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

DATE: June 20, 2001

MEMORANDUM

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

FROM: Paul Chin 6/20/01
Reregistration Branch I
Health Effects Division (7509C)

THROUGH: Jess Rowland, Co-Chair 6/20/01
and
Elizabeth Doyle, Co-Chair 6/20/01
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 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. The conclusions drawn at these meetings are presented in this report.

Committee Members in Attendance

Members present were: William Burnam, Elizabeth Doyle, Pam Hurley, Elizabeth Mendez, David Nixon, Jess Rowland, Yung Yang and Brenda Tarplee.

Also in attendance were: Paula Deschamp and Whang Phang

Data Evaluation / Report Presentation

Paul Chin 6/20/

Paul Chin
Toxicologist
Reregistration Branch I

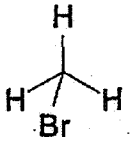
1. INTRODUCTION

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.

2. HAZARD IDENTIFICATION

2.1 Acute Reference Dose (RfD)

2.1.1 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): An uncertainty factor of 100 was applied to account for inter-species extrapolation (10 x) and intra-species variability (10 x).

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) =	$\frac{14 \text{ mg/kg (NOAEL)}}{100 \text{ (UF)}}$ = **0.14 mg/kg**

2.1.2 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): An uncertainty factor of 100 was applied to account for inter-species extrapolation (10 x) and intra-species variability (10 x).

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) =	$\frac{90 \text{ mg/kg (NOAEL)}}{100 \text{ (UF)}}$ = **0.9 mg/kg**

2.2 Chronic Reference Dose (RfD)

Proposed Study: 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): An uncertainty factor of 100 was applied to account for inter-species extrapolation (10X) and intra-species variability (10X).

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.

$$\textbf{Chronic RfD} = \frac{2.2 \text{ mg/kg/day (NOAEL)}}{100 \text{ (UF)}} = \mathbf{0.02 \text{ mg/kg/day}}$$

2.3 Occupational/Residential Exposure

2.3.1 Short-Term (1 - 7 days) Incidental Oral Exposure

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 identified.

2.3.2 Intermediate-Term (1-Week to Several Months) Incidental Oral Exposure

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 identified.

2.3.3 Dermal Absorption

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

2.3.4 Dermal Exposure (All Durations)

The use pattern for methyl bromide (fumigation) does not present a concern for dermal exposure and therefore, no hazard identified.

2.3.5 Short (1-7 days) Term Inhalation Exposure

Study Selected: Developmental Toxicity Study in Rabbits (Inhalation)

Guideline #: 870.3700b

MRID No.: 41580401

Executive Summary: See acute RfD.

Dose and Endpoint for Risk Assessment: Maternal NOAEL 14 mg/kg/day based pm clinical signs of neurotoxicity at 28

Comments about Study/Endpoint: Development effects were also seen at theLOAEL. The maternal NOAEL, therefore, would be protective of the development effects of concern.

2.3.6 Intermediate (1-week to several months) Term Inhalation Exposure

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

Guideline #: 870.3465

MRID No.: 43386802

Executive Summary:

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.

Dose/Endpoint for Risk Assessment: **The systemic LOAEL is 1.43 mg/kg/day based on decreased responsiveness in females following 7 weeks of exposure.**

Comments about Study/Endpoint: A 2-generation reproduction study in rats was available for consideration. However, use of the endpoint from the subchronic inhalation toxicity study in dogs appeared to be more appropriate for the following reasons: In the rat reproduction study, the LOAEL (28 mg/kg/day) was approximately 20X higher than the LOAEL (1.43 mg/kg/day; LDT) from the subchronic inhalation toxicity study in dogs. The decreased activity observed at LOAEL (1.43 mg/kg/day) appears to be a result of the cumulative effects of extended exposures to methyl bromide. This dose level represents a threshold effect level because similar effects (decreased activity) were observed at the higher exposure levels of shorter duration.

2.3.7 Long Term Inhalation Exposure

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

Guideline #: 870.3465

MRID No.: 43386802

Executive Summary: See Intermediate-Term Inhalation Exposure

Dose/Endpoint for Risk Assessment:

The LOAEL is 5 ppm (1.43 mg/kg/day) based on decreased responsiveness in females following 7 weeks of exposure.

Comments about Study/Endpoint:

There are concerns for long-term inhalation exposure to workers (**greenhouse use**) by this route.

A chronic toxicity/carcinogenicity study in rats (inhalation) was available for

consideration. **In this study, 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.** However, the LOAEL (1.9 mg/kg/day) from this study is approximately 33% higher when compared to the LOAEL **(1.43 mg/kg/day; LDT)** based on the decreased responsiveness in females from the subchronic (5- to 7-week) inhalation toxicity study in dogs. Therefore, use of the LOAEL (1.43 mg/kg/day) from the subchronic inhalation toxicity study in dogs would be protective of the nasal cavity lesions seen in the rats.

2.3.8 Margins of Exposure for Occupational/Residential Risk Assessments

The MOE of 100 is adequate for short-term occupational inhalation exposure risk assessment.

A MOE of 300 is required for intermediate- and long-term occupational inhalation exposure risk assessments. This includes the conventional 100 and additional 3x for the use of a LOAEL.

For long-term exposure risk assessments, no additional uncertainty factor is needed for use of subchronic study since no increase in severity (i.e., decrease in body weights) was seen in the 29-month chronic/carcinogenicity study in rats when compared to the 90-day subchronic neurotoxicity study in rats. The NOAELs/LOAELs for these studies were comparable and both LOAELs were based on decreased body weight. (The LOAELs for the chronic and subchronic neurotoxicity studies in rats are 58 and 51 mg/kg/day, respectively. The NOAELs for the chronic and subchronic neurotoxicity studies in rats are 19 and 22 mg/kg/day, respectively.)

The acceptable MOEs for residential exposure will be determined by the FQPA SF committee.

2.4 Recommendation for Aggregate Exposure Risk Assessments

For acute aggregate exposure risk assessment, combine the high end exposure values from food + water should be combined and compared to the acute RfD.

No hazard (endpoint) was identified for short or intermediate-term oral and dermal exposure scenarios based on the use pattern. A common toxicity effect was not selected for long term oral (decreased in body weight/body weight gain) and long term inhalation (decreased responsiveness) routes. Therefore, long-term aggregate risk is not appropriate.

3. CLASSIFICATION OF CARCINOGENIC POTENTIAL

3.1 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.

3.2 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; (c) 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.

3.3 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.

3.4 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.

4. 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 ≥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.

5. FQPA CONSIDERATIONS

5.1 Adequacy of the Data Base

The data base for methyl bromide is adequate for FQPA considerations.

There are acceptable developmental toxicity studies in rats and rabbits and acceptable two-generation reproduction study in rats. Also, there are acute and subchronic neurotoxicity studies in rats and acute and subchronic toxicity studies in dogs.

5.2 Neurotoxicity

Acute Neurotoxicity– See **Acute Reference Dose (RfD)–General** in Section 2.1.2.

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).

5.3 Developmental Toxicity

Developmental Toxicity Study, Rabbit (inhalation)— See Acute RfD (Section 2.1.1) for executive summary.

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, increased incidence/severity of interstitial nephritis were observed only among dams treated at high dose both before and during gestation. This effect is considered treatment-related because there appeared to be a correlation between the dose/length of exposure time and the incidence/severity of interstitial nephritis. The effects of dose/length of exposure time were consistent with those seen in subchronic dog study (MRID 43386802).

> 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 20 ppm. The LOAEL for maternal toxicity is 70 ppm (HDT) based on increase in the incidence/severity of interstitial nephritis.

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

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

5.4 Reproductive Toxicity

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.

5.5 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]

5.6 Determination of Susceptibility

Based on the results of developmental toxicity study in rats, there was no indication of increased susceptibility in young rats to methyl bromide exposure. However, based on the results of developmental toxicity in rabbits, there is **qualitative** evidence of increased susceptibility of rabbit fetuses to *in utero* exposure to methyl bromide as shown by fetal malformations [increased incidence of agenesis of the gall bladder and increased incidence of fused sternebrae] which was supported by decreased fetal body weight (statistically not significant). The increase in the incidence of agenesis of the gall bladder was found to be unrelated to maternal toxicity. In the 2-generation reproduction study in rats, there is a **quantitative** evidence of increased susceptibility of rat fetuses to methyl bromide exposure as shown by an increases in the incidence of reduced pup weight and reduced pup survival at a dose lower than the parental NOAEL/LOAEL.

In addition, methyl bromide exhibited genotoxic potential in germ cell (testicular) DNA following repeated short-term inhalation exposure of male rats.

5.7 Determination of the Need for a Developmental Neurotoxicity Study

The HIARC recommend a developmental neurotoxicity study based on the observance of clinical signs indicative of neurotoxicity, presence of neuropathology and the evidence for increased susceptibility following pre-/post-natal exposures.

5.7.1 Evidence that suggest requiring a Developmental Neurotoxicity study:

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

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.

The results of **2-generation reproduction study in rats (inhalation)** showed an increased susceptibility of rat fetuses to methyl bromide exposure as shown by an increases in the incidence of reduced pup weight and reduced pup survival at a dose lower than the parental NOAEL/LOAEL.

5.7.2 Evidence that **do not** support the need for a Developmental Neurotoxicity study:

No evidence of increased susceptibility in the developmental toxicity study in rats.

6. 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. Both primary dermal and eye irritation studies 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 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).

7. DATA GAPS

A developmental neurotoxicity study in rats have been recommended by the HIARC.

8 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.

9 SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

The doses and toxicological endpoints selected for various exposure scenarios are summarized below.

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary Female 13+	NOAEL = 14	Fetal malformations [agenesis of the gall bladder and increased incidence of fused sternebrae] which was supported by decreased fetal body weight (statistically not significant)	Developmental Toxicity -rabbit
	UF=100	**Acute RfD = 0.14 mg/kg**	
Acute Dietary General population	NOAEL = 90	Decreased activity and alertness as measured by FOB parameters, decreased motor activity and decreased body temperature.	Acute neurotoxicity - rat
	UF=100	**Acute RfD = 0.9 mg/kg**	
Chronic Dietary	NOAEL = 2.2	Decreased body weight, body weight gain and food consumption	Chronic toxicity /carcinogenicity - rats
	U.F. = 100	**Chronic RfD = 0.02 mg/kg/day**	
Cancer	No quantificatio n needed	"Not likely to be carcinogenic to humans" - No evidence of carcinogenicity in rats and mice	
Incidental Oral, Short- /Intermediate Term	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 (Any time Period)	The use pattern does not present a concern for dermal exposure.		
Inhalation (Short-Term)	Maternal NOAEL = 14	Clinical signs of neurotoxcity (on lethargy, ataxia, and lateral recumbency in the dams.	Developmental toxicity study -- rabbits
Inhalation (Intermediate-Long-Term)	LOAEL = 1.43*	Decreased responsiveness in females.	Subchronic (5- to 7-week) inhalation toxicity- dogs

* A MOE of 300 is required for occupational exposure risk assessments.

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Chemical:	**Methyl bromide**
PC Code:	**053201**
HED File Code	***21100 HIARC***
Memo Date:	**06/20/2001**
File ID:	**TX014599**
Accession Number:	***412-02-0006***

HED Records Reference Center
12/05/2001