative effect with increasing numbers of exposures** and **steepness of the dose-response curve** as shown below (see **Table 1** and **Figure 1**). Both table and figure show the NOAEL/LOAEL values from 5-, 6-, and 7-week inhalation toxicity studies in dogs. The NOAEL/LOAEL from the 5-week inhalation toxicity study in dogs was 26 ppm/53.1 ppm. Although no effect was seen up to 5- or 6-weeks of exposure at 5.3 ppm, **clinical effects (decreased activity) were seen after 7-weeks exposure** at 5.3 ppm **(LDT)** in the subchronic studies in dogs. Figure 1 also demonstrates that as the duration of exposure increased the effect is seen at progressively lower doses, and the decrease does not appear to approach a plateau. Therefore, clinical effects could occur in shorter period (less than 7-week) with continuous exposure to methyl bromide. With this consideration along with the steepness of the dose-response curve (Figure 1), HIARC selected the toxicity endpoint (decreased responsiveness in females) from the 7 week exposure for short-term as well as for all other duration of inhalation exposure and the dose of 5.3 ppm (LOAEL).

It should be noted that in the previous HIARC report (dated June 20, 2001), the endpoint for short-term inhalation exposure was determined from the developmental toxicity study in rabbits (MRID No.: 41580401) because duration period of exposure for short-term exposure was defined as 1 to 7 days (as per old policy). However, use of the endpoint from the developmental toxicity in rabbits is inappropriate for the exposure time period of 1day to 1 month (as per current policy).

Table 1: Summary of NOAEL/LOAEL values determined from 5-, 6-, and 7-week inhalation toxicity studies in dogs

	WEEKS OF EXPOSURE TO METHYL BROMIDE		
	5	6	7
Study Report (MRID No.)	43386802	45722801	43386802
NOAEL (ppm)	26	5.3	Not determined
LOAEL (ppm)	53.1	10	5.3 **(LDT)**
Number of animals affected	2/8	1/8	2/8
Clinical effects observed	decreased activity	absence of proprioceptive placing	unresponsiveness



9. Margins of Exposure

Summary of target Margins of Exposure (MOEs) for risk assessment.

Route / Duration	Short-Term (1-30 Days)	Intermediate-Term (1 - 6 Months)	Long-Term (> 6 Months)
Occupational (Worker) Exposure			
Dermal	NA	NA	NA
Inhalation	300	300	1000
Residential (Non-Dietary) Exposure			
Oral	NA	NA	NA
Dermal	NA	NA	NA
Inhalation	3000	3000	10000

NA = Not applicable

The target MOE of 300 for **occupational short- and intermediate-term inhalation** exposure risk assessments will include the conventional 100X (10X for interspecies

extrapolation and 10X for intraspecies variations) and 3X UF_L for the lack of a NOAEL in the dog inhalation studies.

The target MOE of 1000 for **occupational long-term inhalation** exposure risk assessments will include the conventional 100X (10X for interspecies extrapolation and 10X for intraspecies variations), 3X UF_L for the lack of a NOAEL in the dog inhalation studies, and 3X UF_S for use of subchronic data to support a long-term exposure duration.

The target MOE of 3000 for **residential short- and intermediate-term inhalation** exposure risk assessments will include the conventional 100X (10x for interspecies extrapolation and 10x for intraspecies variations), 3X UF_L for the lack of a NOAEL in the dog inhalation studies, and 10X UF_{DB} for the lack of a required DNT study.

The target MOE of 10,000 for **residential long-term inhalation** exposure risk assessments will include the conventional 100X (10x for interspecies extrapolation and 10x for intraspecies variations), 10X UF_L for the lack of a NOAEL in the dog inhalation studies and use of a subchronic study ($UF_{S)}$ to assess long-term effects, and 10X ($UF_{DB)}$ for the lack of a required DNT study.

10. Recommendation for Aggregate Exposure Risk Assessments

As per FQPA, 1996, when there are potential residential exposures to the pesticide, aggregate risk assessment must consider exposures from three major sources: oral, dermal and inhalation exposures. For methyl bromide the use pattern does not indicate the potential for exposure via the oral (incidental oral) or dermal exposures. Therefore, aggregate risk assessments are not required.

IV. CLASSIFICATION OF CARCINOGENIC POTENTIAL

1. Combined Chronic Toxicity/Carcinogenicity Study in Rats (microencapsulated)

MRID No.: 44462501

Executive Summary: See Chronic RfD.

Discussion of Tumor Data: There were no treatment-related increase in tumor incidence in this study.

Adequacy of the Dose Levels Tested: Dosing was adequate based on decreases in body weight, body weight gain and food consumption in males and females.

2. Combined Chronic Toxicity/Carcinogenicity Study in Rats (inhalation)

MRID No.: 44359101, 41213301, 42418301.

Executive Summary:

NOTE: The Executive Summary, below, provides an updated summary of the entire study. Additional details on this study can be found in HED Doc. Nos. 007017 and 009843.

In a chronic toxicity/carcinogenicity study (MRIDs 41213301, 42418301, 44359101), 50 Wistar (Cpb:Wu) rats/sex/dose were exposed to methyl bromide (>98.8% a.i.) by whole body exposure at concentrations of 0, 3, 30 or 90 ppm (0, 0.0117, 0.117 or 0.335 mg/L) for 127 weeks (males) or 129 weeks (females). Four additional groups of 10 animals/ sex/dose were also included for sacrifice as follows: (a) week 13, clinical chemistry/hematology evaluations; (b) week 53, clinical chemistry/hematology evaluations and gross/microscopic pathology; © week 105, gross/microscopic pathology and (d) week 41, behavioral evaluations (males only). A reexamination of nasal cavity microscopic lesions was later conducted by an independent reviewing pathologist and the final diagnosis reached after discussion with the study pathologist (MRID 44359101). (The reexamination was not performed according to recommended protocol for peer review and therefore the conclusions of this review are based on the results from the original report).

At 3 ppm, statistically significant increases in incidence (but not severity) of basal cell hyperplasia of the nasal cavity were observed at termination (27.0%, males and 31.7%, females, vs. 8.7% and 11.9%, controls, respectively. The severity of most lesions was very slight.

At 30 ppm, severity as well as incidence of basal cell hyperplasia of the nasal cavity was increased at termination (46.9%, males and 40.8%, females). The severity of lesions was slight or moderate.

At 90 ppm, decreased survival (at termination, males 30% vs. 16%, controls and females 14% vs. 30%, controls; statistically significant only on a few occasions in each sex), decreased mean body weight (at termination -5%, males; significant frequently during study and -12%, females; significant throughout most of study after Week 4). There were also increased incidence of grossly visible hemothorax in animals found dead or sacrificed *in extremis*, significantly increased incidence of thrombus (43% vs. 10%, controls, males and 33% vs. 8%, females), cartilaginous metaplasia (24% vs. 4%, controls, males) and moderate to severe myocardial degeneration (73% vs. 41%, controls, females; not significant in males - 84% vs. 65%). Irritation of the esophagus and forestomach may have been related to inadvertent ingestion of test material (e.g., during grooming). In males, increases in hyperkeratosis of the esophagus (67% vs. 39%, controls; statistically significant) and stomach (52% vs. 30%, controls; not significant)

were observed. However, in these males at 90 ppm, methyl bromide did not produce treatment-related effects on clinical signs, hematology, clinical chemistries, urinalysis parameters or behavioral parameters.

The NOAEL for local respiratory irritation is <3 ppm (<1.9 mg/kg/day). The LOAEL for local respiratory irritation is 3 ppm (1.9 mg/kg/day), based on increased incidence of basal cell hyperplasia of the nasal cavity in both sexes.

The NOAEL for systemic toxicity is 30 ppm (19 mg/kg/day). The LOAEL is 90 ppm (58 mg/kg/day), based on increased mortality, decreased body weight and relative brain weight, hemothorax, increased incidence of thrombus, cartilaginous metaplasia, myocardial degeneration and irritation of the esophagus and forestomach.

This chronic toxicity/carcinogenicity study is classified **Guideline-Acceptable** for 83-2(a) carcinogenicity study and satisfies the guideline requirements for an inhalation carcinogenicity study in the rodent.

Discussion of Tumor Data: No treatment-related increase in tumor incidence was found in this carcinogenicity study.

Adequacy of the Dose Levels Tested: Dosing was adequate based on increased mortality, decreased body weight and relative brain weight, hemothorax, increased incidence of thrombus, cartilaginous metaplasia, myocardial degeneration and irritation of the esophagus and forestomach.

3. Carcinogenicity Study in Mice (inhalation)

MRID No.: 42504101

Executive Summary:
In a 2-year chronic toxicity/carcinogenicity study (MRID NO. 42504101), 50 B6C3F$_1$ mice/sex/dose were exposed for 102 weeks to methyl bromide by whole body exposure at atmospheric levels of 0, 10, 33 or 100 ppm (0, 0.03876, 0.1279 or 0.3876 mg/l). In addition, groups of 10 animals/sex/dose were exposed for interim sacrifice at 6 months and at 15 months, and groups of 16 animals/sex/dose for neurobehavioral assessment at 3 month intervals. Exposures were conducted 5 days/week for 6 hrs/day. Exposure of all high dose animals was terminated after 20 weeks due to excessive mortality in males and males from the interim sacrifice and neurobehavioral groups were incorporated into the main group to ensure adequate survivors.

No significant toxicity was observed at 10 or 30 ppm in either males or females, although a marginal reduction in body weight gain (-12%) was observed in females at week 100

and abnormal posture was observed late in the study in 1 male and 3 females. Due to the low incidence of the clinical effects and the small decrease in gain, these effects were not considered to be significant treatment-related effects.

At 100 ppm, survival was markedly decreased in males (23% vs. 82%, controls, at termination). Despite termination of exposure of high-dose mice to methyl bromide after week 20, clinical signs such as abnormal posture, tremors, ataxia, limb paralysis and emaciation persisted until termination. Some neurobehavioral effects were also observed (including increased startle response, decreased general activity). In addition, decreased mean body weight gain was observed (-56% less than controls, males and -41% less than controls, females). Microscopic lesions included degeneration of the cerebellum (44%, males; 18%, females vs. 0% in controls), cerebral degeneration (16%, males, 3%, females vs. 0% in controls), chronic cardiomyopathy (54%, males, 58%, females vs. 8% and 2%, male and female controls), cardiac degeneration (45%, males and 12%, females vs. 2%, female controls), sternal dysplasia (15 - 20% vs. 0% in controls) and olfactory epithelium metaplasia or necrosis (2 - 9% vs. 0% in controls).

The NOAEL for systemic toxicity is 33 ppm (0.1279 mg/l). The LOAEL is 100 ppm (0.3876 mg/l), based on mortality (males), neurological signs, decreased body weight/weight gain and microscopic lesions in the brain, heart, sternum and olfactory epithelium.

There was no evidence of carcinogenic potential of methyl bromide. Although excessive toxicity occurred at 100 ppm, the dosing is considered adequate because (1) methyl bromide has a steep dose-time dependent mortality curve and (2) at 33 ppm, marginally lower mean body weight gain in females (-12%) and sporadic incidence of abnormal posture late in the study (1 male, 3 females) were observed.

This study is classified as acceptable/guideline and satisfies the guideline requirements for a carcinogenicity study in mice (83-2b), despite some problems with the dose selection (see Discussion/Conclusions in DER).

Discussion of Tumor Data: No treatment-related increase in tumor incidence was found in this carcinogenicity study.

Adequacy of the Dose Levels Tested: Dosing was adequate based on mortality (males), neurological signs, decreased body weight/weight gain and microscopic lesions in the brain, heart, sternum and olfactory epithelium.

4. **Classification of Carcinogenic Potential**

In accordance with the Draft Guidelines for Carcinogen Risk Assessment (July 1999), the HIARC classified methyl bromide as "not likely to be carcinogenic to humans". This

classification is based on the lack of evidence of carcinogenicity in mice and rats.

V. MUTAGENICITY

Bacterial Reverse Mutation and Mammalian Cell Forward Mutation Studies

Even though several mutagenicity studies (The Registration Standards, EPA, 1986; Moriya et al., Mutat. Res. 116:185-216, 1983; Kramers et al., Mutat. Res. 155: 41-47, 1985; Simmon et al., Progress in Genetic Toxicology, 249-258, 1977) suggest that methyl bromide is mutagen in bacterial reverse mutation and mammalian cell forward mutation studies, formally acceptable studies have not been provided. However, another study is not considered necessary for exposure risk assessment based on the adequacy of existing battery number of mutagenicity studies and due to the lack of evidence of carcinogenicity in rats and mice.

Rodent Micronucleus Induction Study

In a rodent micronucleus induction study (MRID 43786501), 10/sex/dose BDF1 mice and F344 rats were exposed in vivo by inhalation to methyl bromide vapor at concentrations of 0, 154, 200, 260, 338 or 440 ppm (equivalent to 0, 0.597, 0.776, 1.008, 1.311 or 1.706 mg/L) for 6 hrs/day, 5 days/week for 14 days (10 exposures). Micronucleus (MN) induction was evaluated in bone marrow of rats and mice and in peripheral blood of mice.

Methyl bromide demonstrated genotoxic potential in micronucleus induction assay. In mice, significantly increased incidence of MN in bone marrow polychromatic erythrocytes (PCEs) was observed in males at 154 and 200 ppm (2.6- and 10.5-fold, respectively) and in females at 154 ppm (5.8-fold); smaller increases in MN frequency were observed in normochromatic erythrocytes (NCEs). Peripheral blood showed significant increases at 200 ppm in males (32.6-fold) and 154 ppm in females (2.6-fold); MN in NCE showed small increases. Mice exposed to $\geq$260 ppm were not assayed due to excessive mortality.

In rats, MN in PCEs of bone marrow were increased at 338 ppm in males (13.6-fold; statistically significant) and in females at 260 and 338 ppm (3.3-fold; not statistically significant). Rats exposed to 440 ppm were not assayed due to excessive mortality.

This study is classified as Acceptable/guideline and fulfills the guideline requirements for mutagenicity testing (chromosomal aberrations; 84-2) of methyl bromide.

Testicular DNA Alkaline Elution Assay

In a testicular DNA alkaline elution assay (MRID No. 43180201), male Fischer 344 rats were exposed in vivo by inhalation to methyl bromide vapor at concentrations of 0, 75, 150 or 250 ppm (0, 291, 581 or 969 mg/m^3) for 6 hr/day over 5 consecutive days. Animals were sacrificed at 1 hour and at 24 hours post-exposure.

At 250 ppm (HDT), elution rate of testicular DNA was statistically significantly increased (about 4X faster than air controls). Significant toxicity was also observed at this dose, including mortality (2), decreased body weight and neurotoxicity (ataxia, lethargy, spasms, salivation). Less severe toxicity was also observed at 150 ppm, but no mortality occurred.

Methyl bromide demonstrated genotoxic potential in germ cell (testicular) DNA following repeated short-term inhalation exposure of male rats at 250 ppm (HDT).

This study is classified as Acceptable but this study does not satisfy the guideline requirements for mutagenicity testing (84-4) of methyl bromide.

VI. HAZARD CHARACTERIZATION

The available toxicity data indicated that acute oral and inhalation toxicity of methyl bromide to be in toxicity category II and IV, respectively. Primary and eye irritation study indicated methyl bromide to be in toxicity category I. Acute dermal toxicity and dermal sensitization potential studies were not required because severe irritation to skin occur after acute exposure to methyl bromide.

The developmental inhalation toxicity study in rabbits showed that methyl bromide caused fetal malformations [agenesis of the gall bladder and increased incidence of fused sternebrae] which was supported by decreased fetal body weight (statistically not significant) at exposure levels that also caused maternal toxicity. The agenesis of the gall bladder was not related to maternal toxicity. The rat developmental inhalation toxicity study found developmental toxicity at a dose where maternal toxicity was seen. The 2-generation reproductive inhalation toxicity study in rats showed that methyl bromide reduced pregnancy rates.

Both acute and 90-day neurotoxicity inhalation studies in rats showed evidence of neurotoxic effects of methyl bromide (characterized by decreased activity, tremors, ataxia and paralysis). The results of subchronic inhalation studies (5- to 7-week and 6-week) in dogs indicated evidence of neurotoxic effects of methyl bromide (decreased responsiveness or the absence of proprioceptive placing).

The carcinogenicity data showed that methyl bromide did not produce an increase in tumor incidence in either rats (feeding or inhalation) or mice (inhalation). The chronic

feeding toxicity in rats showed that during the first 18 months of the study, methyl bromide caused decreased body weight/weight gain and food consumption. However, by the end of the study (week 104) mean body weight values in both males and females were similar to controls. The chronic **inhalation** toxicity study in rats showed that methyl bromide caused increased mortality, decreased body weight and relative brain weight, hemothorax, increased incidence of thrombus, cartilaginous metaplasia, myocardial degeneration and irritation of the esophagus and forestomach. The chronic **inhalation** toxicity study in mice showed that methyl bromide caused mortality (males), neurological signs (abnormal posture, tremors, ataxia, limb paralysis and emaciation) decreased body weight/weight gain and microscopic lesions in the brain, heart, sternum and olfactory epithelium. With long term inhalation exposure methyl bromide induced an increase in the incidence of basal cell hyperplasia in the nasal cavity of the treated rats; however, this finding was determined to be a local effect not unexpected from a compound that produces severe dermal irritation.

The HIARC classified methyl bromide as "not likely to be carcinogenic to humans" by all routes of exposure based upon lack of evidence of carcinogenicity in rats and mice.

Methyl bromide was positive for demonstrating genotoxic potential in rodent germ cell DNA and in micronucleus induction assay in bone marrow of rats and mice. Several published literature also indicated that methyl bromide could induce mutation in bacteria.

In a metabolism study, rats received a single gavage dose (preparation of test solution was unspecified) of 24 mg/kg/b.w. ^{14}C-methyl bromide. Over a 3-day period, the radioactivity recovered were as follows: carcass (14-17%), expired carbon dioxide (32%), urine (43%) and feces (less than 3%) [International Agency for Research on Cancer (IARC) Monographs Vol 41, p198]. During a 6-hour exposure of rats to 4.75-9874 mg/cu.m ^{14}C-methyl bromide vapor, approximately 27-50% of the compound inhaled was absorbed (IARC Monographs Vol 41, p198).

VII. DATA GAPS/REQUIREMENTS

Developmental Neurotoxicity Study conducted in rats with Methyl Bromide via the inhalation route of administration.

VIII ACUTE TOXICITY

Acute Toxicity of Methyl Bromide

Guideline No.	Study Type	MRID # (s)	**Results**	**Toxicity Category**
81-1	Acute oral (liquid MeBr)	43510301	LD_{50} = 120-160 mg/kg (males) LD_{50} = 86 mg/kg (females)	II
81-2	Acute dermal	N/A	No data available	N/A
81-3	Acute inhalation	Kato et al (1986)	LC_{50} = 3.03 mg/L, 4 hr exposure	IV
81-4	Primary eye irritation	Alexeef, G.; Kilgore, W. (1983)[a] and Hezemans-Boer et al (1988)[b]	Severe irritation following accidental exposure to humans	I
81-5	Primary skin irritation	Alexeef, G.; Kilgore, W. (1983) and Hezemans-Boer et al (1988)	Severe irritation following accidental exposure to humans	I
81-6	Dermal sensitization	N/A	No data available	N/A

N/A: Acute dermal toxicity and dermal sensitization potential studies were not required because severe irritation to skin occur after acute exposure to methyl bromide.

a: Alexeef, G.; Kilgore, W. (1983) Methyl Bromide. In: Gunther, F.; Gunther, J., ed. Residue Reviews. Residues of Pesticides and Other Contaminants in the Total Environment, Vol. 88, p. 102-153. New York, Springer Verlag.

b: Hezemans-Boer, M; Toonstra, J.; Meulenbelt, J.; Zwaveling, J.; Sangster, B.; Van Vloten, W. (1988) Skin Lesions Due to Exposure to Methyl Bromide. Arch. Derm. 124:917-921.

IX SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

Summary of Toxicology Endpoint Selection for Methyl Bromide

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (Females 13-50 years of age)	Dev. NOAEL = **14** mg/kg/day UF = 1000 **Acute RfD** = 0.014 mg/kg/day	FQPA SF = 1X **aPAD** = acute RfD / FQPA SF = 0.014 mg/kg/day	**Developmental Toxicity - Rabbit** LOAEL = 28 mg/kg/day based on agenesis of the gall bladder and increased incidence of fused sternebrae.
Acute Dietary (General population including infants and children)	NOAEL = 90 mg/kg/day UF = 1000 **Acute RfD** = 0.09 mg/kg/day	FQPA SF = 1X **aPAD** = acute RfD / FQPA SF = 0.09 mg/kg/day	**Acute neurotoxicity study --rat** LOAEL = 314 mg/kg/day based on decreased activity and alertness as measured by FOB parameters, decreased motor activity and decreased body temperature.
Chronic Dietary (All populations)	NOAEL= 2.2 mg/kg/day UF =1000 **Chronic RfD** = **0.002** mg/kg/day	FQPA SF = 1X **cPAD** = chronic RfD / FQPA SF = 0.002 mg/kg/day	**Chronic/carcinogenicity study -- rats (Microencapsulated MeBr)** LOAEL =11.1 mg/kg/day based on decreased body weight, body weight gain and food consumption
Incidental Oral Short- and Intermediate-Term Residential Only	Methyl bromide is a gas at room temperature and atmospheric pressure. Use pattern and physical properties indicates no residual exposure via this route. Therefore, no hazard identified.		
Dermal All durations	The use pattern does not present a concern for dermal exposure.		
Short- and Intermediate-Term Inhalation (1 day to 6 months)	LOAEL = 5.3 ppm (1.43 mg/kg/day)	**Residential** LOC for MOE = 3000 **Occupational** LOC for MOE = 300	**Subchronic (5- to 7-week) inhalation toxicity study - dogs** LOAEL = 5.3 ppm (1.43 mg/kg/day) based on decreased responsiveness in females; a NOAEL was not established.

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Long-Term Inhalation (>6 months)	LOAEL = 5.3 ppm (1.43 mg/kg/day)	**Residential** LOC for MOE =10000 **Occupational** LOC for MOE = 1000	**Subchronic (5- to 7-week) inhalation toxicity study - dogs** LOAEL = 5.3 ppm (1.43 mg/kg/day) based on decreased responsiveness in females; a NOAEL was not established.
Cancer	Classification: Not likely to be carcinogenic to humans		

UF = uncertainty factor, FQPA SF = Special FQPA safety factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD = population adjusted dose (a = acute, c = chronic), RfD = reference dose, MOE = margin of exposure, LOC = level of concern, NA = Not Applicable

* ***NOTE:*** The Special FQPA Safety Factor recommended by the HIARC **assumes** that the exposure databases (dietary food, drinking water, and residential) are complete and that the risk assessment for each potential exposure scenario includes all metabolites and/or degradates of concern and does not underestimate the potential risk for infants and children.

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R058836

Chemical:	**Methyl bromide**
PC Code:	**053201**
HED File Code	**21100 HIARC Reports**
Memo Date:	**01/06/2003 12:00:00 AM**
File ID:	**TX0051439**
Accession Number:	**412-04-0047**

HED Records Reference Center
01/07/2004