

METHYL BROMIDE

RISK CHARACTERIZATION DOCUMENT

Volume III

AGGREGATE EXPOSURE

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I. TECHNICAL SUMMARY

This document assessed the aggregate exposure of workers and residents to methyl bromide via inhalation and oral routes of exposure.

I.A. TOXICOLOGY PROFILE

Pharmacokinetic studies showed that after inhalation, intraperitoneal, and oral administration, methyl bromide was rapidly absorbed and radioactivity was distributed to all tissues examined. About 50% and 100% of the dose were absorbed by inhalation and oral exposures, respectively. After inhalation exposure in rats, the lungs had the highest tissue level. The primary excretion route was the exhaled air with carbon dioxide accounting for almost 50% of the dose. After oral and intraperitoneal exposure, the highest radioactivity levels in rats were measured in the liver, kidneys, and testes. After oral exposure, the primary route of excretion was via the urine. Biliary metabolites of methyl bromide were reabsorbed from the gut.

The primary acute inhalation toxicity of methyl bromide was neurotoxicity. The severity of the effects depended on the dose and duration of exposure. Acute clinical signs included decreased activity and tremors. Tissue lesions were observed in the brain and other organs. For chronic toxicity, the nasal cavity, brain, and heart were major target organs in rodents after chronic inhalation exposure to methyl bromide. Olfactory epithelial damage and myocardial degeneration were observed in rats and mice. Cerebellar and cerebral degeneration was detected in mice, while reduced brain weight was observed in rats.

The acute oral toxicity of methyl bromide in experimental animals included hypoactivity, ataxia, prostration, labored respiration, hypothermia, and mortality. Squamous cell hyperplasia in the stomach was reported in both acute and subchronic exposure studies with rats. This toxicity endpoint may be due to a direct irritation effect of methyl bromide on the stomach lining. When rats were exposed to methyl bromide in microcapsules mixed in the feed, the primary effect was body weight reduction. Possible treatment-related lesions were found in the spleen, liver, pancreas, and lungs. While methyl bromide is genotoxic in bacterial and mammalian assays, it has not been shown to be oncogenic in experimental animals.

Methyl bromide caused developmental effects in both rats and rabbits after inhalation exposure. The findings in the fetuses included delayed skull ossification in rats and fused sternebrae, gall bladder agenesis, and other effects in rabbits. Methyl bromide did not cause any significant developmental effects in rats and rabbits after oral exposure.

I.B. RISK CHARACTERIZATION FOR AGGREGATE EXPOSURE

I.B.1. Hazard Identification for Aggregate Exposure

For aggregate exposure, common endpoints from inhalation and oral studies were determined. For comparison between routes, the No-Observed-Effect Levels (NOEL) were adjusted doses to account for the difference in the absorption factors for inhalation (50%) and oral (100%) exposures.

The presence of clinical signs was selected as the common endpoint for acute aggregate exposure. The clinical signs observed in dogs after inhalation exposure were clearly due to neurotoxicity while those observed in rats after gavage administration could be attributed to neurotoxicity. The NOELs (as absorbed doses) were 22.8 mg/kg/day and 8 mg/kg/day for inhalation and oral exposures, respectively. Reduced body weight in rats after chronic oral or inhalation exposure to methyl bromide was considered the common endpoint for risk characterization of aggregate chronic exposure. The NOELs (as absorbed doses) were 10 mg/kg/day and 2.2 mg/kg/day for inhalation and oral exposures, respectively.

I.B.2. Aggregate Exposure Assessment

The aggregate exposure of methyl bromide was the combined inhalation (via the air) and oral (via the diet) exposures for workers and residents (representing the general population). The linkage of the spatial, temporal, and demographic characteristics of aggregate exposure was considered only to a limited extent because of insufficient exposure data. The population was divided into workers and residents and was further subdivided based on job tasks (workers) or monitored sites (residents) to determine the inhalation component of the exposures. The spatial nature of the exposure was addressed by assigning ambient air monitoring data for 12 sites to residential exposures. The temporal nature of methyl bromide exposure was accounted for by excluding chronic exposure for some workers. Demographic characteristic was considered primarily in terms of dietary exposure where worker and resident exposures were selected from those delineated for 20 population subgroups.

Occupational inhalation exposures were estimated for soil and commodity fumigations. For soil fumigation, only the worker exposures monitored under current DPR regulations were selected for aggregate exposure. For shallow shank and tarped bed fumigation, the regulations required the use of swept-back shank and a closing device with rollers to compress the soil before tarp application. The upper-bound acute exposures were 4 ppb for applicators, 58 ppb for copilots, and 1 ppb for shovel-men. For tarp removal, the worker exposures ranged from 22 ppb to 1058 ppb. No chronic exposures were expected for workers in field fumigation. For commodity fumigation, the acute exposure of workers in potting soil, grain products and raisins fumigation was limited to 210 ppb. For grain product workers, the range of chronic exposures was 0.01 ppb (aerators of tarpaulin fumigation) to 8 ppb (forklift drivers emptying sea containers/truck trailers). For raisin workers, the range of chronic exposures was 1 ppb (forklift drivers) to 26 ppb (fumigators). For workers in a brewery, the acute exposure was 210 ppb for both applicators and aerators. There was no chronic exposure estimated for these workers.

For acute residential inhalation exposure, the 95th percentile daily exposure levels spanned more than 120-fold and ranged from 0.239 ppb to 30.2 ppb. The mean of the weekly mean values for each site (0.084 ppb to 7.68 ppb) was used to estimate chronic exposure.

For both workers and residents, the oral exposure component was selected from the dietary exposures of 20 population subgroups. The dietary exposure for workers was based on the exposure of adults (16+ years old, the 95th percentile exposure of 4.649 ug/kg/day) and adults (20+ years old, mean exposure of 0.143 ug/kg/day) for acute and chronic exposures, respectively. The dietary exposure for residents was based on the highest exposed group which was children 1-6 years old. The 95th percentile acute and mean chronic dietary exposures for this group were 8.195 ug/kg/day and 0.200 ug/kg/day, respectively.

I.B.3. Risk Characterization for Aggregate Exposure

For aggregate exposure, the risk was determined by a total margin of exposure (MOE) approach using exposures from both routes and route-specific NOELs. The NOELs were based on common toxicological endpoints which were clinical signs and reduced body weights in experimental animals for acute and chronic exposure, respectively. The magnitude of the total MOE expressed only the risks for these endpoints.

For aggregate occupational inhalation and dietary exposures, the total acute MOEs for workers in shallow-shank and tarped field fumigation were greater than 100 except for the tractor drivers and basket-men in the second tarp removal study. The MOEs for these latter workers were 42 and 44, respectively. The acute MOE was 1143 for both applicators and cultipackers in deep shank and non-tarped fumigation. The total acute MOEs for all workers in commodity fumigation were 191 since the same inhalation and dietary exposure values were applied to all scenarios. The total chronic MOEs ranged from 375 (raisins fumigators) to 15152 (aerators of tarped fumigation of grain products). For residential inhalation and dietary exposures, the acute total MOEs ranged from 453 to 967 depending on the location of the monitored site. The chronic total MOEs ranged from 1285 to 10160.

I.C. RISK APPRAISAL FOR AGGREGATE EXPOSURE

The aggregate exposure risk characterization was based on clinical signs and reduced body weights in experimental animals after acute and chronic exposures, respectively. While it was clear that the clinical signs observed in dogs after inhalation exposure were due to neurotoxicity, the signs observed in rats after oral exposure may be a combination of neurotoxicity and general stress of the animals due to severe irritation to the stomach lining.

There was also uncertainty for the endpoint of reduced body weight for aggregate chronic toxicity. For both routes of exposure, the reduction occurred throughout the study and was about 10% of control values. While the reduction was statistically significant for some time points in these studies, the toxicological significance was uncertain since the magnitude of the reduction varied little with continued exposure.

The uncertainties related to the aggregate exposures were those associated with the individual and combined routes. Data for methyl bromide allowed only limited consideration of spatial, temporal, and demographic characteristics of groups instead of individuals. The aggregate exposures may be over- or under- estimation of actual exposures for some workers and residents whose exposures are not represented by the data used in this document.

The interpretation of the total MOEs for aggregate exposure should be limited to the endpoints used to characterize the risk. The NOELs for these endpoints were higher than those used for inhalation exposure alone due to common endpoint considerations. The oral NOELs were the same for dietary and aggregate exposures. The difference in the NOELs resulted in scenarios with higher total MOE than that for inhalation route alone. For example, the higher acute total MOE of 42, compared to inhalation MOE of 22, for tractor drivers in tarp removal, was because of a higher NOEL used to calculate the total MOE. The dietary exposure contribution to the total exposure was relatively minor (4.69 $\mu\text{g}/\text{kg}/\text{day}$) compared to that for inhalation (535 $\mu\text{g}/\text{kg}/\text{day}$). A higher total MOE does not mean that there is lower risk

associated with aggregate exposure. The appraisal of risks associated with the use of methyl bromide should consider the exposures for individual and combined routes. Also, this assessment did not address the potential interaction between other effects and the overall burden of multiple effects to the body from multiple routes of exposure. The toxicological database did not provide any evidence of potential increased sensitivity of infants and children to methyl bromide toxicity after aggregate exposure.

I.D. CONCLUSIONS FOR AGGREGATE EXPOSURE

The human health risk from potential aggregate exposure was evaluated in this **Volume** of the Methyl Bromide Risk Characterization Document. The assumption was that workers and residents may be exposed to methyl bromide by both the oral (via the diet) and inhalation (via the air) routes under acute and chronic durations. Due to the paucity of inhalation exposure data, only a limited number of scenarios were assessed. The potential risks were evaluated based on clinical signs and reduced body weight observed in experimental animals for acute and chronic exposures, respectively. The risks, expressed as total margins of exposure, were calculated for inhalation and oral exposures. For non-oncogenic effects based on animal data, the total MOEs were compared with a benchmark of 100 to determine whether the exposure would be of a potential health concern.

For field fumigation, the total acute MOEs were greater than 100 for all workers except those for some tarp removers (tractor drivers and basket-men) with MOEs of 42 and 44. The low MOEs were attributed to the relatively high inhalation exposure (1003-1058 ppb). The mitigation of inhalation exposure of these workers should lead to an increase in the total MOEs. For commodity fumigation, the total acute MOEs were at 191 since the exposure was set at 210 ppb by regulation. The total chronic MOEs were greater than 100 and ranged from 375-15152 for all workers. For residential aggregate exposure, the acute total MOEs ranged from 453 to 967. The chronic total MOEs were greater than 1000.

The total MOEs in this document should be viewed in light of the uncertainties and the limitations used in the hazard identification and exposure assessment of methyl bromide by the inhalation and oral routes, as individual routes and in combination. Additional data are needed to better define common toxicological endpoints and to characterize the aggregate exposures. In addition, the magnitude of the total MOEs should consider the methodology used to calculate these values. For certain scenarios, higher total MOEs from aggregate exposure than the MOEs for inhalation exposure alone should not be interpreted as lower risk because different NOELs and endpoints were used. The NOELs used to calculate the total MOEs were higher than those NOELs for inhalation MOEs which were based on more sensitive route-specific endpoints. The relative contribution of inhalation and dietary exposures to the aggregate exposure equation was also a factor in the magnitude of the total MOEs. Therefore, the risk management decision on methyl bromide use in California should consider the risks associated with exposures from individual and combined routes.

II. INTRODUCTION

This **Volume III** of the Methyl Bromide Risk Characterization Document focuses on the potential risk of aggregate exposure to methyl bromide. Aggregate exposure is the combined exposure of multiple pathways such as air, food, and drinking water. For methyl bromide, the likely aggregate exposure routes are via the air by inhalation and the diet by oral routes. The risk assessment draws upon toxicology and exposure information contained in **Volumes I and II** for inhalation exposure (DPR, 2002a) and dietary exposure (DPR, 2002b), respectively. Technical summaries for these Volumes are included in Attachments A and B.

III. TOXICOLOGY PROFILE

The complete pharmacokinetic and toxicology database for methyl bromide for all routes of exposure was presented in **Volume I (III. TOXICOLOGY PROFILE** in DPR, 2002a). A draft of the Volume (DPR, 1999) was reviewed by the National Research Council panel of scientists (NRC, 2000). In this Volume, only those toxicity studies considered for critical endpoints in the risk characterization of aggregate exposure are discussed in detail.

III.A. PHARMACOKINETIC

After inhalation, intraperitoneal, or oral administrations, methyl bromide was rapidly absorbed and radioactivity (^{14}C) was distributed to all tissues (Medinsky *et al.*, 1984 and 1985; Raabe, 1986 and 1988). With inhalation exposure, the percentages of the administered doses absorbed were similar in several species; they were 48% in the rat, 40% in the dog, and 52 to 55% in humans. The inhalation absorption factor of 50% is used in this document. In the rat, the highest levels in the tissues, principally in the lungs, were reached immediately after exposure (Medinsky *et al.*, 1985; Bond *et al.*, 1985; Jaskot *et al.*, 1988). With oral and intraperitoneal administration to rats, more than 90% of the dose was absorbed with the highest radioactivity levels measured in the liver, kidneys, and testes (Medinsky *et al.*, 1984). Based on this result, the oral absorption factor is considered 100%. Methyl bromide was extensively biotransformed into unidentified products and carbon dioxide (Bond *et al.*, 1985; Medinsky *et al.*, 1985; Jaskot *et al.*, 1988). In the rat, within 1 hour after inhalation exposure, less than 10% of the radioactivity in the tissues was intact methyl bromide. In humans, both methyl bromide and inorganic bromide were detected in the tissues 5 hours after a lethal dose inhalation exposure (Michalodimitrakis *et al.*, 1997). The primary routes of excretion were the exhaled air for inhalation and intraperitoneal exposures, and the urine for oral exposure (Bond *et al.*, 1985; Medinsky *et al.*, 1984 and 1985; Raabe, 1986 and 1988). Carbon dioxide accounted for almost 50% (inhalation and intraperitoneal routes), and 30% (oral route) of the radioactivity in the exhaled air. After oral administration, biliary metabolites of methyl bromide were reabsorbed from the gut (Medinsky *et al.*, 1984).

III.B. ACUTE TOXICITY

III.B.1. Oral

For acute oral exposure, the critical endpoint and NOEL were selected from the following study.

Albino rats (5/sex/group) were given methyl bromide (99.5% pure) either as a liquid in corn oil or microencapsulated mixed with corn oil (Kiplinger, 1994). In the liquid methyl bromide testing, methyl bromide was given once by gavage at 50, 100, or 150 mg/kg in initial testing and at 0, 80, 120 or 160 mg/kg in retesting. Only results from the retesting are presented in this document. For the microencapsulated groups, the reported doses were 98, 146, or 195 mg/kg. Rats were fasted for 18-20 hours prior to dosing and feed was made available 3-4 hours after dosing. Rats were observed at approximately 1, 3, and 4 hours after dosing (post-dosing day 0) and once in the morning and once in the afternoon on post-dosing days 1 through 14 (day of scheduled sacrifice). As shown in Table 1, clinical signs and death were reported for all treated groups. The mortality incidences were 0 for control groups, 2/10 (corn oil) and 1/10 (microcapsules) for low dose, 6/10 (corn oil) and 7/10 (microcapsules) for the mid-dose, and 10/10 (corn oil) and 9/10 (microcapsules) for the high dose groups. The clinical signs observed before death included: hypoactivity, ataxia, prostration, labored respiration, hypothermia, and tremors. Other findings with increased incidences included wet yellow urogenital staining and mucoid feces in the treated animals. Rats died on or before post-dosing day 2 with one dying on post-dosing day 4. The LD50s for the liquid methyl bromide group were 86 mg/kg for females and between 120 and 160 mg/kg for males (combined LD50 of 104 mg/kg). The LD50s for the microencapsulated group were 105 mg/kg and 159 mg/kg for females and males, respectively (combined LD50 was 133 mg/kg).

For both the liquid and microencapsulated methyl bromide groups, decreased food consumption and body weight gain were reported (Table 1). These effects were related to the dose in most cases. However, the food consumption reduction was greater for the first week than the second week. The stomach was the main organ affected regardless of how methyl bromide was mixed in corn oil. Hemorrhage, edema, and squamous cell hyperplasia were due to severe irritation of the stomach lining. To determine the relative toxicity between liquid and microencapsulated methyl bromide, DPR needs clarification on the following concerns: (1) whether the microcapsules dissolved before dosing and (2) whether the procedure for the methyl bromide content analyses was appropriate. The acute lowest-observed-adverse-effect levels (LOAELs) were 80 mg/kg for liquid, and 98 mg/kg for microencapsulated methyl bromide for reduced food consumption, clinical signs, stomach lesions, and mortality in treated rats. This study was considered supplemental information by DPR.

Table 1. Clinical findings in rats after acute oral exposure.^a

Clinical Findings	Dosage (mg/kg)						
	Control 80 (----- Corn oil-----)	120	160	98	146	195	(---- Microcapsules----)
MALES							
<u>Food Consumption</u>	Average (grams of feed /animal/day)						
Week 0-1	22	2	2	1	4	2	6
Week 1-2	33	15	9	1	21	11	15
<u>Body Weight Gain</u>	Average (grams/animal)						
Week 0-2	+32	-6	-6	NA	-7	-6	+1
<u>Clinical Signs</u>	Incidences^b						
Hypoactivity	0/5	4/5	4/5	5/5	0/5	4/5	5/5
Ataxia	0/5	1/5	2/5	3/5	0/5	1/5	2/5
Prostration	0/5	1/5	0/5	0/5	0/5	0/5	0/5
Labored respiration	0/5	1/5	1/5	1/5	0/5	1/5	0/5
Hypothermia	0/5	1/5	1/5	1/5	0/5	1/5	0/5
Tremors	0/5	0/5	0/5	1/5	0/5	1/5	0/5
Death	0/5	1/5	1/5	5/5	0/5	2/5	4/5
<u>Histology- Stomach</u>							
Squamous cell hyperplasia	0/5	3/5	4/5	0/5	4/5	3/5	1/5
Autolysis, hemorrhage, edema ^c	0/5	1/5	1/5	5/5	0/5	2/5	4/5
FEMALES							
<u>Food Consumption</u>	Average (grams of feed /animal/day)						
Week 0-1	15	2	1	NA	3	1	NA
Week 1-2	24	7	1	NA	9	NA	NA
<u>Body Weight Gain</u>	Average (grams/animal)						
Week 0-7	+6	-13	NA	NA	-7	NA	NA
<u>Clinical Signs</u>	Incidences^b						
Hypoactivity	0/5	2/5	5/5	5/5	0/5	5/5	4/5
Ataxia	0/5	1/5	2/5	4/5	0/5	3/5	4/5
Prostration	0/5	0/5	2/5	1/5	0/5	1/5	2/5
Labored respiration	0/5	1/5	2/5	2/5	0/5	1/5	3/5
Hypothermia	0/5	1/5	2/5	2/5	0/5	1/5	2/5
Death	0/5	1/5	5/5	5/5	1/5	5/5	5/5
<u>Histology- Stomach</u>							
Squamous cell hyperplasia	0/5	4/5	0/5	0/5	3/5	0/5	0/5
Autolysis, hemorrhage, edema ^c	0/5	1/5	5/5	5/5	1/5	5/5	5/5

a/ Data from Kiplinger, 1994. NA=not available, the animals died.

b/ Incidences were expressed as number of animals affected/ total animals in the group. Death was observed on day 0 (day of dosing) to post-dose day 2 (2 days after dosing) except for one death noted on post-dose day 4. Effects were those observed during the day of dosing to post-dose day 4.

III.B.2. Inhalation

For acute inhalation exposure, developmental toxicity and neurotoxicity were the two critical endpoints considered for risk characterization.

III.B.2.a. Developmental Toxicity

In the definitive study for developmental toxicity, pregnant New Zealand white rabbits were exposed to methyl bromide (99.6% pure; nominal concentrations of 0, 20, 40, or 80 ppm in Part I; and 0 or 80 ppm in Part II) for 6 hours per day by inhalation from days 7 to 19 of gestation (Breslin *et al.*, 1990). The Part II experiment was designed to determine if the gall bladder agenesis observed in Part I was associated with a particular male used for artificial insemination. Rabbits (in Part II) designated as naive controls were inseminated with sperm from the suspect male.

Maternal effects were observed only in the 80 ppm group and included: decreased body weight gain (Parts I and II), decreased feces, and neurotoxicity (3 of 26 rabbits in Part I only; lethargy, right-sided head tilt, slight ataxia, and slight lateral recumbency). Neurotoxicity was observed on gestation day 19, the last day of exposure. The body weight gain was reduced in both Part I and II 80 ppm groups, but only the reduction in Part II was statistically significant ($p \neq 0.05$). This reduction in maternal body weight gain in the 80 ppm group in Part II was seen in the presence of reduced fetal weights. DPR estimated the maternal body weight as the difference between terminal body weight and gravid uterine weight and showed that there was no difference between the control and treated groups (Table 2). In addition, the significance of any maternal body weight gain reduction is uncertain because body weight changes in rabbits during pregnancy are more variable than other species (U.S. EPA, 1991). The maternal NOEL was 40 ppm based on neurotoxicity.

Fetal effects were also observed primarily in the 80 ppm groups (Table 2). The fetal effects included omphalocele, hemorrhaging (with or without generalized edema), retro-esophageal right subclavian artery, gall bladder agenesis, fused sternbrae, and decreased fetal body weight (13% in Part II). In the 80 ppm group (Part I), the incidences of gall bladder agenesis and fused sternbrae were significantly ($p \neq 0.05$) different from the controls. The increased incidences of gall bladder agenesis and fused sternbrae were independent of maternal toxicity because these effects were observed in fetuses from both normally behaving and affected (with neurotoxicity) does. The finding of gall bladder agenesis was confirmed in Part II with approximately the same litter incidence (29%) as for Part I (26%). Additionally, gall bladder agenesis was not associated with a particular male since the malformation was not observed in the naive controls (in Part II) which had been inseminated only with sperm from the suspect male. The historical control incidences of gall bladder agenesis are in Attachment B of **Volume I**. The distribution of affected fetuses with respect to neurotoxicity in the does is shown in the footnotes of Table 2. The developmental NOEL was 40 ppm based on omphalocele, hemorrhaging, retro-esophageal right subclavian artery, gallbladder agenesis, fused sternbrae and decreased fetal body weight at 80 ppm. This study was considered acceptable to DPR according to FIFRA guidelines.

Table 2. The incidences of fetal effects in rabbits after inhalation exposure to methyl bromide during gestation.^a

Effects ^b	Methyl bromide Concentrations							
	Part I				Part II			
	0	20	40	80ppm	0	0	80ppm	
# Examined:								
fetuses	190	137	143	159	114	102	92	
litters	21	15	19	19	16	13	14	
<u>Fetal body weight</u> (g)	31.8	32.2	35.0	30.4	36.2	33.8	31.4*	
<u>External Effects</u>								
omphalocele	0	0	0	2/2 (11%) ^d	0	0	0	
hemorrhage (with or without edema)	0	0	0	2/2 (11%) ^d	0	0	1/1 (7%) ^d	
<u>Soft Tissues</u>								
retro-esophageal right subclavian artery	0	0	0	2/2 (11%) ^d	0	0	0	
gall bladder agenesis	2/1 (5%)	1/1 (7%)	1/1 (5%)	13/5* ^e (26%) ^d	1/1 (6%)	0	4/4 ^e (29%) ^d	
<u>Skeletal Effects</u>								
fused sternebrae	0	0	3/2 (11%)	20/10* ^f (53%) ^d	NA ^g	NA ^g	NA ^g	
<u>Maternal</u>								
Terminal body weight- gravid uterine weight (grams, day 28)	3863	3659	3805	3636	3428	3391	3344	

^{a/} Incidence data were expressed as the number of fetuses affected/number of litters affected. Data were from Breslin *et al.* (1990) with does exposed to methyl bromide 6 hours/day on days 7 to 19 of gestation. Parts I and II were two separate experiments. Statistical significance in comparison to the controls, * (p # 0.05), is indicated after each incidence.

^{b/} Omphalocele is the protrusion of intestines through a defect in the abdominal wall at the umbilicus. Hemorrhage is subdermal hematoma with either multiple petechiae or edema. Retro-esophageal right subclavian artery refers to the placement of the artery posterior to the esophagus. Fused sternebrae is the premature fusion of the sternum segments.

^{c/} These rabbits were designated as naive controls and were inseminated with sperm from suspect male.

^{d/} Percent of litters affected= (affected litters/total litters examined) x 100.

^{e/} Of the 13 fetuses with missing gall bladder in Part I, 6 were from 3 does without neurotoxicity and 7 were from 2 does with neurotoxicity. In part II, all 4 affected fetuses were from 4 does without neurotoxicity.

^{f/} Of the 20 fetuses with fused sternebrae, 19 were from 9 does without neurotoxicity, and 1 from 1 doe with neurotoxicity.

^{g/} NA=skeletal examination was not performed.

III.B.2.b. Neurotoxicity

Beagle dogs (2-4 dogs/sex/group) were exposed to methyl bromide (100% pure) by whole body inhalation at 7 hours per day, 5 days per week, for two exposure durations (Newton, 1994a). The durations of exposure were: 23 to 24 exposure days (0, 26, 53, or 103 ppm) or 30 exposure days (24 exposure days at 11 ppm, then 6 exposure days at 158 ppm). Air concentrations were based on measured concentrations. Serum bromide levels increased with the dose at 26 ppm. The 158 ppm group showed decreased activity on the second exposure day (the first dose was on a Friday and the second dose was on the following Monday). They were reported in poor condition during the final (6th) exposure and showed severe neurotoxicity with lesions to the brain, adrenal, and olfactory tissues. No effects were observed in the 103 ppm dogs after 8 days of exposure. On day 9, some of the dogs in this group showed decreased activity (3/8) and emesis (1/8). On day 10, tremor was noted in one dog. The acute NOEL was 103 ppm for decreased activity seen in the 158 ppm group after 2 exposures, and severe neurotoxicity after 6 exposures, and lack of acute effects at 103 ppm. Neurotoxicity observed in dogs in this study and another study (Newton, 1994b) is presented in Table 3.

Table 3. The neurotoxicity of methyl bromide in dogs after acute exposure.^a

Concentration mean " standard deviation (ppm)	Duration of exposure ^a	First signs of neurotoxicity and Incidence ^b	Clinical signs with additional exposure
394± 20	3 hours	hunched appearance and tremors (1/1)	hunched appearance and tremors, mucoid nasal discharge, labored breathing
350± 13	3 hours	labored breathing (1/1)	labored breathing, decreased activity, hunched appearance, tremors, excessive salivation and swallowing response
345± 8	3 hours	tremors (1/1)	tremors, labored breathing, hunched appearance, excessive salivation, and gasping
314± 6	4 hours	decreased activity (2)	tremors, hunched appearance, and restlessness (2/2)
283 ± 13	6 hours	salivation, labored breathing, emesis (1/3)	excessive salivation (2/3), labored breathing (3/3), and emesis (2/3)
268± 19	7 hours	no effects	day 2: labored breathing (1/3) and decreased activity (3/3)
233± 21	5 hours	trembling (1/1)	panting, rapid eye blinks, and tremors
158± 7 °	7 hours ^c	decreased activity (8/8)	day 3: decreased activity; day 6: severe neurotoxicity; brain, and adrenal lesions, olfactory degeneration (8/8)
156± 15	5 hours	lacrimation (2)	day 3 and 4: lacrimation and labored breathing (2/2), prostrate (2), and decreased activity (2/2); day 4 post-exposure: irregular gait (2/2)
103" 9 °	8 days	no effects	day 9: start of decreased activity (3/8) and emesis (1/8); day 10: tremor (1/8); week 5: cerebellar lesions (1/8) at sacrifice
53± 4 °	13 days	no effects	day 14: decreased activity (2/8)
55	4 days	no effects	(experiment terminated after 4 days)

^{a/} Data from Newton (1994 a and b). Hours of exposure for onset of neurotoxicity.

^{b/} Incidences as number of dogs affected/ total are shown in parentheses.

^{c/} The first exposure was on a Friday with no effects reported. However, decreased activity was observed during the second exposure, on the following Monday.

III.C. CHRONIC TOXICITY

III.C.1. Oral

For chronic oral toxicity, the following study was used to establish the critical endpoint and NOEL.

Sprague-Dawley rats (70/sex/group, except for 0.5 and 2.5 ppm with 50/sex/group) were given feed mixed with microencapsulated methyl bromide for two years (Mertens, 1997). Corn oil containing methyl bromide was microencapsulated using starch and sucrose. Two types of microcapsules were produced. One was a blend of 7 production runs; it had a methyl bromide content of 0.48% w/w. The second type was a blend of five production runs; its methyl bromide content was 3.44% w/w. The two types of microcapsules differed also in terms of corn oil, starch, and sucrose content and age of the material at the start of testing. Nominal methyl bromide concentrations in the diet were as follows: 0 (basal diet), 0 (diet containing placebo microcapsules), 0.5, 2.5, 50 or 250 ppm. The blend containing 0.48% methyl bromide was used to prepare the two low doses, while the blend containing 3.44% was used to prepare the two high doses. The highest dose tested was selected on the basis of a two-week range-finding study. The daily ration of feed varied as follows: for test weeks 0-65, males and females each received 30 and 23 g, respectively; for test weeks 66-104, males and females received 35 and 30 g, respectively. One outcome of this feeding strategy appeared to have been that a fraction of the animals in the control and 0.5 to 50 ppm groups had their feed consumption restricted during the first 65 weeks of the study. In test week 53, interim sacrifices were performed on 18-20 rats/sex for the following dose levels: 0 (basal diet), 0 (placebo microcapsules), 50 and 250 ppm. The reported dosages (male/female) were 0, 0.02/0.03, 0.11/0.15, 2.20/2.92, or 11.10/15.12 mg/kg/day for 0, 0.5, 2.5, 50, or 250 ppm, respectively.

Survival was statistically increased in the 250 ppm male group and in the 50 and 250 ppm female groups when compared to the placebo-microcapsule groups. Body weight was reduced in the 250 ppm groups; the reduction reached a maximum (about 90% of control) in the early weeks of testing in both sexes (Table 4). A further reduction in body weight relative to the controls (placebo-microcapsule groups) did not occur despite continued exposure and reduced food consumption throughout the study (Table 4). Since a reduction (about 10%, $p < 0.05$) in feed consumption occurred in the 250 ppm groups (both sexes) starting with the first exposure week (Table 4), the body weight reduction would appear to be due mainly to the reduced feed consumption.

No treatment-related effects were reported in the following areas: clinical observations, ophthalmology, hematology, serum chemistry or urinalysis. Effects on absolute organ weights (only brain, kidneys, liver, testes/ovaries were measured) and organ weights relative to body weight appeared to be due to the body weight reduction in the 250 ppm groups; this was true for animals sacrificed at test week 52 as well as for the survivors at the end of the study. An increased incidence of dark red areas was observed on the livers of the 50 ppm females surviving to test week 104 (0 ppm, basal: 5/20; 0 ppm, placebo: 3/19; 0.5 ppm: 8/22; 2.5 ppm: 4/24; 50 ppm: 14/27; and 250 ppm, 8/29). No statistical analyses were supplied for the histology data. Also, the lesion-incidence summary table did not present autolysis and lesion-grade data and may not have been corrected for tissues lost to autolysis. Possible treatment-related effects include: increased incidence of pancreatic acinar atrophy at 250 ppm (both

sexes), increased incidence of adrenal cortical hypertrophy at 250 ppm (females), and increased incidence of pulmonary arterial mineralization at 50 ppm (females). Two rare tumor types, adenocarcinoma of the prostate and endometrial stromal sarcoma of the cervix, were seen at 4% incidence at 250 ppm. By experimental design, the histological examinations of the pancreas, prostate, spleen, adrenal glands, cervix, and uterus at the 0.5 to 50 ppm dose levels were limited to those rats that did not survive to terminal sacrifice. Autolysis was a frequent observation in the gastrointestinal organs in rats that did not survive to the end of the study (all groups, both sexes). While an increased incidence of spongiosis hepatitis was seen in the 50 ppm females, the relationship of this lesion to angiectasis and the necropsy finding of dark red liver spots that also occurred at the 50 ppm dose level needs clarification.

A possible, treatment-related finding at necropsy was statistically increased incidences of enlarged spleens in the 2.5 ppm and 50 ppm groups, but not the 250 ppm group. While the physical dimensions (length, width, and height) of the enlarged spleens were given, neither the criteria for enlargement nor the dimensions for non-enlarged spleens were stated in the report. Histological findings of the spleens included extramedullary hematopoiesis and congestion. One incident of lymphoma was found in the 2.5 ppm and 50 ppm groups; however, not all spleens were sectioned. The NOEL was 0.5 ppm (0.02 mg/kg/day for males) for increased incidences of enlarged spleens at 2.5 and 50 ppm. When first reviewed, the study was considered unacceptable pending the submission of the supplemental information regarding: range-finding study; analytical methods; cause and extent of autolysis; histological examinations for the lower dose groups; and clarification of liver gross and histological findings. Additional information was submitted and this study was considered marginally acceptable to DPR. The NRC in the review of the draft inhalation RCD (DPR, 1999) considered a NOAEL of 50 ppm (2.2 mg/kg/day) for this study based on decreased body weight (NRC, 2000). The enlarged spleen was not considered to be treatment-related since there were no clear dose-response relationship, histological correlates in the spleen, and effects on hematology and clinical chemistry parameters. The U.S. EPA also established a NOEL of 50 ppm for this study based on reduced body weights, body weight gain, and food consumption in both gender during the first 18 months of the study (Gross, 1999).

III.C.2. Inhalation

For chronic inhalation toxicity, the following study was used to establish the critical endpoint and NOEL.

Wistar rats (90/sex/group) were exposed to methyl bromide (98.8% pure; nominal concentrations of 0, 3, 30, or 90 ppm) 6 hours per day, 5 days per week (Reuzel *et al.*, 1987 and 1991). The main group for each dose consisted of 50 rats of each sex and were exposed to methyl bromide for 29 months. There were 4 satellite groups (10/sex/group except noted): week 13-14 hematology and blood chemistry analyses, week 41 behavioral effects, 1 year interim sacrifice, and 2 years interim sacrifice.

Table 4. Food consumption and body weight in rats during chronic exposure to methyl bromide.^a

Duration (weeks)	Methyl Bromide concentration (ppm)						
	Microcap 0 ppm	0.5	2.5	50	250 ppm		
Male	0	0.02	0.11	2.20	11.10		
					mg/kg/day		
Food Consumption (mean, g/animal/day)						% Control	
0 to 1	26	26	26	25	23**	88	
26 to 27	27	27	27	26	24**	89	
52 to 53	27	27	28	27	25**	93	
78 to 79	28	27	27	27	26	93	
103 to 104	25	25	19	23	23	92	
Body Weight (mean, g)							
1	252	256	252	250	242**	96	
26	589	600	589	575	521**	88	
52	683	697	684	661	595**	87	
78	760	773	762	737	691*	91	
104	685	725	673	667	700	102	
Female	0	0.03	0.15	2.92	15.12		
					mg/kg/day		
Food Consumption (mean, g/animal/day)							
0 to 1	18	18	18	19	17**	94	
26 to 27	20	20	20	19	18**	90	
52 to 53	21	21	21	21	20*	95	
78 to 79	24	23	23	23	21	87	
103 to 104	20	20	19	19	19	95	
Body Weight (mean, g)							
1	171	169	170	173	166	97	
26	305	303	300	305	281**	92	
52	360	359	353	359	330**	92	
78	462	449	443	465	418	90	
104	488	455	445	489	454	93	

^{a/} Only selected values are presented in this Table (Mertens, 1997). There were 60 to 70 animals (Microcap, 50 ppm, and 250 ppm) or 48 to 50 animals (0.5 ppm and 2.5 ppm) per group for the first 53 weeks. From week 53 to week 104, the number of male rats per group decreased from 57 to 17 (Microcap), 49 to 16 (0.5 ppm), 50 to 16 (2.5 ppm), 59 to 22 (50 ppm), and 60 to 30 (250 ppm) for the groups. For week 53 to week 104, the number of female rats decreased from 59 to 19 (Microcap), 50 to 22 (0.5 ppm), 48 to 22 (2.5 ppm), 48 to 24 (50 ppm), and 59 to 30 ppm (250 ppm) for the groups. Statistical significance was based on the Dunnett's test with *, ** for p <0.05 and p <0.01, respectively. % Control was based on values for Microcapsules only as the control.

In the 90 ppm group, the 2 year and 2.5 year mortality rates for both sexes (male/female) were 52%/46% and 84%/86%, respectively. These rates were considered higher than those for the control groups which were 32% for 2 years and about 72% for 2.5 years, for both sexes. The mean body weight of the 90 ppm female group was significantly ($p \# 0.05$) lower than that of the controls throughout most of the study with the maximal reduction (12%) at the end of the study. The mean body weight of the 90 ppm male group was significantly ($p \# 0.05$) decreased (maximum of 6%) on occasion. Absolute kidney weights were significantly ($p \# 0.05$) decreased in the 30 ppm (89% of control) and 90 ppm (84% of control) females, and in the 90 ppm males (85% of control) when compared to control values at the 1 year sacrifice. Absolute brain weights of the 90 ppm females were reduced at the 1-year and 2-year sacrifices (Table 5). At 29 months, the absolute brain weights were significantly decreased in the 30 ppm males and females, and the 90 ppm females. Brain weight reduction also was seen in the 90 ppm male group at 29 months but was not statistically significant probably due to the small number of survivors ($n=8$). The NOAEL was 3 ppm for brain weight reduction.

There were increased incidences of heart thrombi and myocardial degeneration in rats that died or were killed when moribund (Table 5). These lesions may be the cause of increased mortality in the high dose groups. Statistical comparison to the control group did not identify any increased tumor incidences. Few tumors were observed: brain glioma in the 30 ppm group (1 male and 1 female), granular cell myoblastoma in the 30 ppm group (2 males), and 90 ppm group (1 male, and 2 females), spinal cord glioma in the control (1 male) and 90 ppm group (1 female). The historical control data (1974-1988) for Wistar rats showed the following incidences (male and female, respectively): 8/873 and 3/876 for brain glioma, 2/685 and 1/701 for spinal cord glioma, and 2/873 and 8/876 for granular cell myoblastoma.

At 12-24 months, the incidences of nasal cavity lesions of the 30 and 90 ppm groups were significantly ($p \# 0.05$) different from those of the control group (Table 5). At 24-29 months, there was a dose-related increase in the incidences of nasal cavity degeneration/hyperplasia, heart lesions (thrombus, myocardial degeneration, and cartilaginous metaplasia), esophageal hyperkeratosis, and stomach hyperkeratosis in all treatment groups. The finding of epithelial cell degeneration/basal cell hyperplasia in the olfactory epithelium of the nasal cavity was both dose- and time-related in incidence and severity (Table 5). The lesions were described as very slight at the lower doses to moderate at the higher doses. There were thinning (atrophy) of the epithelial layer and the formation of cyst-like glandular structures in the submucosa layer. The LOAEL for the basal cell hyperplasia/degeneration were >90 ppm, 30 ppm, and 3 ppm for exposures lasting 12 months, 12-24 months, and 24-29 months, respectively. The results from the reexamination of the nasal cavity histological slides (Hardisty, 1997) did not change the LOAELs because: (1) the rereading of the slides was not conducted in accordance with standard procedures for a peer review, and (2) dose response for incidence and severity remained the same with effects observed at 3 ppm. This study was considered acceptable to DPR according to FIFRA guidelines.

Table 5. The effects of methyl bromide in rats after chronic inhalation exposure.^a

Exposure duration		Methyl Bromide Concentration (ppm)			
		0	3	30	90
MALE					
		Mean Absolute Organ weight (g)^b			
Brain Weight:	1 year	2.01±0.03	2.12±0.01*	2.03±0.03	1.93±0.03
	2 year	2.09±0.07	2.15±0.02	2.08±0.03	1.99±0.06
	29 months	2.15±0.02	2.11±0.03	2.03±0.04*	2.02±0.05
		Incidences			
Nasal Cavity: Degeneration/ hyperplasia	12-24 months	6/30++ (20%)	1/26 (4%)	11/35 (31%)	22/39** (56%)
	24-29 months	4/36++ (11%)	12/37* (32%)	16/32*** (50%)	20/28*** (71%)
Heart: died before end of study ^c		Incidences			
	Cartilaginous metaplasia	1/33++	2/25	5/34	12/41**
	Myocardial degeneration -moderate/severe	21/33++	16/25	8/34	36/41*
	Thrombus	4/33++	3/25	10/34	20/41**
<hr style="border-top: 1px dashed black;"/>					
FEMALE					
		Mean Absolute Organ weight (g)^b			
Brain Weight:	1 year	1.94±0.02	1.95±0.03	1.85±0.04	1.81±0.03**
	2 year	1.97±0.02	1.91±0.01	1.88±0.03	1.84±0.05*
	29 months	2.01±0.02	1.96±0.02	1.92±0.02*	1.77±0.06**
		Incidences			
Nasal Cavity Degeneration/ hyperplasia	12-24 months	7/38++ (18%)	5/34 (15%)	16/39* (41%)	26/42*** (62%)
	24-29 months	5/40++ (13%)	16/42** (38%)	15/38** (39%)	25/35*** (71%)
Heart: died before end of study ^c		Incidences			
	Cartilaginous metaplasia	4/41	10/33	2/35	14/51*
	Myocardial degeneration -moderate/severe	13/41++	5/33	5/35	38/51**
	Thrombus	5/41++	8/33	1/35	20/51*

^{a/} Data from Reuzel *et al.* (1987, 1991). Incidence rates were the number of animals affected/number of animals examined. Rats in the 12-24 month group were those in the 1-year and 2-year sacrifice groups, and in the main group which died before two years. Rats in the 24-29 month group were those in the main group which died between days 736 and terminal sacrifice, and those at terminal sacrifice. *, **, ***, +, ++ Level of statistical significance, p # 0.05 (* or +), p # 0.01 (** or ++), or p # 0.005 (***). Significance for incidences was based on a dose-weighted chi-square trend test and the Fisher's Exact Test. For brain weights, significance was based on ANOVA and Dunnett tests.

^{b/} The number of animals per group for the 29 months data were: 15, 25, 16, and 8 for the males; and 18, 25, 24, and 9 for the females for 0, 3, 30, and 90 ppm, respectively.

^{c/} Incidences of heart lesions in those animals dead before the end of the study.

IV. RISK ASSESSMENT FOR AGGREGATE EXPOSURE

IV.A. HAZARD IDENTIFICATION FOR AGGREGATE EXPOSURE

The critical endpoints to evaluate aggregate exposure were based on the common endpoint approach with the same effect observed in the individual routes of exposure (U.S. EPA, 1999 and 2001). In this section, the NOELs are discussed in terms of adjusted doses to account for the difference in the intake rates and absorption factors for inhalation (50%) and oral (100%) exposures.

IV.A.1. Acute Exposure

For inhalation exposure to methyl bromide, the critical endpoint was developmental toxicity with a NOEL of 40 ppm (absorbed dose of 10.5 mg/kg/day¹) (Breslin *et al.*, 1990; DPR, 1999; DPR, 2002a). This was apparently a route-specific effect as developmental toxicity had only been observed by the inhalation route in either rats or rabbits (Sikov *et al.*, 1981; Breslin *et al.*, 1990). Developmental toxicity was not reported for studies conducted using the oral route in either species (Kaneda *et al.*, 1998). In risk characterization, this endpoint was applied to the adult population, in particular, women of child-bearing age. For exposure of children, neurotoxicity was considered a more appropriate critical endpoint for risk characterization. The NOEL was 103 ppm (absorbed dose of 22.8 mg/kg/day²) for clinical signs (decreased activity) in dogs (Newton *et al.*, 1994a). At higher concentrations or longer exposure, the dogs showed labored breathing, irregular gait, prostration, and tremors. The lower NOEL for developmental toxicity was chosen for the risk characterization of acute inhalation exposure as women of child-bearing age may be part of the workforce as well as in the general population.

For oral exposure to methyl bromide, one of the acute critical endpoints was the presence of clinical signs in rats after gavage administration of methyl bromide (Kiplinger, 1994; DPR, 2002b). The estimated NOEL was 8 mg/kg/day (absorbed dose of 8 mg/kg/day) based on a LOEL of 80 mg/kg/day and a default uncertainty factor of 10. The clinical signs were hypoactivity, ataxia, prostration, labored respiration, hypothermia, and tremors in treated rats. These signs may be indications of systemic neurotoxicity from absorbed methyl bromide. They could also, in part, reflect general stress in the treated animals due to severe damage (hemorrhage, edema, and squamous cell hyperplasia) to the stomach.

Based on the considerations on the acute critical endpoints, the presence of clinical

¹ The absorbed dose for developmental toxicity from inhalation exposure is calculated based on the air concentration, respiration rate (m³/kg/day) of rabbits, duration of exposure, and % of absorption.

$$40 \text{ ppm} \times \frac{3.89 \text{ mg/m}^3}{\text{ppm}} \times 0.54 \text{ m}^3 / \text{kg} / \text{day} \times \frac{6 \text{ hr}}{24 \text{ hr/day}} \times \frac{7 \text{ days}}{7 \text{ days/week}} \times 50\% = 10.5 \text{ mg} / \text{kg} / \text{day}$$

² The absorbed dose for neurotoxicity from inhalation exposure is calculated based on the air concentration, respiration rate (m³/kg/day) of dogs, duration of exposure, and % of absorption.

$$103 \text{ ppm} \times \frac{3.89 \text{ mg/m}^3}{\text{ppm}} \times 0.39 \text{ m}^3 / \text{kg} / \text{day} \times \frac{7 \text{ hr}}{24 \text{ hr/day}} \times \frac{5 \text{ days}}{7 \text{ days/week}} \times 50\% = 22.8 \text{ mg} / \text{kg} / \text{day}$$

signs was selected as the common endpoint for acute aggregate exposure. The clinical signs observed in the acute inhalation study (Newton *et al.*, 1994a) were clearly due to neurotoxicity, while those observed in the oral study (Kiplinger, 1994) could be attributed to neurotoxicity. The NOELs (as absorbed doses) were 22.8 mg/kg/day and 8 mg/kg/day for inhalation and oral exposures, respectively (Table 6). The NOEL of 22.8 mg/kg/day is 2-fold higher than the NOEL (21 ppm, 10.5 mg/kg/day for developmental toxicity) for inhalation exposure alone (Table 6).

IV.A.2. Chronic Exposure

For chronic inhalation exposure to methyl bromide, the critical endpoint was nasal cavity lesions in rats with a NOEL of 0.2 ppm (absorbed dose of 0.067 mg/kg/day³) (Reuzel *et al.*, 1987 and 1991). This endpoint has also been observed in dogs after inhalation exposure (Newton, 1994a) but has not been reported when methyl bromide is given by the oral route. Boorman *et al* (1990) suggested that toxicity to the nasal region was due to an abundance of endoplasmic reticula with high metabolic activity. Since nasal cavity lesion is a route-specific endpoint, it was considered inappropriate for use in aggregate exposure. Instead, body weight reduction was selected since it is a common endpoint for both inhalation and oral exposures. Compared to other endpoints (decreased brain weight and nasal epithelial hyperplasia/ degeneration) in the study, the reduction in body weight in the inhalation chronic toxicity study with rats was not the most sensitive endpoint (Reuzel *et al.*, 1987 and 1991). The mean body weight of the 90 ppm female group was significantly (p # 0.05) lower than that of the controls throughout most of the study but the maximal reduction was only 12% at the end of the study. The mean body weight of the 90 ppm male group was significantly (p # 0.05) decreased (maximum of 6%) on occasion. The NOEL was at 30 ppm (absorbed dose of 10 mg/kg/day⁴). It was not known if the reduced body weight was associated with reduced food consumption since rats were derived of water and food during exposure but feeding was *ad libitum* after exposure.

For chronic oral exposure to methyl bromide, the critical endpoint was reduced body weight with a NOEL of 2.2 mg/kg/day (absorbed dose of 2.2 mg/kg/day) in rats exposed to methyl bromide microcapsules in the feed for 2 years (Mertens, 1997). This effect was accompanied by reduced food consumption and was observed throughout the study. The decrease in food intake may be related to the irritation effect of methyl bromide on the stomach lining, a finding in an acute study using microencapsulated methyl bromide mixed in corn oil (Kiplinger, 1994).

Therefore, reduced body weight in rats was considered the common endpoint for risk

³The absorbed dose for nasal cavity lesions from inhalation exposure is calculated based on the air concentration, respiration rate (m³/kg/day) of rats, duration of exposure, and % of absorption.

$$0.2 \text{ ppm} \times \frac{3.89 \text{ mg/m}^3}{\text{ppm}} \times 0.96 \text{ m}^3 / \text{kg} / \text{day} \times \frac{6 \text{ hr}}{24 \text{ hr/day}} \times \frac{5 \text{ days}}{7 \text{ days/week}} \times 50\% = 0.067 \text{ mg} / \text{kg} / \text{day}$$

⁴The absorbed dose for reduced body weights from inhalation exposure is calculated based on the air concentration, respiration rate (m³/kg/day) of rats, duration of exposure, and % of absorption.

$$30 \text{ ppm} \times \frac{3.89 \text{ mg/m}^3}{\text{ppm}} \times 0.96 \text{ m}^3 / \text{kg} / \text{day} \times \frac{6 \text{ hr}}{24 \text{ hr/day}} \times \frac{5 \text{ days}}{7 \text{ days/week}} \times 50\% = 10 \text{ mg} / \text{kg} / \text{day}$$

characterization for aggregate chronic exposure. The NOELs (as absorbed doses) were 10 mg/kg/day and 2.2 mg/kg/day for inhalation and oral exposures, respectively (Table 6). The NOEL of 10 mg/kg/day is 150-fold higher than the NOEL (0.2 ppm, 0.067 mg/kg/day for nasal epithelial hyperplasia) for inhalation exposure alone (Table 6).

IV.A.3. Oncogenicity

The current database of inhalation and oral oncogenicity and chronic toxicity studies does not show clear evidence of oncogenicity for methyl bromide (Reuzel *et al.*, 1987 and 1991; NTP, 1992; Eustis, 1992; Danse *et al.*, 1984; Boorman *et al.*, 1986; Hubbs, 1986).

Table 6. Critical No-Observed-Effect Levels for aggregate exposures.^a

	Inhalation Exposure Only	Dietary Exposure Only	Aggregate Exposure
Acute	21 ppm [10.5 mg/kg/day] Developmental toxicity in rabbits (Breslin <i>et al.</i> , 1990)	[8 mg/kg/day] Clinical signs (hypoactivity, ataxia, prostration, labored respiration and others) in rats (Kiplinger, 1994)	Inhalation: 22.8 mg/kg/day Oral: 8 mg/kg/day Clinical signs in rats (Kiplinger, 1994; Newton, 1994a)
	103 ppm [22.8 mg/kg/day] Decreased activity in dogs (Newton, 1994a)		
Chronic	0.2 ppm [0.067 mg/kg/day] Nasal epithelial hyperplasia in rats 30 ppm [10 mg/kg/day] Reduced body weight in rats (Reuzel <i>et al.</i> , 1987 and 1991)	[2.2 mg/kg/day] Reduced body weights in rats (Mertens, 1997)	Inhalation: 10 mg/kg/day Oral: 2.2 mg/kg/day Reduced body weight in rats (Mertens, 1997; Reuzel <i>et al.</i> , 1987 and 1991)

^{a/} Bolded values are those used for the calculation of margins of exposure for individual route and aggregate exposures.

IV.B. AGGREGATE EXPOSURE ASSESSMENT

Aggregate exposure is the combined exposure of multiple pathways such as air, food, and drinking water. As stated in the U.S. EPA guidelines, aggregate exposure should link spatial (*i.e.*, all pathways agree in place/location), temporal (*i.e.*, all pathways agree in time), and demographic (*i.e.*, all pathways agree in age/gender/ethnicity and other demographic characteristics) characteristics of each route in effort to derive a consistent and reasonable assessment of total exposure (U.S. EPA, 1999 and 2001). The estimation of exposure and risk should focus on the individual with each of the individual sub-assessments Alinked back to the same person and the aggregate intake should reflect the food, drinking water, and residential intakes that are for the same individual at the same time, in the same place, and under the same demographic conditions (U.S. EPA, 1999). The collective exposures and risks for individuals are then used to develop those values for population subgroups and the entire population.

For methyl bromide, the underlying assumption was that there is potential for aggregate exposure because methyl bromide residues have been detected in both the air and food, but not in the drinking water⁵. Due to insufficient exposure data, it was not possible to estimate the aggregate exposure at an individual level. Instead in this assessment, the population was broadly divided into workers (who work with methyl bromide) and residents (those who do not handle methyl bromide) (Table 7). Specific details on how the exposures values were selected are in sections **IV.B.1. and IV.B.2.** The temporal nature of some exposures, such as in preplant fumigation where the exposure is limited to the beginning of season, was accounted for by excluding chronic exposure estimates. For spatial considerations, the range of potential residential inhalation exposures was represented by 12 sites in three counties (ARB, 2000 and 2001; DPR, 2001a). Analysis of the data showed that the magnitude of the detected levels corresponded to the use (field and commodity fumigations) during the monitored period (DPR, 2001b). When weekly averages of these data are used for chronic exposure, residents were assumed to be exposed to the same levels throughout the year.

For both workers and residents, the demographic characteristics of their exposures were considered in terms of age-related differences in the intake (respiration rate and consumption rate). The methyl bromide air concentrations were converted to absorbed doses using age - adjusted breathing rates. For workers, the methyl bromide air levels were converted to the absorbed dose using a default adult breathing rate of 0.26 m³/kg/day. For residents, the air levels were converted to the absorbed dose using the higher default children breathing rate of 0.46 m³/kg/day. Similarly, the age factor was accounted for in the dietary component of aggregate exposure. The dietary exposures for workers were based on the exposure of adults (16+ years old) and adults (20+ years old) from individual consumption surveys for acute and chronic exposures, respectively. The adult (16+ years old) group was selected because 16 years old is the minimum age requirement for workers. Since the dietary exposure software does not calculate chronic exposure for the same age group, the 20+ years old group with the highest exposure was used instead. The dietary exposures for residents was based on the

⁵The potential exposure from methyl bromide in drinking water was not included in this assessment because residues have not been detected (<1 ppb) in the monitored wells (**II.G. ENVIRONMENTAL FATE** in **Volume I**).

highest exposed group which was children (1-6 years old).

There was greater variability in inhalation than dietary exposures. For most of work tasks, the inhalation exposure was much higher than that for dietary exposure. The range of acute inhalation exposure was 1 to 535 $\mu\text{g}/\text{kg}/\text{day}$ (1 ppb to 1058 ppb) for both field and commodity fumigation workers (Table 8). In comparison, the range of acute dietary exposure for adults were 3.387 $\mu\text{g}/\text{kg}/\text{day}$ to 4.993 $\mu\text{g}/\text{kg}/\text{day}$ (DPR, 2002b). With residents, the range of acute inhalation exposures depended on the location of the monitored sites and ranged from 0.21 to 27.02 (0.239 ppb to 30.2 ppb). The acute 95th percentile exposures for all groups ranged from 3.504 $\mu\text{g}/\text{kg}/\text{day}$ (non-nursing infants) to 8.195 $\mu\text{g}/\text{kg}/\text{day}$ (children 1-6 years old) (DPR, 2002b).

Table 7. Components for aggregate exposures of workers and residents to methyl bromide.^a

Exposed Groups	Aggregate Exposure	Selected exposure values	
		Inhalation Exposure	Dietary Exposure
Workers	Acute	Upper bound of measured values or 210 ppb for each worker scenario	95 th percentile exposure for 16+ years old group
	Chronic	Mean measured values for each worker scenario	Mean exposure for 20+ years old group
Residents	Acute	95 th percentile exposure for children ^b from ambient air monitoring	95 th percentile exposure for 1-6 year old group
	Chronic	Mean of weekly means for children ^b from ambient air monitoring	Mean exposure for 1-6 year old group

^{a/} The aggregate exposure was based on exposures by the inhalation and oral (dietary) routes. Exposure scenarios and levels are provided in Tables 8 to 10.

^{b/} Children exposure values ($\text{mg}/\text{kg}/\text{day}$) were calculated based on the 95th percentile measured methyl bromide air concentration and the default breathing rate for children ($0.46 \text{ m}^3/\text{kg}/\text{day}$). Since the children breathing rate is higher than that for adults ($0.26 \text{ m}^3/\text{kg}/\text{day}$), the use of children's higher exposure levels to determine the risk will protect those of adults.

IV.B.1. Occupational/Residential Exposure (Inhalation route)

The estimation of occupational and residential inhalation exposures was described in **Volume I** (DPR, 2002a).

Occupational Inhalation Exposure

As discussed in **Volume I**, the database for worker exposures was very limited. For many scenarios, there was either no data or only few samples were collected. In the absence of data, some acute exposures were assumed to be 210 ppb, the current DPR regulatory level. Worker exposures were available only for those involved in soil and commodity fumigation. Applicators in structural fumigation were not included in this assessment because they are required to wear self-containing breathing apparatus when handling methyl bromide. There were no data for other workers of this use.

For soil fumigation, only the worker exposures monitored under current DPR regulations were selected for aggregate exposure (Table 8a). For shallow shank and tarped bed fumigation, the regulations required the use of swept-back shank and a closing device with rollers to compress the soil before tarp application. The acute exposures were 4 ppb for applicators, 58 ppb for copilot, and 1 ppb for shovel-men. There were two studies on tarp removal under similar conditions where the tarp was cut 5 days after fumigation and removed after 1 day of aeration. The first study showed 202 ppb for cutters and 215 ppb for pullers. In the second study, lower exposures were measured for these workers (138 ppb for cutter and 22 ppb for end puller) but much higher exposures for the tractor driver (1058 ppb) and basket-men (1003 ppb). No chronic exposures were expected for workers in field fumigation.

For commodity fumigation, only scenarios with exposure values collected by personal monitoring of individuals doing specific work tasks were considered (Table 8b). The work tasks included those for fumigation (applicators, aerators, tarp removers) and those for handling of fumigated products (forklift drivers, stem pickers, hopper operators). Area sampling data, such as those for walnut workers as shown in **Volume I**, were not used since they showed only air concentrations at the work stations and not actual exposures. For workers involved in the fumigation of potting soil in greenhouses, the maximum acute exposure was set at 210 ppb (Table 8b). Their actual exposures were relatively low because tarp venters are required to wear self-containing breathing apparatus and tarp removal occurs after 48 hours of venting. No data were available for other workers, e.g., applicators, associated with this use. No chronic exposures were expected. The acute exposure of workers in grain products and raisins fumigation was also limited 210 ppb (Table 8b). The chronic exposure was based on the average of measured values. For grain product workers, the range of chronic exposures was 0.01 ppb (aerators of tarpaulin fumigation) to 8 ppb (forklift drivers emptying sea containers/truck trailers). In comparison, forklift drivers emptying non-certifying fumigation chambers had a lower chronic exposure of 3 ppb. For raisin workers, the range of chronic exposures was 1 ppb (forklift drivers) to 26 ppb (fumigators).

For workers in a brewery, exposures were estimated for applicators and aerators at various locations (Table 8b). This type of fumigation is similar to structural fumigation and no other workers are allowed in the facility during fumigation. The acute worker exposure was 210 ppb and no chronic exposure was estimated.

Residential Inhalation Exposure

For acute residential inhalation exposure, the ambient air monitoring data for 12 sites in three counties during the use season were used to represent exposures from all uses (ARB, 2000 and 2001; DPR, 2001a; Powell, 2001) (Table 9). This is a reasonable approach since there were no data for exposure to structural fumigation and some of the sites were located at

high methyl bromide use areas. Each site was a single geographic point and monitored for only 3-4 days per week for 7-8 weeks. The 95th percentile daily exposure levels spanned more than 120-fold and ranged from 0.239 ppb (Mettler Fire Station) to 30.2 ppb (Pajaro Middle School in Watsonville) (Powell, 2001). The mean of the weekly mean values for each site (0.084 ppb to 7.68 ppb) was used to account for potential chronic exposure.

IV.B.2. Dietary Exposures (Oral route)

In **Volume II** for dietary exposure, acute and chronic dietary exposure analyses were conducted with consumption rates based on the 1989-1992 data from the USDA Continuing Survey of Food Intakes by Individuals (CSFII) and residue data submitted by The Methyl Bromide Industry Panel (complete references in **Volume II Attachment A**). When a commodity did not have any residue data, a residue value from another commodity in the same or similar crop group was used as a surrogate representative. Over 230 commodities and their food forms were included in the acute and chronic dietary exposures. These analyses included consideration of potential loss or accumulation of residues during processing of the commodities and adjustment for less than 100% of the crop treatment.

The dietary exposure levels for aggregate exposure estimates were selected from appropriate population subgroups (Table 10). The dietary exposure for workers was based on the 95th percentile acute exposure of adults who were 16+ years old (4.649 $\mu\text{g}/\text{kg}/\text{day}$) and annual chronic exposure for adults 20+ years old (0.143 $\mu\text{g}/\text{kg}/\text{day}$). The acute 95th percentile exposures for all adult groups ranged from 3.387 $\mu\text{g}/\text{kg}/\text{day}$ (Females 13-19 years; not pregnant, not nursing) to 4.993 $\mu\text{g}/\text{kg}/\text{day}$ (Females 20+ years old, not pregnant, not nursing). The chronic exposures for all adult groups ranged from 0.060 $\mu\text{g}/\text{kg}/\text{day}$ (Females 13-19 years; not pregnant, not nursing) to 0.149 $\mu\text{g}/\text{kg}/\text{day}$ (Females 13+ years old, nursing). The dietary exposures for residents were based on the highest exposed group (children 1-6 years old) instead of using all 20 subgroups to simplify the assessment. The acute 95th percentile exposures for all groups ranged from 3.504 $\mu\text{g}/\text{kg}/\text{day}$ (non-nursing infants) to 8.195 $\mu\text{g}/\text{kg}/\text{day}$ (children 1-6 years old). The chronic exposures for all groups ranged from 0.014 $\mu\text{g}/\text{kg}/\text{day}$ (non-nursing infants) to 0.200 $\mu\text{g}/\text{kg}/\text{day}$ (children 1-6 years old).

Table 8. Acute and chronic occupational inhalation exposures to methyl bromide.^a

Type of Application	Acute Exposure		Chronic Exposure	
	ppb	ug/kg/day	ppb	ug/kg/day
a. Field Fumigation				
(1) Shallow-shank/ tarp			No exposure	
Applicator	4	2		
Copilot	58	29		
Shovel-man	1	1		
<u>Tarp removal study 1</u>				
Cutter	202	102		
Puller	215	109		
<u>Tarp removal study 2</u>				
Tractor driver	1058	535		
basket-man	1003	507		
end puller	22	11		
cutter	138	70		
(2) Deep-shank/ non-tarp				
Applicator	13	7		
Cultipacker	13	7		
b. Commodity Fumigation				
(1) Soil in greenhouses			No exposure	
Tarp venter and remover	210	106		
(2) Grain products				
Aerator (sea container/trailer)	210	106	0.3	0.15
Aerator (tarp)	210	106	0.01	0.01
Forklift driver(container/trailer)	210	106	8	4.05
Forklift driver (chamber)	210	106	3	1.52
(3) Raisins - Fumigator	210	106	26	13.15
Aerator	210	106	19	9.61
Stem picker	210	106	12	6.07
Forklift driver	210	106	1	0.51
Hopper operator	210	106	8	4.05
(4) Brewery-			No exposure	
Applicator	210	106		
Aerator	210	106		

^{a/} From Table 19 of Inhalation exposure RCD (DPR, 2002a). Exposures were upper bound and mean values for acute and chronic exposures, respectively. Absorbed daily dose was determined using a default adult breathing rate of 0.26 m³/kg/day x 50% absorption factor:

$$\text{ug / kg / day} = \text{ppb} \times \frac{3.89 \text{ ug/m}^3}{\text{ppb}} \times 0.26 \text{ m}^3 / \text{kg} / \text{day} \times 50\%$$

Table 9. Acute and chronic residential inhalation exposures to methyl bromide at ambient air monitoring sites.^a

Sites in California		Acute Exposure 95th percentile Daily		Chronic Exposure weekly mean	
		ppb	ug/kg/day (absorbed)	ppb	ug/kg/day (absorbed)
1	Chualar School, Chualar	2.26	2.02	0.644	0.58
2	La Joya Elementary School, Salinas	18.5	16.6	3.79	3.39
3	Oak Avenue School, Greenfield	1.21	1.08	0.387	0.35
4	Pajaro Middle School, Watsonville	30.2	27.0	7.68	6.87
5	Ambient Monitoring Station, Salinas	6.17	5.52	1.29	1.15
6	Salsepuedes Elementary School, Watsonville	12.2	10.9	2.6	2.33
7	Ambient Monitoring Station, Bakersfield	0.556	0.498	0.189	0.17
8	Cotton Research Station, Shafter	25.4	22.7	2.16	1.93
9	Mettler-Fire Station, Mettler	0.239	0.214	0.084	0.08
10	Mountain View School, Lamont	0.262	0.236	0.092	0.08
11	Shafter-Walker Ambient Monitoring Station	3.98	3.56	0.792	0.71
12	Vineland School District, Bakersfield	0.292	0.262	0.099	0.09

^{a/} Monitoring data for 12 sites in Monterey, Santa Cruz and Kern counties from ARB (2000, 2001), DPR (2001a), and Powell (2001). Absorbed dose (ug/kg/day) was determined using a default children breathing rate of 0.46 m³/kg/day x 50% absorption factor and the following equation:

$$\text{ug / kg / day} = \text{ppb} \times \frac{3.89 \text{ ug/m}^3}{\text{ppb}} \times 0.46 \text{ m}^3 / \text{kg} / \text{day} \times 50\%$$

Table 10. Acute and chronic oral exposures to methyl bromide in the diet.^a

Groups	Acute exposure (ug/kg/day)	Chronic exposure (ug/kg/day)
Workers	4.649 (Adults 16+ years)	0.143 (Females 20+ years old, not pregnant, not nursing)
Residents-	8.195 (Children 1-6 years old)	0.200 (Children 1-6 years old)

a/ Values from Table 7 of **Volume II** for dietary exposure (DPR, 2002b). The acute and chronic exposures were 95th percentile and mean value, respectively.

IV.C. RISK CHARACTERIZATION FOR AGGREGATE EXPOSURE

The potential health hazard associated with the use of methyl bromide was considered for inhalation and oral exposures in combination. In the assessment of single route of exposure, the risk for non-oncogenic effect was characterized in terms of a margin of exposure (MOE), defined as the ratio of the critical human equivalent NOEL to the estimated human exposure levels. For aggregate exposure, the risk was determined by a total MOE approach⁶ (U.S. EPA, 1999). This approach is used when there is a common effect with different NOELs for the different routes of exposure but with the same uncertainty factor (UF) applied for both routes. The magnitude of the total MOE expressed only the risks for specified endpoints. When the uncertainty factors are different for each route, other approaches include aggregate risk index (ARI) and hazard index (HI) methods are used (U.S. EPA, 1999). The aggregate risk index is considered an extension of the total MOE method. The uncertainty factors are incorporated into the equation (replace the value of 1 in the total MOE equation with the uncertainty factor). The hazard index (HI) is an aggregation of individual hazard quotients (HQ) for each route of exposure. This method also incorporates the uncertainty factors from each route into the equation⁷. The risk increases with increasing values of HQ or HI with a value of <1 generally considered of little concern. Since HI is essentially the same as the ARI (the reciprocal of ARI), HI was eliminated from the U.S. EPA revised aggregate exposure document (U.S. EPA, 2001). ARI is also preferred over HI because it includes dissimilar uncertainty factors.

$${}^6 \text{ Total MOE} = \frac{1}{\frac{1}{\text{MOE}_{\text{oral}}} + \frac{Y1}{\text{MOE}_{\text{inhalation}}}}$$

$${}^7 \text{ HI total} = \text{HQ}_{\text{oral}} + \text{HQ}_{\text{inhalation}}$$

$$\text{HI} = \frac{\text{Exposure}_{\text{oral}}}{\text{NOEL}_{\text{oral}} / \text{UF}} + \frac{\text{Exposure}_{\text{inhalation}}}{\text{NOEL}_{\text{inhalation}} / \text{UF}}$$

IV.C.1. Occupational Inhalation and Dietary Exposures

For aggregate exposure, the total acute MOEs for workers in shallow-shank and tarped fumigation were greater than 100 except for the tractor drivers and basket-men in the second tarp removal study (Table 11a). The MOEs for these latter workers were 42 and 44, respectively. The acute MOE was 1143 for both applicators and cultipackers in deep shank and non-tarped fumigation.

The total acute MOEs for all workers were 191 since both the inhalation exposures and dietary exposures were the same for all scenarios (Table 11b). The total chronic MOEs ranged from 375 (raisins fumigators) to 15152 (aerators of tarped fumigation of grain products).

IV.C.2. Residential Inhalation and Dietary Exposures

For residents, the total MOEs for acute aggregate exposure ranged from 453 to 967 for the 12 sites (Table 12). The total MOEs for chronic aggregate exposure were greater than 1000 and ranged from 1285 to 10160.

IV.C.3. Comparison of MOEs

The MOEs for inhalation exposures only (DPR, 2002a) were included in the Tables 11 and 12 for comparison. The MOEs for dietary exposures of the selected adult groups were 1720 and 15430 for acute and chronic exposures, respectively (DPR, 2002b). The difference between the total MOE and the individual route MOEs for each scenarios may be due to differences in the magnitude of the NOELs and/or the exposure levels for each route. The NOELs for total MOEs (for example, 22.8 mg/kg/day for acute inhalation component) were higher than those for inhalation exposure alone, which had a much lower NOEL (for example, 21 ppm or 10.5 mg/kg/day for acute inhalation alone). As a result, the acute total MOE for tractor drivers in tarp removal was 42, 2-fold higher than the inhalation MOE of 22. The dietary exposure contribution to the total exposure was relatively minor (4.69 ug/kg/day) compared to that for inhalation (535 ug/kg/day). On the other hand, the MOEs for applicators in shallow-shank and tarped field fumigation decreased from 5250 (inhalation alone) and 1720 (dietary alone) to 1482 (aggregate exposure) because of the increased total exposure with the addition of dietary exposure (4.69 ug/kg/day) to the inhalation exposure(2 ug/kg/day).

Table 11. Total margins of exposure for aggregate occupational inhalation and dietary exposures.^a

Type of Application	Acute Exposure		Chronic Exposure			
	Aggregate MOE	Inhalation MOE ^c	Aggregate MOE	Inhalation MOE ^c		
a. Field Fumigation						
(1) Shallow-shank/ tarp -Applicator	1482 ^b	5250	No exposure			
Copilot	534	362				
Shovel-man	1644	21000				
<u>Tarp removal study 1</u> -Cutter	197	104				
Puller	187	98				
<u>Tarp removal study 2</u> - Tractor driver	42	20				
Basket-man	44	21				
End puller	931	955				
Cutter	274	152				
(2) Deep-shank/ non-tarp - Applicator	1143	1615				
Cultipacker	1143	1615				
b. Commodity Fumigation						
(1) Green house soil - Tarp venter and remover	191	100			No exposure	
(2) Grain products - Aerator (sea container/trailer)	191	100	10526	667		
Aerator (tarp)	191	100	15152	20000		
Forklift driver(container/trailer)	191	100	2256	25		
Forklift driver (chamber)	191	100	2740	67		
(3) Raisins - Fumigator	191	100	375	8		
Aerator	191	100	509	11		
Stem picker	191	100	791	17		
Forklift driver	191	100	6061	200		
Hopper operator	191	100	1156	25		
(4) Brewery - Applicator	191	100	No exposure			
Aerator	191	100				

^{a/} The margins of exposure were based on occupational inhalation exposures (absorbed doses) in Table 8 and dietary exposures of 4.649 ug/kg/day and 0.143 ug/kg/day for acute and chronic oral exposures, respectively (Table 10). They were calculated using a total MOE equation with inhalation NOEL of 22.8 mg/kg/day and oral NOEL of 8 mg/kg/day for clinical signs in dogs and rats after acute exposure, and inhalation NOEL of 10 mg/kg/day and oral NOEL of 2.2 mg/kg/day for reduced body weights in rats after chronic exposure.

^{b/} Total MOE =
$$\frac{22800 \text{ ug/kg/day} + 8000 \text{ ug/kg/day}}{2 \text{ ug/kg/day} + 4.649 \text{ ug/kg/day}} = 1482$$

^{c/} Inhalation MOEs were based on NOELs of 21 ppm (10.5 mg/kg/day) and 0.2 ppm (0.067 mg/kg/day), for acute and chronic exposures, respectively.

Table 12. Total margins of exposure for aggregate residential inhalation and dietary exposures.^a

	Sites	Acute Exposure		Chronic Exposure	
		Aggregate MOE	Inhalation MOE ^c	Aggregate MOE	Inhalation MOE ^c
1	Chualar School, Chualar	898 ^b	9292	6733	No data
2	La Joya Elementary School, Salinas	571	1135	2326	
3	Oak Avenue School, Greenfield	933	17355	7966	
4	Pajaro Middle School, Watsonville	453	695	1285	
5	Ambient Monitoring Station, Salinas	790	3404	4847	
6	Salsepuedes Elementary School, Watsonville	665	1721	3091	
7	Ambient Monitoring Station, Bakersfield	956	37770	9275	
8	Cotton Research Station, Shafter	495	827	3519	
9	Mettler-Fire Station, Mettler	967	87866	10160	
10	Mountain View School, Lamont	967	80153	10087	
11	Shafter-Walker Ambient Monitoring Station	847	5276	6182	
12	Vineland School District, Bakersfield	965	71918	10023	

^{a/} The margins of exposure were based on residential inhalation exposures (absorbed doses) in Table 9 and acute dietary exposure of 8.195 ug/kg/day (Table 10). They were calculated using a total MOE equation with inhalation NOEL of 22.8 mg/kg/day and oral NOEL of 8 mg/kg/day for clinical signs in rats and dogs after acute exposure.

^{b/}
$$\text{Total MOE} = \frac{1}{\frac{2.02 \text{ ug/kg/day} + 8.195 \text{ ug/kg/day}}{22800 \text{ ug/kg/day} + 8000 \text{ ug/kg/day}}} = 898$$

^{c/} Inhalation MOEs were based on an acute NOEL of 21 ppm (10.5 mg/kg/day). There were no chronic MOEs for inhalation exposure only due to lack of data. The subchronic inhalation exposure values were used as default for aggregate chronic exposures.

V. RISK APPRAISAL FOR AGGREGATE EXPOSURE

V.A. INTRODUCTION

The aggregate exposure of methyl bromide was conducted for combined inhalation and oral (dietary) exposures for workers and residents. As with the assessment of individual routes, certain assumptions and extrapolations were incorporated into the hazard identification, dose-response assessment, and exposure assessment processes. This, in turn, resulted in uncertainty in the risk characterization which integrated all the information from the previous three processes. Specific areas of uncertainty associated with this risk assessment of methyl bromide are delineated in the following discussion.

V.B. HAZARD IDENTIFICATION FOR AGGREGATE EXPOSURE

The aggregate hazard identification was based on clinical signs and reduced body weights in experimental animals after acute and chronic exposures, respectively. As discussed in **IV.A.**, there were uncertainties related to the selection of these endpoints. While it was clear that the clinical signs observed in dogs after inhalation exposure was due to neurotoxicity, the signs observed in rats after oral exposure may be a combination of neurotoxicity and general stress of the animal due to severe irritation to the stomach lining. This possibility may explain the lower absorbed NOEL (8 mg/kg/day) for oral exposure compared to that (22.8 mg/kg/day) for inhalation exposure.

There was also uncertainty for the endpoint of reduced body weight for inhalation and oral chronic toxicity. For both routes of exposure, the reduction occurred throughout the study and was about 10% of control values. While the reduction was statistically significant for some time points during the experiments, the toxicological significance was uncertain since the magnitude of the reduction varied little with continued exposure. For inhalation exposure, methyl bromide effects on other organs (such as nasal epithelial hyperplasia/degeneration) were more severe and at lower doses than that for the reduction in body weights. On the other hand, reduced body weight was the only significant finding for chronic oral toxicity. As with the NOELs for acute aggregate exposure, the oral absorbed NOEL (2.2 mg/kg/day) for this endpoint was higher than that for inhalation absorbed NOEL (10 mg/kg/day).

V.C. AGGREGATE EXPOSURE ASSESSMENT

Aggregate exposures were estimated for the highly exposed individuals by using the upper bound (worker inhalation) or 95th percentile exposures (worker dietary, residential inhalation and dietary) for acute exposures. For chronic exposures, the mean values were used as exposures likely to fluctuate over time. The assessment also considered the higher exposures of children than adults due to differences in the intake rates (i.e. dietary and inhalation). For the residential inhalation exposure component, methyl bromide air concentrations from ambient air monitoring were converted to absorbed doses using the higher breathing rates of children (Table 9). Similarly, the residential dietary exposure component was based on the exposures for children (Table 10).

The uncertainties related to the aggregate exposures were the same as those associated with the individual routes alone and when they are considered in combination. The uncertainties for the inhalation and dietary exposures, alone, were those discussed previously in **Volumes I and II**. For inhalation exposure of workers, data were available for few scenarios, and some acute exposures were assumed to be or limited to 210 ppb. Depending on actual working conditions (e.g. hours worked, methyl bromide application rate), the use of 210 ppb exposures might be over- or underestimation of acute exposures.

Of the available exposure data on field and commodity fumigations, there were many deficiencies in the overall database. They included: (1) studies not in compliance with Good Laboratory Practices, in particular, absence of field fortification recovery studies; (2) some data are from interim, internal, or draft reports; (3) missing application rate and field fortification recovery information; and (4) lack of duration and frequency of exposure values for some work scenarios. Many exposure data were obtained from studies employing short monitoring periods and then amortized to the 24-hour time-weighted average. These amortized exposure data could overestimate or underestimate the actual exposures. Two potential areas of underestimation were the assumptions that (1) workers of specific work task will not have additional exposure from working in other work task(s) for the remainder of the workday, and (2) there was no overtime work during peak use season. The magnitude of these uncertainties can not be quantified at this time. One area of overestimation was the use of 50% recovery value to adjust all data. In some field studies, the adjustment resulted in more methyl bromide volatilized than was applied.

With respect to specific studies in field fumigation (Table 8a), one uncertainty in the exposure estimates was that they were based on few measurements. These data were generated to test equipment modifications, which were later adopted into regulation. The values were considered upper bound values; however, they were not true statistical upper bounds because they were based on few values. Nevertheless, these values were higher than the highest values obtained in each study for almost all cases. The use of the highest measured value is a general default approach when the database is limited. For workers involved in commodity fumigation, the sample size was also small (1 to 2 samples) for almost all cases. Since the acute exposure was limited to 210 ppb, the reference level, this sample size problem applied mainly to the short-term, subchronic, and chronic exposure durations.

There were also uncertainties in the residential inhalation exposure estimates (Table 9). These were based on ambient air monitoring data collected during the year 2000 for three counties. While the sites were monitored during the use season, the exposures of these residents at other times of the year and those in other counties were unknown (there are 58 counties in California). On the other hand, the current methyl bromide air concentration may be lower because of regulatory restrictions promulgated after the monitored period. The preliminary year 2000 use report indicated continued decline in methyl bromide use in California (DPR, 2001c). The ARB monitoring study being conducted will provide more current data for the evaluation of residential exposure.

Dietary exposure analyses were conducted for more than 200 commodities and their food forms (Table 10). There were potential sources of overestimation of exposure because of limitations in the data. For example, the residues for several major contributors to the total dietary exposures were based on fumigation using the maximum label rate. Depending on the

circumstance, the actual use rate may be lower. Another source of overestimation was the assumption, in the absence of data, of no loss of residue during processing and 100% of crop treated for some commodities such as spices, some dried beans, and some vegetables. Most of these commodities had low consumption rates and were not major contributors to the total exposure. The use of the detection limit to assign residue levels for samples with residue levels at or below the detection limit or the use of surrogate data could either over- or under-estimate the exposure. The dietary exposure may be an underestimate since composite samples were analyzed. This approach masked potential higher residue values of single units that a consumer may encounter in an acute exposure. Single-unit residue data were not available for any commodity. One area of uncertainty was that the exposure did not consider the presence of metabolites. There were no residue data on the metabolites of methyl bromide in the treated commodities.

As discussed in **IV.B.**, data for methyl bromide allowed only limited consideration of spatial, temporal, and demographic characteristics of aggregate exposures. The approach used focused primarily on the exposures of groups rather than individuals. The values used for each exposure component were considered reasonable for some population subgroups, for example children (1-6 years old) living in the areas represented by the air monitoring data and consumed a variety of commodities included in the dietary exposure. These levels could be over-estimates for those with lower inhalation (lower breathing rate in adults) and/or lower dietary (those with lower consumption rate or those who with a limited diet) exposures. On the other hand, they could be under-estimates for those who live adjacent to treated field or fumigation facilities where air levels may be higher than those from ambient air monitoring especially during methyl bromide application or aeration. The current permit condition limits the methyl bromide level to 210 ppb at the perimeter of the buffer zone; it is 7 times higher than the highest value (30.2 ppb for site #4 and a total MOE of 453) from ambient air monitoring (Table 12). Assuming that there are children who live near buffer zones and consume a diet at the 95th percentile of dietary exposure (8.195 $\mu\text{g}/\text{kg}/\text{day}$) at an acute setting, the total MOE would be 108 for this group. Data analyses showed that the magnitude of the methyl bromide maximum air concentration along the buffer zone perimeter was related to the size of the field and emission rate (depending on the method of application) (DPR, 2002a). For example, the maximum concentration along the buffer zone perimeter was 143 ppb for 1 acre fumigation and 80 lbs emission rate under 6449 (90% of 7166 input) different 24-hour meteorological data sets. At this same 90th percentile, the air concentrations were at or less than 210 ppb for other emission rates and acreage. At the 95th percentile, a level generally selected for risk characterization, the exposure ranges for each field sizes were: 161-174 ppb (1 acre), 163-215 ppb (10 acre), 201-225 ppb (20 acres), 213-230 ppb (30 acres), and 221-236 ppb (40 acres). It should be noted that the maximum concentration determined in these analyses occurred only on a portion of the buffer zone perimeter, and these analyses addressed only acute exposure.

V.D. RISK CHARACTERIZATION FOR AGGREGATE EXPOSURE

The total MOEs for potential acute and chronic aggregate exposures were based on NOELs for common toxicity endpoints observed in laboratory animals. When the NOEL for non-oncogenic effects is based on animal data, a MOE of 100 is generally considered adequate for protection against potential acute or chronic toxicity of a chemical. This benchmark of 100 includes an uncertainty factor of 10 for interspecies extrapolation and a factor of 10 for intraspecies variability. These uncertainty factors were the same as those determined for individual routes of exposure to methyl bromide. In the inhalation RCD (**Volume I**, DPR, 2002a), the potential for increased susceptibility by individuals with glutathione-S-transferase

(GST) polymorphism was discussed. However, it was not possible to conclude that GST polymorphism would lead to increased susceptibility to methyl bromide toxicity and to determine whether or not the variation was sufficiently addressed by the 10-fold default intra-individual uncertainty factor.

For aggregate exposure, the magnitude of the total MOEs should be viewed with respect to the toxicity endpoints used to characterize the risk. As discussed in earlier sections (**IV.A. HAZARD IDENTIFICATION FOR AGGREGATE EXPOSURE**), the toxicity endpoints were not the most sensitive endpoints when compared to those used to characterize inhalation exposure alone. However, they were the common endpoints reported for both routes of exposure. Developmental toxicity and nasal cavity lesions were observed only after inhalation exposures. Therefore, when a total MOE (Tables 11 and 12) is higher than that for inhalation exposure alone (in DPR, 2002a), it should not be interpreted to mean that a lower risk associated with the aggregate exposure. Also, the risk characterization was limited to common effects and assumed the total risks from these endpoints were additive. Synergistic or antagonistic relationships may be possible but can not be determined at this time. Due to lack of methodology and data, the potential interaction between other effects and the overall burden of multiple effects to the body from multiple routes of exposure to methyl bromide were not evaluated.

While acknowledging that the nasal cavity lesion was an inhalation route-specific effect, OEHHA proposed the use of developmental toxicity as a common endpoint to address acute exposure (Appendix C). The proposal was based on the assumption that, in the absence of conclusive evidence, the mechanism of action for developmental toxicity was the same for both inhalation and oral exposures. OEHHA supported the assumption with the results from the oral developmental toxicity studies (Kaneda *et al.*, 1998) in which the data were interpreted to show limited evidence of adverse developmental effects. OEHHA was also concerned that the doses tested were at or lower than those used for the inhalation developmental toxicity studies.

DPR considered the OEHHA proposal to have limited application. The developmental toxicity endpoint could only be applicable for women of childbearing age. In comparison, the neurotoxicity endpoint used in this RCD was applicable for all population subgroups. Furthermore, there were more uncertainties associated with the use of developmental toxicity than for neurotoxicity as the critical endpoint. Clinical signs associated with neurotoxicity had been reported for oral and inhalation routes whereas developmental toxicity had not been observed with the oral route. DPR disagreed with OEHHA's position that developmental toxicity was demonstrated in the oral developmental toxicity studies. DPR considered the effects reported not treatment related; they were not statistically significant from the concurrent control group and they were not dose-related. The rabbits in the oral study might or might not have been adequately dosed since comparison of absorbed doses only provided a limited estimation of the target tissue doses. Pharmacokinetic studies with methyl bromide showed differences in the disposition of methyl bromide when given by inhalation compared to gavage route of administration. These differences were expected especially since inhalation exposure involved continuous exposure at the same dose for several hours compared to a single one-time bolus dosing with gavage administration. Furthermore, the oral dose could not be much higher than 10 mg/kg/day, the highest dose tested in the rabbit study, since 30 mg/kg/day caused severe erosion of the stomach lining of pregnant rats (Kaneda *et al.*, 1998).

V.E. ISSUES RELATED TO THE FOOD QUALITY PROTECTION ACT

The toxicological database for individual routes of exposure to methyl bromide did not provide any data to determine the potential increased sensitivity of infants and children to methyl bromide toxicity after aggregate exposure. For inhalation alone exposure to methyl bromide, there was some evidence for increased sensitivity to the prenatal and post-natal toxicity of methyl bromide when NOELs for developmental or reproductive toxicity were compared with those for maternal toxicity (see **Volume I** section **V.E.**). The National Research Council scientists did not recommend an additional uncertainty factor for the inhalation exposure since the critical NOELs were considered conservative (NRC, 2000).

For oral exposure, the current database did not suggest increased sensitivity to methyl bromide by infants and children. A NOEL could not be established in the oral reproductive toxicity study (Kaneda *et al.*, 1993) where rats were given methyl bromide fumigated feed and the actual dose was not determined. No developmental toxicity was observed in rabbits (gestation day 6-18) and rats (gestation day 6-15) given methyl bromide by gavage (Kaneda *et al.*, 1998). The highest doses tested were 30 mg/kg/day in the rat and 10 mg/kg/day in the rabbit. In comparison, these doses were similar to the equivalent dose for the NOEL (40 ppm or absorbed dose of 10.5 mg/kg/day) for developmental toxicity in the rabbit by inhalation (Breslin *et al.*, 1990).

VI. CONCLUSIONS FOR AGGREGATE EXPOSURE

The human health risk from potential aggregate exposure was evaluated in this **Volume III** of the Methyl Bromide Risk Characterization Document. The assumption was that workers and residents may be exposed to methyl bromide by both the oral (via the diet) and inhalation (via the air) routes under acute and chronic durations. Due to the paucity of inhalation exposure data, only a limited number of scenarios were assessed. The potential risks were evaluated based on clinical signs and reduced body weight observed in experimental animals for acute and chronic exposures, respectively. The risks, expressed as total margins of exposure, were calculated for inhalation and oral exposures. For non-oncogenic effects based on animal data, the total MOEs were compared with a benchmark of 100 to determine whether the exposure would be of a potential health concern.

For field fumigation, the total acute MOEs were greater than 100 for all workers except those for some tarp removers (tractor drivers and basket-men) with MOEs of 42 and 44. The low MOEs were attributed to the relatively high inhalation exposure (1003-1058 ppb). The mitigation of inhalation exposure of these workers should lead to an increase in the total MOEs. For commodity fumigation, the total acute MOEs were at 191 since the exposure was set at 210 ppb by regulation. The total chronic MOEs were greater than 100 and ranged from 375-15152 for all workers. For residential aggregate exposure, the acute total MOEs ranged from 453 to 967. The chronic total MOEs were greater than 1000.

The total MOEs in this document should be viewed in light of the uncertainties and the limitations used in the hazard identification and exposure assessment of methyl bromide by the inhalation and oral routes, as individual routes and in combination. Additional data are needed to better define common toxicological endpoints and to characterize the aggregate exposures. In addition, the magnitude of the total MOEs should consider the methodology used to calculate these values. For certain scenarios, higher total MOEs from aggregate exposure than the MOEs for inhalation exposure alone should not be interpreted as lower risk because different NOELs and endpoints were used. The NOELs used to calculate the total MOEs were higher than those NOELs for inhalation MOEs, which were based on more sensitive route-specific endpoints. The relative contribution of inhalation and dietary exposures to the aggregate exposure equation was also a factor in the magnitude of the total MOEs. Therefore, the risk management decision on methyl bromide use in California should consider the risks associated with exposures from individual and combined routes.

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VIII. ATTACHMENTS

ATTACHMENT A

**TECHNICAL SUMMARY OF RISK CHARACTERIZATION DOCUMENT FOR INHALATION
EXPOSURE
(DPR, 2002a)**

I. TECHNICAL SUMMARY

I.A. INTRODUCTION

In 1992, the Department of Pesticide Regulation (DPR) conducted a Preliminary Risk Assessment on methyl bromide to address acute inhalation exposures of residents reentering fumigated home. The risk assessment concluded that the reentry level of 5 ppm for residents posed a health hazard and an emergency regulation was promulgated to decrease the exposure. Subsequently, permit conditions were developed to reduce the acute exposure of workers and the residents living near fumigated fields and fumigation chambers. In 1999, a draft of the risk characterization for inhalation of methyl bromide was completed. This draft was reviewed by the National Research Council. This Volume I of the Risk Characterization Document is a revision of the 1999 draft.

I.A.1. Chemical Identification

Methyl bromide is a gaseous fumigant that kills insects, rodents, nematodes, weeds, and organisms that cause plant diseases. Since methyl bromide is released into the air during and after its use, there is a potential for exposure by the workers as well the general population living near the use sites. Methyl bromide is a restricted use pesticide for structural, soil, and commodity fumigations. In 2001, 54 products containing methyl bromide were registered in California. From 1996-1999, 11-16 million pounds were used each year in California.

The primary route of human exposure to methyl bromide is inhalation. Exposure may occur from accidental spills, drift, leakage, or residual levels of methyl bromide released after treatment. Signs and symptoms of inhalation exposure depend on the concentration and exposure duration. Early symptoms of acute exposure to lethal concentrations include: malaise, headache, visual disturbances, nausea, and vomiting. Later symptoms include delirium, convulsions, and respiratory failure or cardiovascular collapse leading to death. Nonlethal exposures result in neurological effects similar to the early symptoms for fatal exposure. These symptoms may persist after exposure, depending on the severity of the effects. Exposure of skin to methyl bromide results in vesication and swelling of the skin. The general population may also be exposed to methyl bromide-treated foods.

Since methyl bromide is acutely toxic, chloropicrin has been added to some methyl bromide formulations as a warning agent. However, there may not be a correlation between methyl bromide concentration in the air and the extent of the irritation induced by chloropicrin due to the differences in physical and chemical properties between these compounds. Also, chloropicrin itself is acutely toxic. With its increased use as a replacement for methyl bromide, there are increased concerns regarding the health effects from chloropicrin exposure.

I.A.2. Regulatory History

The Federal agencies have established regulatory levels for the uses of methyl bromide. For food uses, the U.S. Environmental Protection Agency (U.S. EPA) established tolerances based on inorganic bromide with the assumption that methyl bromide is completely degraded. The U.S. EPA oral chronic reference dose (RfD) is 0.0014 mg/kg/day. In the drinking water, the one-day, ten-day, and longer-term health advisories are 0.1 mg/L for children. The longer-term

health advisory is 0.5 mg/L for an adult. The lifetime health advisory is 0.01 mg/L.

For methyl bromide in the air, the U.S. EPA inhalation reference concentration (RfC) is 5×10^{-3} mg/m³. The Agency for Toxic Substances and Diseases Registry minimum risk levels (MRLs) are 50 ppb, 50 ppb, and 5 ppb for acute, intermediate, and chronic exposure scenarios, respectively. For occupational exposure, the federal Occupation Safety and Health Administration permissible exposure limit (PEL) is 20 ppm while California established a lower limit of 5 ppm and a ceiling of 20 ppm. The reentry level is 1 ppm for structural fumigation within the wall voids. Methyl bromide is a Class I ozone depleter and its use is regulated by the U.S. Clean Air Act and the United Nations Montreal Protocol.

In California, the use of methyl bromide is continually being evaluated as regulations/permit conditions are modified to limit exposures. Additional ambient methyl bromide exposure data are being developed in 2001-2002 to determine seasonal (subchronic) exposures. The need for the permit conditions was initially based on the Preliminary Risk Assessment conducted in 1992 to address potential health hazard associated with acute exposures after structural fumigation (Attachment A). In 1993, methyl bromide, as a structural fumigant, was administratively listed as a developmental toxicant by the Office of Environmental Health Hazard Assessment of the California Environmental Protection Agency under Proposition 65 via the provision for listing due to the federal label warning requirement. However, the Proposition 65 Developmental and Reproductive Toxicity Identification Committee decided not to expand the listing to all uses of methyl bromide because results from laboratory animals did not clearly show that methyl bromide was a developmental toxicant.

I.A.3. Environmental Fate

Methyl bromide is degraded in the environment. The rate of hydrolysis was enhanced by elevated temperature, ultraviolet irradiation, aerobic conditions, and high organic matter in the soil. Once applied to the soil, methyl bromide volatilized into the air or adsorbed onto soil particles. Because of degradation, methyl bromide residues were not detected in the groundwater or commodities grown on fumigated soil. Residues were found in treated commodities after post-harvest fumigation.

I.B. TOXICOLOGY PROFILE

I.B.1. Pharmacokinetics

Pharmacokinetic studies showed that after inhalation, intraperitoneal, and oral administrations, methyl bromide was rapidly absorbed and radioactivity (¹⁴C) was distributed to all tissues examined. With inhalation exposure, the percentages of the administered doses absorbed were similar in several species; they were 48% in the rat, 40% in the dog, and 52 to 55% in human. In the rat, the highest levels in the tissues, principally in the lungs, were reached immediately after exposure. With oral and intraperitoneal administration to rats, more than 90% of the dose was absorbed, with the highest radioactivity levels measured in the liver, kidneys, and testes. Methyl bromide was extensively biotransformed into unidentified products and carbon dioxide. In the rat, within 1 hour after inhalation exposure, less than 10% of the radioactivity in the tissues was intact methyl bromide. In humans, both methyl bromide and inorganic bromide were detected in the tissues 5 hours after a lethal dose exposure. The

primary routes of excretion were the exhaled air for inhalation and intraperitoneal exposures, and the urine for oral exposure. Carbon dioxide accounted for almost 50% (inhalation and intraperitoneal routes), and 30% (oral route) of the radioactivity in the exhaled air. After oral administration, biliary metabolites of methyl bromide were reabsorbed from the gut.

I.B.2. Acute Toxicity

Methyl bromide is a Toxicity Category I compound because of its acute inhalation toxicity. Severe irritation to eyes, skin, and mucous membranes occur after acute exposure; therefore, acute oral, ocular and dermal studies are not required for registration. Neurotoxicity has been observed in humans and laboratory animals after inhalation exposure to methyl bromide. The severity of the effects depended on the dose and duration of exposure. In humans exposed to high concentrations, neurological effects included ataxia, convulsion, and tremors. The nonlethal effects observed in laboratory animals included changes in brain catecholamines and tyrosine hydroxylase activity, tissue degeneration (nasal, brain, and adrenal glands), and neurotoxicity (ataxia and paralysis). Signs of oral toxicity in the dog included prostration, increased heart rates, lesions in multiple organs including the stomach and brain, hypoactivity, hypothermia, and death. Human dermal exposure resulted in skin lesions.

I.B.3. Subchronic Toxicity

Subchronic inhalation exposure of laboratory animals to methyl bromide resulted in altered brain catecholamine levels, decreased brain tyrosine hydroxylase activity, neurotoxicity, tissue degeneration (brain, nasal cavity, heart, testes, adrenal glands, thymus, spleen, and kidneys), and death. Based on overt signs of neurotoxicity, the dog, rabbit, and monkey were more sensitive to methyl bromide than other species (rat, mouse, and guinea pig). The primary finding after repeated oral exposure by gavage in the rat was hyperplasia of the forestomach. A decrease in body weight gain and food consumption was observed in rats given micro-encapsulated methyl bromide mixed in the feed.

I.B.4. Chronic Toxicity

The nasal cavity, brain, and heart were major target organs in rodents after chronic inhalation exposure to methyl bromide. Olfactory epithelial damage (hyperplasia, metaplasia, and necrosis) and myocardial degeneration were observed in rats and mice. Cerebellar and cerebral degenerations were detected in mice while reduced brain weight was observed in rats. When rats were exposed to methyl bromide in microcapsules mixed in the feed, the primary effect was body weight reduction. Possible treatment-related lesions were found in the spleen, liver, pancreas, and lungs. In male dogs given methyl bromide-fumigated feed, decreased hematocrit and hemoglobin levels were observed.

I.B.5. Genotoxicity

Methyl bromide was genotoxic in several *in vitro* and *in vivo* assays. It was a base-pair substitution mutagen in the *Salmonella* assays. It was a direct-acting mutagen since a liver S-9 fraction was not required for mutagenicity. It caused micronuclei formation in female mice and an increased frequency of sister chromatid exchanges in CHO cells and in mouse bone marrow cells *in vivo*. It did not induce unscheduled DNA synthesis in rat hepatocytes or cause

sperm abnormalities in mice. DNA alkylation was detected in both rats and mice after *in vivo* exposure by oral, intraperitoneal, or inhalation routes while DNA damage was found in the germ cells of rats after inhalation exposure. There was some evidence of genotoxicity in workers exposed to methyl bromide. Elevated levels of sister chromatid exchanges in lymphocytes and S-methylcysteine adducts in the blood were measured in soil fumigators. An increased frequency of hypoxanthine-guanine phosphoribosyl transferase gene (*hprt*) mutations in the lymphocytes and an increased incidence of micronuclei in oropharyngeal cells were observed in structural fumigators.

I.B.6. Reproductive Toxicity

In a 2-generation reproductive toxicity study in rats by inhalation, methyl bromide reduced the fertility rate of the F₁ parents during the second mating trial. While the body weights of the treated pups at birth showed varied responses, their body weights were significantly lowered during lactation. Brain weight and cerebral cortex width were reduced in the F₁ parents.

I.B.7. Developmental Toxicity

Methyl bromide caused developmental effects in both rats and rabbits after inhalation exposure. The findings in the fetuses included delayed skull ossification in rats and fused sternbrae, gall bladder agenesis, and other effects in rabbits. Methyl bromide did not cause any significant developmental effects in rats and rabbits after oral exposure.

I.C. RISK ASSESSMENT FOR INHALATION EXPOSURE

I.C.1. Hazard Identification for Inhalation Exposure

The evaluation of risks from exposure to methyl bromide followed the four steps of risk assessment: hazard identification, dose-response assessment, exposure evaluation, and risk characterization. In the hazard identification and dose-response assessment, a comprehensive review of the toxicology database from studies submitted by the registrant and published articles was conducted. From this review, the toxicity and the estimates of how much methyl bromide that could potentially cause an adverse effect as well as no-effect levels are identified for each study. Since human case reports did not provide sufficient details to derive the critical no-observed-effect levels (NOELs), results from experimental animal studies were used assuming that the effects observed in the animals would also be observed in humans. The NOELs were expressed as human equivalents (adult or child) to correct for the difference in respiration rates between humans and experimental animals. The studies with most relevant findings for risk assessment were then selected and the associated NOELs were expressed as critical NOELs to be used in the calculation of the margin of exposure (MOE) in the risk characterization step of the process. For methyl bromide, critical NOELs were determined for acute (one-time exposure), short-term (1-2 weeks), subchronic (7-13 weeks, seasonal), and chronic (a year or more) exposures. The National Research Council scientists (NRC) in their review of the draft RCD/1999 agreed with DPR selection of critical endpoints and NOELs for risk characterization.

For acute exposure, neurotoxicity is the primary effect of concern and has been observed in both experimental animals and humans. The clinical signs observed include: decreased activity, ataxia, paralysis, convulsion, and tremors. Of the laboratory animals studied, there was a species sensitivity to the neurotoxicity of methyl bromide after short-term exposure. Based on the comparisons of the lowest-observed-effect level (LOEL) for neurotoxicity, the dog and rabbit

showed greater sensitivity than the guinea pig, mouse and rat. For example, dogs exposed to 156 ppm (human equivalent level of 68 ppm) showed severe neurological effects in 2 to 7 days of exposure while rats exposed to the same concentration in terms of human equivalent level (65 ppm; 70 ppm actual air concentration) for the same exposure duration did not show any neurotoxicity. In pregnant animals, the rabbit was more sensitive to methyl bromide than the rat. For pregnant rabbits, severe neurotoxicity was observed at the LOEL of 70 ppm (Sikov *et al.*, 1981; Breslin *et al.*, 1990) while no neurotoxicity was reported in the pregnant rats at the same level (Sikov *et al.*, 1981).

The selection of results from the most sensitive species, in this case the dog, is consistent with the U.S. EPA Neurotoxicity Risk Assessment guidelines (U.S. EPA, 1998a). The critical NOEL was 103 ppm from short-term inhalation studies in the dog (Newton, 1994a and b). At this dose of 103 ppm, no effects were observed until the 8th day of exposure. Although the dog inhalation toxicity studies were not designed to be a neurotoxicity study as defined by the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) guideline, they were conducted under Good Laboratory Practices and DPR considered the results valid for hazard identification. These same data were used by the Methyl Bromide Industry Panel (MBIP) to support their position that a chronic inhalation toxicity study in the dog should not be required (CMA, 1994).

The selection of the 103 ppm dose as the acute NOEL considered three major factors: subjectiveness of the observations, severity of the neurotoxicity at higher concentrations, and possibility of delayed neurotoxicity. The finding of no effect at 103 ppm in the dogs was based on gross observations. Neurotoxicity may have been present but not detected unless more refined methods such as the Functional Observation Battery were used. Therefore it is possible that the actual NOEL may be lower than 103 ppm. Furthermore, severe neurotoxicity was observed at higher doses (1.5 times the NOEL) with a few additional days of exposure. At 156 ppm, one of two dogs showed lacrimation (tearing) on the first day. This finding by itself may arguably be considered less significant with respect to adversity. However, there were only two dogs in this group. With 2-3 days of additional exposure, there was significant toxicity as both dogs showed difficulty breathing and decreased activity. In another study, all dogs (8 in the group) exposed to 158 ppm showed decreased activity before the end of the second exposure day. With 5 additional days of exposure, all showed severe neurotoxicity and brain lesions. The selection of 103 ppm as the acute NOEL also addresses, indirectly, the possibility of delayed neurotoxicity which has been reported in humans after accidental poisonings. Since no effects were observed in the dogs at 103 ppm for 7 days of continuous exposure, it is unlikely that there would be delayed neurotoxicity within one week after a single exposure to the same level. The human equivalent NOEL (25 ppm) from the dog study was two-fold or less than those for the acute effects observed in the rats and guinea pigs.

Another endpoint DPR considered for acute exposure risk assessment is the developmental toxicity observed in experimental animals after methyl bromide exposure. In a developmental toxicity study, the pregnant animals were exposed continuously to methyl bromide during a specified period of gestation (when organ formation occurs). Any adverse effect observed in the fetus is considered an acute effect under the current assumption that only a single exposure at a critical time is necessary for the induction of developmental adverse effects according to the U.S. Environmental Protection Agency Guidelines for Developmental Toxicity Risk Assessment. Since this endpoint is the result of exposure during pregnancy, it is only used for the assessment of exposure by women of childbearing age in the work force and the general population.

The critical NOEL for developmental toxicity was 40 ppm from a study with rabbits

(Breslin *et al.*, 1990). The result from this study was the basis for the emergency regulation and permit conditions currently used in California. U.S. EPA also considered these endpoints of concern and has used the same study in a Section 18 evaluation on the use of methyl bromide on imported fruits at ports of entry. In this rabbit developmental toxicity study, fetuses exposed to 80 ppm *in utero* showed gall bladder agenesis (no gall bladders), fused sternbrae (early fusion of the sternbrae), and lowered body weights. The missing gallbladder finding was seen in Part I of the experiment, which by itself is a complete study and fulfilled FIFRA guidelines for an acceptable study. The investigator was concerned with the finding as it was rarely observed in the negative-control litters in the conducting laboratory as well as in other laboratories using the same rabbit strain. When the experiment (Part II) was repeated three months later, missing gall bladders were again observed in fetuses exposed to methyl bromide *in utero*. The fused sternbrae found in Part I was not confirmed since a skeletal examination was not performed in Part II.

The developmental toxicity effects observed in fetuses should not be discounted because of maternal toxicity (body weight changes and neurotoxicity) reported at the same dose level. Consideration must be given to when the effects were observed. First, the decrease in the body weight gain of the 80 ppm group does was not a consistent finding. Statistically significant decreases were reported for gestation days 13-16 in Part I and gestation days 7-20 and 10-13 periods in Part II. The reduced weight gain in the does of Part II occurred concomitantly with a reduction in the mean fetal body weight. Second, there was no significant difference in the strictly maternal parameter calculated as the terminal body weight minus gravid uterine weight. Third, body weight changes in pregnant rabbits are known to be more variable than in rodents. As a result, body weight changes often do not carry as much support as an indicator for maternal toxicity as for rodents as discussed in the U.S. EPA Developmental Toxicity Risk Assessment guidelines. Fourth, maternal neurotoxicity was characterized by clinical signs, including: lethargy, head tilt, slight ataxia and slight lateral recumbency. These signs were observed in only 3 of 43 does (7%) dosed at 80 ppm, and they did not appear until gestation days 19-20 (the last days of the 13-day exposure period). Based on the description and comparison with observations reported in other studies, DPR does not consider these signs as indicators of excessive toxicity.

Furthermore, the failure of gall bladders to form in some fetuses was independent of maternal neurotoxicity. In Part I, 6 of the fetuses with missing gallbladders were from 3 does without neurotoxicity while the remaining 7 affected fetuses were from 2 does with neurotoxicity. In Part II, none of the does showed neurotoxicity while 4 fetuses (from 4 does) had missing gallbladders. In addition, the development of the gall bladder in rabbits can be considered an acute event since it takes place in one to two days after its onset on gestation day 11.5 (Hoar and Monie, 1981). The maternal neurotoxicity reported on gestation days 19-20 would have occurred too late to have been a factor in the agenesis of the gall bladder.

Similar findings have not been reported in the rat developmental toxicity studies. While it is worth noting that rats do not have gall bladders, the absence of these findings in another species should not negate their significance as indicators of the potential for methyl bromide to cause developmental toxicity in humans. Species specificity in developmental effects has been demonstrated for some chemicals. Developmental toxicity testing under FIFRA guidelines requires two species to be tested, a rodent and a non-rodent species, typically the rabbit, for identifying species susceptibility. The need to test non-rodent species arose from the findings of thalidomide where it was demonstrated that this human teratogen did not exhibit significant

teratological effects in rats but caused at least some significant effects in rabbits (Schardein, 1985). As stated in the U.S. EPA Developmental Toxicity Risk Assessment guidelines, developmental effects may not be evident in more than one species. The findings from the most sensitive species are appropriate to use to estimate human risk.

The significance of the developmental toxicity findings was discussed in a 1994 Proposition 65 meeting to determine whether methyl bromide should be listed for all uses. The emergency regulation in 1992 resulted in methyl bromide being listed as a chemical known to the State of California to be a reproductive toxicant. The Developmental and Reproductive Toxicity Identification (DART) Committee was presented with results from animal developmental toxicity (absence of gall bladders and fused sternbrae) and reproductive toxicity (decreased pup body weight) studies. After much discussion, the Committee voted not to expand the listing of methyl bromide from structural fumigation to all uses because there was not enough evidence to support the Aclearly shown@ criteria as mandated by the Proposition. However, the members expressed several concerns: the need for more experimental studies to clarify the findings, potential for exposure to methyl bromide via the milk during lactation, and the lack of information on human exposure especially during pregnancy.

After this meeting, DPR received additional data to support the consideration of reproductive or developmental toxicity as a pertinent endpoint for risk assessment and regulatory actions. First, supplemental data on the rat reproductive toxicity study showed that methyl bromide caused a reduction in the width of a certain part of the brain (cerebral cortex) in the F₁ adults exposed to methyl bromide *in utero* (American Biogenics Corp., 1986). Second, a study received by DPR in 1998 showed that methyl bromide caused a breakage of DNA in the testicular cells isolated from rats after inhalation exposure (Bentley, 1994). It is not known whether the effect was due to methyl bromide or a metabolite.

DPR also considered studies which showed that methyl bromide caused biochemical changes in the brain which may be associated with neurotoxicity. In the rat, acute exposure to methyl bromide has been shown to alter catecholamine (chemicals involved in the transmission of brain signals) levels and tyrosine hydroxylase (an enzyme involved catecholamine formation) activity in the brain. However, an extensive review of the published articles on this subject by DPR showed inconsistencies in the findings; thus, they were considered not appropriate for use in the determination of regulatory levels. The results of one of these study were used by the Agency for Toxic Substances and Diseases Registry of the Public Health Service to derive a minimum risk level as a screening tool for regulatory agencies to determine the need for regulation. As such, the study review did not critically analyze the results. This minimum risk level has not been adopted as an action level by any regulatory agency.

Therefore, two acute NOELs were selected to address the different human sub-populations. The NOEL of 40 ppm for developmental toxicity in the rabbit was most appropriate for workers and residents since women of child bearing age are in both groups. For children, the NOEL was 103 ppm for neurotoxicity in the dog. When these NOELs are converted to human equivalent NOELs taking into consideration of duration of exposure and the differences in the respiration rates between species, and between adults and children, the human equivalents were 21 ppm and 25 ppm, respectively, for developmental toxicity and neurotoxicity. The use of the lower human equivalent NOEL of 21 ppm compared to 25 ppm to address occupational and residential exposures would protect children from the effects of methyl bromide.

For short-term and subchronic exposures, neurotoxicity was also selected as the endpoint for the determination of the critical NOELs and was based on the same considerations as discussed for acute exposure. For short-term (1week) exposure, a NOEL was established to address the potential exposure of residents returning to fumigated homes, living near fumigated fields, and workers. The critical NOEL was 20 ppm based on neurotoxicity (convulsion, paresis) in the rabbit after exposure to 70 ppm for 1 week (Sikov *et al.*, 1981). Three of 26 does died after 9 to 10 days of exposure.

For subchronic exposures of longer duration (90 days, seasonal), the critical NOEL was an estimated NOEL (ENEL) of 0.5 ppm based on a lowest-observed-adverse-effect level (LOAEL) of 5 ppm for decreased responsiveness in two of eight dogs during a neurological examination after 6 weeks of exposure (30 exposure days) and a default factor of 10 for the calculation of a NOEL from a LOAEL (Newton, 1994b). While the duration is shorter than the 13-week generally considered for subchronic exposure, it was chosen because of the endpoint (neurotoxicity) and species sensitivity (the dog is a more sensitive species than the rat to methyl bromide) considerations. It is possible that the NOEL may be lower if the dogs were exposed to methyl bromide for 13 weeks.

This ENEL was lower than the NOEL (3 ppm) for lowered body weights of rat pups from dams exposed to methyl bromide before mating and during part of the pregnancy in the reproductive toxicity study (American Biogenics Corp., 1986). Another study also showed a NOEL (estimated) of 3 ppm based on a dose-related decrease in brain weight at 30 ppm and higher concentrations in the female rats (Norris *et al.*, 1993 a and b). The brain weight was also significantly decreased in the 140 ppm male rats. This effect on the brain weight was considered biologically significant since the brain is a target organ of methyl bromide. The absence of neurotoxicity by Functional Observational Battery testing at the same dose (30 ppm) does not diminish the importance of the brain weight finding since the causes of the two effects are not necessarily related.

For chronic inhalation exposure, all chronic studies conducted with rodents (rats and mice), reproductive toxicity study, and subchronic dog inhalation toxicity study were considered in the determination of the chronic critical NOEL. After chronic inhalation exposure, tissue damage was noted in the nasal cavity, brain, and heart of rodents. The critical NOEL was an ENEL of 0.3 ppm based on a LOAEL of 3 ppm for the induction of an increase in the number of cells (hyperplasia) and change in cell type and function (degeneration) in the nasal cavity of rats after 24-29 months of exposure and a default factor of 10 for the calculation of a NOEL from a LOAEL (Reuzel *et al.*, 1987 and 1991). While the exposure duration was considered a life-time for the rodents, the actual duration in the standard chronic toxicity studies is two years. Since humans may be exposed to methyl bromide on a yearly basis, not just one or two years in the lifetime, the NOEL from the chronic toxicity study after two years of exposure was, therefore, appropriate for use. This NOEL may underestimate the risk of repeated yearly exposure as there is evidence of cumulative toxicity, in particular, neurotoxicity. The LOEL (3 ppm) from this 29-month study for nasal olfactory epithelial damage (Reuzel *et al.*, 1987 and 1991) is further supported by the LOEL of 4 ppm from a 24-month study for lesions at the same site (Gotoh *et al.*, 1994). The U.S. EPA also used the same LOAEL from this study in the determination of the chronic reference dose (RfC).

The significance of the finding in the nasal cavity is that it showed methyl bromide not only injured the cells but also changed the normal function of the cells in the nasal cavity. Such

damage may result in the loss of the animal's sense of smell. Tissue damage in other organs occurred at higher concentrations. With acute exposure to 200 ppm, the damage to the rat olfactory epithelium included epithelial disruption, fragmentation, and exfoliation (Hurtt *et al.*, 1988). Repair of the epithelium included replacement by a squamous epithelium, loss of sensory cells, and respiratory metaplasia (conversion of the olfactory epithelium to a ciliated respiratory type). In other short-term studies, the damage to the nasal epithelium was described as necrosis and degeneration (Eustis *et al.*, 1988) and dysplasia (NTP, 1992; Eustis, 1992). In the chronic inhalation toxicity study, nasal olfactory epithelial hyperplasia and degeneration were observed in the rat (Reuzel *et al.*, 1987 and 1991).

While the effect on the nasal cavity may generally be considered a finding confined to the rat due to anatomical considerations, it is not the case with methyl bromide. Dogs exposed to 156 ppm methyl bromide for only 6 days showed moderate to moderately severe olfactory degeneration (Newton, 1994b). In addition, the rodent studies are the only available studies to evaluate the chronic toxicity. The requirement for a non-rodent (dog) study was waived by DPR based on the evaluation of short-term studies in the dog which showed that a chronic study would have to be conducted at relatively low dose levels. For comparison, the ENEL of 0.3 ppm for nasal cavity effects when expressed as human equivalent level (0.1 ppm) was the same as the human equivalent level for neurotoxicity after subchronic exposure (ENEL of 0.5 ppm). This implied that the actual NOEL for chronic exposure if based on neurotoxicity could be lower than that based on the effects in the nasal cavity. However, it is not possible to extrapolate such a NOEL at this time because the subchronic NOEL was already an estimated NOEL based on a LOEL which was reduced by a 10-fold uncertainty factor.

The oncogenicity of methyl bromide can not be evaluated at this time because experimental studies showed neither dose-related increased incidence of tumors after treatment nor sufficient data to determine the incidences. There is evidence that methyl bromide causes damage to the genetic material in experimental animals and humans, which is generally considered to play a significant role in the process of tumor formation.

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A summary of the critical NOELs for inhalation exposure risk characterization is presented below:

Scenarios	Experimental NOEL	Human Equivalent NOEL ^a		Reference Concentration ^d	Effects in Animal Studies	Ref ^e
		Adult ^b	Child ^c			
Acute	40 ppm	21 ppm	na	210 ppb	Developmental toxicity (pregnant rabbit)	1*
	103 ppm ^f	45 ppm	25 ppm		Neurotoxicity (dog)	2
Subchronic 1 week	20 ppm	12 ppm	7 ppm	120 ppb(adult) 70 ppb (child)	Neurotoxicity (pregnant rabbit)	3
6 weeks	0.5 ppm (ENEL)	0.2 ppm	0.1 ppm	2 ppb (adult) 1 ppb (child)	Neurotoxicity (dog)	2
Chronic	0.3 ppm (ENEL)	0.2 ppm	0.1 ppm	2 ppb (adult) 1 ppb (child)	Nasal epithelial hyperplasia(rat)	4*

a/ Experimental NOELs were converted to human equivalents using equations in Attachment G. na= child equivalent NOEL were not calculated because the effects were observed in pregnant animals. ENEL=estimated NOEL and is 1/10 of the LOEL in the study.

b/ The adult equivalent NOELs are appropriate to address worker exposures. They are also used for residential exposures when child equivalent NOELs were not calculated.

c/ The child equivalent NOELs are appropriate to address resident exposures (see footnote b).

d/ The reference concentration was the ratio of the human equivalent NOEL and a default uncertainty factor of 100 since the NOEL was derived from experimental animal studies.

e/ * indicates study was acceptable to DPR according to FIFRA guidelines. References: 1. Breslin *et al.*, 1990b; 2. Newton, 1994b; 3. Sikov *et al.*, 1981; 4. Reuzel *et al.*, 1987 and 1991.

f/ The NOEL and human equivalents are presented in this Table for comparison purposes only. They are not used for risk characterization.

I.C.2. Exposure Assessment for Workers and Residents

Human exposure assessment was conducted for occupational and residential inhalation exposures to methyl bromide. Compared to the draft RCD/1999, this exposure assessment was revised to incorporate NRC recommendations and changes after re-evaluation of the database, methodology, and DPR regulations.

Occupational Exposure

The inhalation exposures of applicators in structural fumigation were not determined because they are required to wear self-contained breathing apparatus. No data were available for other workers such as tarp removers.

For field fumigation, monitoring studies were conducted primarily to determine the effectiveness of modifications to existing application procedures and aeration of treated fields.

With shallow-shank and tarp fumigation, workers involved in the application with no modifications had higher exposures than those in other methods. The acute exposures of applicator, copilot, and shovel-man ranged from 188 ppb to 245 ppb. The best method involved both swept-back shank and closing shoes where the applicators, copilots, and shovel-men exposures were 1 ppb to 58 ppb. The driver (7 ppb) and copilot (62 ppb) of the tractor in the placement of tarp had lower acute exposures than those involved in the application. For tarp cutting and removal, one study showed acute exposures of 202 ppb and 215 ppb while another study showed workers with higher acute exposures (22 to 1058 ppb). With deep-shank injection, the applicators with only overhead fan had the highest acute exposure at 281 ppb. Lower acute exposures were measured for applicators in tractors with modifications such as overhead fan and scrapers and rollers (104 ppb), enclosed cab (161 ppb and 171 ppb), and enclosed cab with scrapers (13 ppb). When a second tractor with a disc or cultipacker was involved, the drivers had relatively lower exposure (13-181 ppb) than those for applicators, except for the disc driver (934 ppb). For both short-term and subchronic exposures in shallow-shank and deep-shank methods, the exposure patterns were similar to those for acute exposures which were the basis for the calculations. Chronic exposure was not expected for any of the work scenarios. For workers at adjacent fields, there were no data and their exposures were assumed to be at 210 ppb.

For workers with potting soil in greenhouses, the maximum acute exposure was 210 ppb. Their actual exposures were relatively low because tarp venters are required to wear self-containing breathing apparatus, and tarp removal occurs after 48 hours of venting. The short term exposures, based on measured values, were 0.001 ppb and 0.14 ppb for these two group of workers. No subchronic or chronic exposures were determined for this activity. No data were available for other workers, e.g., applicators, associated with this use.

For commodity fumigation workers, the acute exposure was 210 ppb and the exposures for other durations based on the average of measured values. For workers involved in the fumigation of grain products, the range of short-term exposures was 0.02 ppb to 11 ppb. The forklift drivers of sea containers/trailers had higher subchronic and chronic exposures (8 ppb) than those (3 ppb) for non-certifying fumigation chambers. For workers involved in the fumigation of raisins, the range of short-term exposures was 3 ppb to 180 ppb. For workers in a walnut processing plant, workers in clearing plant (178 ppb) and vacuum chamber (180 ppb) had

the highest short-term exposure compared to other areas. The lowest average short-term level (25 ppb) was measured in the special cracking area. For both raisin and walnut workers, the short-term and subchronic exposure levels were similar. Chronic exposure was considered for raisin processing workers but was not expected for most walnut processing workers.

For workers in a brewery, exposures were estimated for applicators and aerators at various locations. The acute exposure was assumed to be at 210 ppb. The short-term exposure level ranges were 7-49 ppb for aerators and 8-12 ppb for applicators. No seasonal or chronic exposures were expected.

For workers in the facilities but whose tasks were not directly related to commodity fumigation, data were available only for raisin and walnut fumigations. The exposure levels were either based on the acute level of 210 ppb or measured by ambient and area sampling. The range of short-term exposures ranged from 7 ppb to 180 ppb. The subchronic and chronic exposures (except for walnut processing) were comparable to those for short-term levels because of the frequency of exposure.

Residential Exposures

The exposures of residents returning to homes after fumigation and aeration were not estimated due to lack of data on current practices. DPR regulations limit the maximum acute exposure at 210 ppb.

Residential exposures to field fumigation were determined using monitoring data and computer modeling of the data. Maximum methyl bromide air concentration was related to the size of the field and emission rate (depending on the method of application). At the 95th percentile, the exposure ranges for each field sizes were: 161-174 ppb (1 acre), 163-215 ppb (10 acre), 201-225 ppb (20 acres), 213-230 ppb (30 acres), and 221-236 ppb (40 acres).

The acute exposure for residents living near commodity fumigation facilities was limited to 210 ppb. The exposures for the longer-term durations were 90-180 ppb (short-term), 70-175 ppb (subchronic), and 86-106 ppb (chronic).

For residents living in methyl bromide use areas, which may include field, commodity, and structural fumigations, ambient air monitoring at the 95th percentile daily exposure levels ranged from 0.239 ppb (Mettler Fire Station) to 30.2 ppb (Pajaro Middle School in Watsonville). Levels at these two sites also provided the ranges for weekly (0.163 to 17.1 ppb), and 7-8 week (0.084 to 7.68 ppb) exposure durations. Additional monitoring has been conducted by the Air Resources Board and the registrant to characterize the exposures.

I.C.3. Risk Characterization for Inhalation Exposure

The NOEL at which adverse effects did not occur was used to assess the non-cancer hazard for potential human exposures to methyl bromide. The margin of exposure (MOE) was compared with a conventional benchmark level of 100. The MOEs varied from <1 to greater than 1000 for occupational and residential exposures.

Occupational Exposure

Margins of exposures were not calculated for workers involved in structural fumigation. The acute MOE for the applicators was assumed to be greater than 100 since these workers are required to be in a self-contained breathing apparatus.

With shallow-shank/tarp/broadcast fumigation, the acute MOEs were 112 (applicator), 86 (copilot), and 110 (shovel-man) for workers Noble plow and overhead fan. The MOEs were higher for the workers in shallow-shank/tarp/bed fumigation and various equipment modifications. The MOEs for these applicators were 144 to 5250 for swept-back shank and closing device. For copilots, the MOEs varied depending on the modification. The MOE was 69 when a conventional shank was used, even though scrapes/closing shoes were added. The MOEs were 111 when the copilot was in a raised platform and 362 when swept-back shank and closing device were used in the application. The MOEs for the driver and copilot in the second tractor for tarping were 3000 and 339, respectively. The MOEs for workers in tarp cutting and removal varied depending on the study even though similar procedures were used. In one study, the MOEs were 104 and 98; in the second study, the range of MOEs was 20 to 955. With deep-shank injection, the applicators with only overhead fan had the lowest MOE of 75. The range of MOEs was: 130 to 1614. The MOEs for driver in the second tractor with a cultipacker were also higher when scrapers were used after application. The MOE increased from 116 (no modifications) to 164-1615 (use of scrapers and/or rollers). The MOE was only 22 for the disc driver. For both shallow-shank and deep-shank methods, the MOEs for almost all short-term exposures were 100 while subchronic exposures were less than 100. Chronic exposure was not expected for any of the work scenarios. For workers at adjacent fields, the acute MOE could be assumed to be 100 with the exposure not to exceed 210 ppb.

The acute MOEs for all workers in commodity fumigation facilities were 100 because their upper exposure limit was 210 ppb. For tarp ventors and removers of potting soil fumigation in greenhouses, the MOEs for short-term exposures were greater than 80,000 because of their relatively low actual exposures. No data were available for other workers. In the fumigation of grain products, MOEs for these workers were greater than 100 for the aerators for all exposure periods. For forklift drivers, the short-term MOEs were > 1000 but the subchronic and chronic MOEs were less than 100 (MOEs of 25 and 67). For workers involved in the fumigation of raisins, the range of MOEs for short-term exposures was 67 to 4000. The MOE of 67 was based on the use of 210 ppb as the daily exposure value. The MOEs for subchronic and chronic exposures were less than 100, except for the forklift drivers with a MOE of 100. For workers in a walnut processing plant, the MOE was 67 for workers with the highest exposures (in clearing plant or vacuum chamber). This MOE was based on measured values (cleaning plant) and the 210 ppb limit (vacuum chamber). The highest MOE was 480 for workers at the special cracking area. The MOEs for subchronic and chronic exposures were less than 10. For workers in a brewery, the MOEs for applicators and aerators were ranged from 245 to 1714.

For workers in fumigation facilities, not directly related to fumigation, the short-term exposure MOEs were generally greater than 100 (MOE of 121 to 1714) for raisin facilities. The short-term MOE for walnut processing was 500 based on area sampling but was 67 based on 210 ppb as the daily exposure level in sorting and packaging areas. However, the subchronic and chronic exposure MOEs for both raisins and walnut processing facilities were less than 100 based on either measured values or 210 ppb.

Residential Exposure

For residents living in treated home after aeration, the acute MOEs were assumed to be at least 100 since regulations were based on the 210 ppb for acute exposure.

For residents living along the buffer zone perimeter of field fumigation, the MOEs for the 95th percentile methyl bromide air concentration were at least 100 (98 to 131) for 1 and 10 acres and all emission rates. For 20 and 30 acres, the MOEs were around 100 (96 to 104) with the exception of 91 and 93 for 80 lbs emission rate. For 40 acres, the MOEs were 89 to 95 for all emission rates. At the 90th percentile air concentration, all MOEs were at or greater than 100.

The acute MOE for residents living near commodity fumigation facilities was 100 because the exposure was assumed to be 210 ppb. However, the MOEs were 39-78, 1, and 1, respectively, for short-term, subchronic, and chronic exposures based on 210 ppb as the average daily exposure levels.

For residents living around methyl bromide uses, ambient air monitoring of 12 sites showed MOEs ranged from 695 to >80,000 for acute exposure, and from 409 to > 40,000 for short-term exposures. For 7-8 weeks of exposure, the MOEs for 7 of the sites were greater than 100 (range from 126 to 1190). The MOEs for the remaining sites ranged from 13 (Pajaro Middle School) to 78 (Salinas Ambient Monitoring Station).

I.D. RISK APPRAISAL FOR INHALATION EXPOSURE

Certain limitations and uncertainties were incorporated into the hazard identification, exposure assessment, and risk characterization of methyl bromide.

I.D.1. Hazard Identification

For acute inhalation exposure to methyl bromide, the critical NOEL was based on developmental effects observed in rabbits with the assumption that methyl bromide will also cause developmental toxicity in humans. There are no data to support or refute this assumption. The reference concentration (210 ppb) for this NOEL was only 1.5-fold lower than that for neurotoxicity in humans (350 ppb). The endpoints for the critical short-term and subchronic exposures were based on neurotoxicity in the pregnant rabbit and dogs, respectively. There were uncertainties associated with the use of hyperplasia/degeneration to the nasal cavity of rats as the endpoint to evaluate chronic inhalation toxicity. One uncertainty was the interspecies variability in the nasal cavity between rodents and humans. Additional information on the pharmacokinetics of methyl bromide in the nasal cavity epithelium of animals and humans would permit additional consideration of this endpoint.

In this RCD, both the subchronic and chronic NOELs were estimated from the LOEL, the lowest dose tested. The estimated subchronic NOEL was 0.5 ppm based on neurotoxicity observed in two of eight dogs exposed to 5 ppm for 34 exposures. Due to limitation in the database, a default factor of 10 was used for the extrapolation. For chronic exposures, the estimated NOEL was 0.3 ppm based on a LOEL of 3 ppm for nasal epithelial hyperplasia and degeneration in the rat and an uncertainty factor of 10. The mildness of the lesion at the LOEL suggested that an UF of less than 10 might be sufficient to estimate the NOEL from the LOEL.

I.D.2. Inhalation Exposure Assessment

The major limitation in the worker (all uses) and residential (commodity fumigation) exposure assessment was that data were not available for many scenarios as some acute exposures were assumed to be or limited to 210 ppb. The use of 210 ppb exposures might be over- or underestimation of actual acute exposures. Of the available data, there were many deficiencies in the overall database and they included: small sample size, incomplete report, and short monitoring period. Potential areas of underestimation were the assumptions of single work task per day and no overtime worked. One area of overestimation was the use of 50% recovery value to adjust all data.

For residential exposure to field fumigation, there were also uncertainties in the determination of the maximum methyl bromide air concentration distribution along buffer zone perimeter of fumigated fields. These uncertainties included: the precision and accuracy of the sampling and analytical methods, influence of environmental factors on air concentrations, application variability, use of default weather conditions, and use of default assumptions in estimating air concentrations associated with overlapping applications. Actual exposure may be underestimated or overestimated because of these uncertainties.

I.D.3. Risk Characterization

For risk characterization, the uncertainties included the use of uncertainty factors to address extrapolation of no-effects from experimental animals to humans (interspecies), and accounting for intraspecies variations. The sensitivity of humans and laboratory animals to methyl bromide toxicity was difficult to compare because of inadequate exposure information in human case reports. The current DPR default factor of 10-fold was used to address interspecies extrapolation. For intraspecies variation in the response to methyl bromide, the default uncertainty factor of 10 was also used because human illness/poisoning reports did not provide sufficient information to derive another factor. Studies on genetic polymorphism of glutathione-S-transferase (GST) in humans provided some evidence for variations in human response to methyl bromide. However, there were insufficient data to conclude that GSTT polymorphism leads to increased susceptibility to methyl bromide toxicity and to determine whether or not the variation is sufficiently addressed by the 10-fold default intra-individual uncertainty factor.

I.D.4. Issues related to the Food Quality Protection Act

There may be a potential for increased sensitivity of infants and children to the neurotoxicity of methyl bromide based on consideration of the maturity of the central nervous system. Given that methyl bromide is a potent neurotoxicant and there are no data on developmental toxicity, an additional uncertainty factor was suggested to address the potential increased sensitivity for infants and children. However, the NRC in the review of the draft RCD/1999 did not recommend such a factor mainly because the DPR selected NOELs for risk characterization that were considered adequately protective for these groups.

As for other Food Quality Protection Act issues, there could be a potential for aggregate exposure from occupation or residential exposures and dietary exposures. This aspect is being addressed in a separate document. There is a potential for cumulative toxicity between methyl bromide and other alkylating agents. However, appropriate approaches are not available at this

time. Based on available studies, methyl bromide has not been shown to cause endocrine disruption effects.

I.E. CONCLUSIONS FOR INHALATION EXPOSURE

The human health risk from potential inhalation exposure to methyl bromide was evaluated in this Volume I of Risk Characterization Document. The critical toxicity endpoints were derived from experimental animals: developmental toxicity for acute exposure, neurotoxicity for short-term and subchronic exposures, and tissue damage to the nasal cavity for chronic exposures. For acute and chronic exposure endpoints, neurotoxicity was also considered in the determination of the critical NOELs. The risks, expressed as the margins of exposure, were calculated for workers and residents involved or living in the vicinity of structural, field and commodity fumigations. Generally, a MOE of at least 100, which takes into account the possibility of 10-fold variations in susceptibility within the human population as well as between laboratory animals and humans, is considered adequate to protect humans from the effects of concern. Exposure scenarios with MOEs of less than 100 should be considered in the risk management process.

With structural fumigation, the acute MOEs for workers and residents were assumed to be at least 100 based on restrictions in the DPR regulations. However, data are needed to estimate actual exposures for acute and short-term exposures for workers and residents.

For field fumigation, the acute MOEs for workers were at or greater than 100 because of the most effective equipment modifications and work hour restrictions were placed in DPR regulations. However, there were work tasks with acute and short-term MOEs of less than 100 which are not specifically excluded in the regulations. They were: disc driver (acute MOE of 22, deep shank injection), and tractor drivers and basket-men in tarp removal (acute MOE of 20-21, tarp shallow with Noble plow shanks). For subchronic exposure, most of the worker tasks had MOEs of less than 100; many were less than 10 and included applicators, copilots, disc drivers, and tarp removers. The MOE for workers at adjacent fields was assumed to be 100 since they work outside of the buffer zone. Actual data are needed to verify this assumption as analyses for the effectiveness of buffer zones showed MOEs of less than 100 for some applications (in particular large fields and certain emission rates). For residents living at the buffer zone perimeter of fumigated fields, the acute MOEs were generally around 100 for the 95th percentile exposure except for a MOE of 91 for 30 acres and 80 lbs emission rate, and MOEs of 89-95 for 40 acres and all emission rates. The acute MOEs were generally greater than 100 at the 90% percentile exposure. No assessment was conducted for repeated exposures.

For commodity fumigation, the acute MOEs for workers involved in fumigation were at 100 because DPR regulation sets work hour restrictions to limit the maximum exposure at 210 ppb. The actual MOEs were likely higher as the upper limit may not be reached in some scenarios. The short-term MOEs were greater than 100 for all work tasks based on actual measurements; the only exception was a MOE of 67 for the task of cleaning plant. The MOE was also 67 when the daily exposure was set at 210 ppb for raisin (clear chamber) and walnut (vacuum chamber) workers. The subchronic and chronic MOEs were generally less than 100 based on measured values and exposures amortized from 210 ppb.

For workers doing other tasks in commodity fumigation facilities, the acute MOEs and

many of the short-term MOEs were at or greater than 100. The only exception was the short-term MOE of 67 for workers at the sorting or packaging areas and their exposures were based on 210 ppb as daily exposure. The subchronic and chronic MOEs for all workers were at or less than 67. Additional data are needed to characterize the exposures of these workers at the facilities. For residents living near fumigation facilities, the MOEs for all durations were based on 210 ppb used for acute exposure, and not actual measurements. The MOEs were between 1 and 78 for short-term, subchronic and chronic exposures.

The ambient air monitoring of three counties in California showed acute and short-term MOEs greater than 400. However, the 7-8 week MOEs were less than 100 (MOEs of 13 to 78) in some locations. Additional monitoring are being conducted to better characterize these exposures.

This risk assessment concluded that human inhalation exposure to methyl bromide resulted in margins of exposure of greater than 100 in some scenarios but less than 100 in other scenarios. The significance of these MOEs need to be viewed in the context of the limitations and uncertainties discussed. Many scenarios were based on exposure data with few samples or assumed exposure levels (i.e. 210 ppb for acute exposure). There were also scenarios which were not addressed in this document. Additional exposure data are needed to better characterize the exposure. In addition, the overall risk from methyl bromide exposure should consider the risks from other exposure routes. The risk characterization of dietary exposure and aggregate exposure is in Volumes II and III, respectively.

ATTACHMENT B

**TECHNICAL SUMMARY OF RISK CHARACTERIZATION DOCUMENT FOR DIETARY
EXPOSURE
(DPR, 2002b)**

I. TECHNICAL SUMMARY

I.A. TOXICOLOGY PROFILE

The acute oral toxicity of methyl bromide in experimental animals included hypoactivity, ataxia, prostration, labored respiration, hypothermia, and mortality. Squamous cell hyperplasia in the stomach was reported in both acute and subchronic exposure studies with rats. This toxicity endpoint may be due to a direct irritation effect of methyl bromide on the stomach lining. Decreased food consumption and body weight gain were observed in the subchronic and chronic studies. Additional effects from chronic exposure were enlarged spleen in the rat and decreased hemoglobin and hematocrit levels in the dog. Methyl bromide has not been shown to be oncogenic in experimental animals.

I.B. RISK CHARACTERIZATION FOR DIETARY EXPOSURE

I.B.1. Hazard Identification for Dietary Exposure

For acute oral exposure, the critical NOEL was an estimated NOEL of 8 mg/kg for clinical signs after a single gavage dose of 80 mg/kg in rats. For chronic oral exposure, two endpoints were considered. The first endpoint was enlarged spleens with a NOEL of 0.02 mg/kg/day in rats. The other endpoint was decreased body weight with a NOEL of 2.2 mg/kg/day from the same study. This latter endpoint and NOEL were selected for chronic exposure risk characterization, as recommended by the National Research Council scientists.

The oncogenicity of methyl bromide by the oral route was not evaluated at this time because experimental studies did not provide sufficient evidence for oncogenic potential. There is evidence that methyl bromide causes damage to the genetic material in experimental animals and humans, which is generally considered to play a significant role in the process of tumor formation.

I.B.2. Dietary Exposure Assessment

The dietary exposure was estimated based on residue data for post-harvest fumigation and the consumption data from the 1989-1992 Continuing Survey of Food Intakes by Individuals. The potential acute dietary exposure of methyl bromide from all labeled uses ranged from 3.387 $\mu\text{g}/\text{kg}/\text{day}$ to 8.195 $\mu\text{g}/\text{kg}/\text{day}$ for the 95th percentile of user-days exposures for all population subgroups. Children (1-6 years) had the highest potential acute dietary exposure (8.195 $\mu\text{g}/\text{kg}/\text{day}$) to methyl bromide residues in the diet. The mean potential chronic dietary exposure for all population subgroups ranged from 0.014 $\mu\text{g}/\text{kg}/\text{day}$ to 0.201 $\mu\text{g}/\text{kg}/\text{day}$. The population subgroup of children (1-6 years) also had the highest potential chronic exposure (0.201 $\mu\text{g}/\text{kg}/\text{day}$).

I.B.3. Risk Characterization for Dietary Exposure

For acute exposure, the lowest MOE was 980 for children 1-6 years old. Other children, infants, and adult groups had MOEs greater than 1500. For chronic exposure, the MOE was 11,000 for both children 1-6 years and 7-12 years old. The MOEs for infants were greater than 120,000. The MOEs for the adult subgroups were greater than 14,000.

I.C. RISK APPRAISAL FOR DIETARY EXPOSURE

The uncertainties associated with the hazard identification included the use of results from bolus dosing in the acute toxicity study, the estimation of the NOEL from the LOEL in the acute study, and the selection of the critical endpoints. Overall, these resulted in health protective NOELs for both acute and chronic toxicity assessments.

The dietary exposure estimate was based on fumigation chamber studies with residue levels reduced by processing factors and percent of crop treatment when data were available. The potential sources of overestimation included use of maximum label rate in the studies, 100% crop treatment, and no loss due to processing for some commodities. The use of the detection limit to assign residue levels for samples with residue levels at or below the detection limit or the use of surrogate data could either over- or under-estimate the exposure. The exposure might be underestimated because the samples were composites which could mask higher residue levels in individual units. There was no residue information for potential metabolites in the treated commodities.

For the risk characterization, two 10-fold default uncertainty factors were used to address the uncertainties associated with the extrapolation of data from experimental animals to humans and the variations in response to methyl bromide between individuals. Since there were no data to determine the magnitude of the factors, these factors could overestimate or underestimate the risks for human exposure to methyl bromide.

I.D. CONCLUSIONS FOR DIETARY EXPOSURE

The human health risk from potential dietary exposure to methyl bromide was evaluated in this Volume II of the Risk Characterization Document. The potential risks were evaluated based on clinical signs and decreased body weights observed in experimental animals given methyl bromide orally for acute and chronic exposures, respectively. The risks, expressed as margins of exposure, were calculated for human population subgroups based on region, age, and gender. For non-oncogenic effects based on animal data, the MOEs were compared with a benchmark of 100 to determine whether the exposure would be of a potential health concern.

The dietary exposures were considered reasonable estimates of actual exposures. The ranges of MOEs were 980 to 2360 and 10,930 to 162,600 for acute and chronic exposures, respectively. Other variables discussed in this document which potentially underestimate or overestimate actual dietary exposures should also be considered in the evaluation of these MOEs.

Since methyl bromide residues are found in treated commodities, there is a need for tolerances to be established for methyl bromide *per se* for food uses.

ATTACHMENT C

**COMMENTS AND RESPONSES TO COMMENTS FROM THE OFFICE OF ENVIRONMENTAL
HEALTH HAZARD ASSESSMENT**

Office of Environmental Health Hazard Assessment



Winston H. Hickox
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Gray Davis
Governor

MEMORANDUM

TO: Gary Patterson, Ph.D., Chief
Medical Toxicology Branch
Department of Pesticide Regulation
P.O. Box 4015
Sacramento, California 95812-4015

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

DATE: August 26, 2002

SUBJECT: COMMENTS ON THE DRAFT RISK CHARACTERIZATION DOCUMENT
FOR AGGREGATE EXPOSURE TO METHYL BROMIDE


Thank you for the opportunity to review the draft risk characterization document (RCD) for aggregate exposure to methyl bromide prepared by the Department of Pesticide Regulation (DPR). This is the third of three draft RCDs prepared by DPR for methyl bromide exposure, the first draft RCD being for inhalation exposure and the second for dietary exposure. Our comments on the draft RCD for aggregate exposure to methyl bromide are provided in this memorandum.

Our primary concern with regard to this draft RCD is that the total estimated aggregate risk for inhalation plus oral exposure is lower than either inhalation or oral exposure alone. We think that this outcome is an artifact of the methodology employed in the RCD to estimate the aggregate risks and we recommend that an alternative method be used to aggregate inhalation and oral exposure to methyl bromide.

The U.S. Environmental Protection Agency (U.S. EPA) prepared guidelines for measuring and aggregating risk for single chemical, multi-route, multi-source assessments (U.S. EPA, 1999, 2001). The method used in the draft RCD to estimate risk of aggregate exposure to methyl bromide, called the "total margin of exposure (MOET) method," is based on the assumption that it is scientifically justified to combine exposures occurring by different pathways/routes only when the toxicological endpoints for the pathways/routes are related with respect to target organ and nature of adverse effect. When the relevant toxicological endpoints for all routes/pathways are not the same, U.S. EPA recommends that a separate aggregate assessment be conducted for each toxic effect of concern.

California Environmental Protection Agency

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Following U.S. EPA's guidelines, the assessment for aggregate risk of acute exposure to methyl bromide in the draft RCD is based on a common toxicological endpoint for both inhalation and oral exposure, which is clinical signs of toxicity. These clinical signs were clearly attributed to neurotoxicity when inhalation exposure was involved, and according to the draft RCD could be attributed to neurotoxicity in the case of oral exposure. The acute no-observed-adverse-effect levels (NOAELs) used in this assessment are 22.8 mg/kg-day for inhalation exposure (based on a 23 to 30-day dog study) and 8 mg/kg-day for oral exposure (based on acute oral LD₅₀ study in rats). In comparison, a NOAEL of 10.5 mg/kg-day for developmental toxicity, which is the most sensitive toxicological endpoint for acute methyl bromide exposure, was selected in the assessment of inhalation exposure alone. This acute NOAEL selected for use in the inhalation exposure RCD is two times lower than the acute NOAEL chosen for the inhalation component of the aggregate exposure assessment. The acute NOAEL of 8 mg/kg-day for oral exposure is used in both the dietary exposure RCD as well as the aggregate exposure RCD.

The developmental toxicity study used in the draft RCD for acute inhalation exposure was conducted with New Zealand white rabbits exposed to methyl bromide (99.6 percent) at 0, 20, 40, or 80 ppm for six hours per during days 7 to 19 of gestation. Equivalent absorbed doses used in this experiment were: 0, 5.2, 10.5, and 21 mg/kg-day. The developmental NOAEL is 40 ppm (10.5 mg/kg-day) based on omphalocele, hemorrhaging, retro-esophageal right subclavian artery, gall bladder agenesis, fused stembrae, and decreased fetal body weight at 80 ppm (21 mg/kg-day). The data demonstrate that developmental toxicity caused by inhaled methyl bromide is a systemic effect and not a local effect.

In the oral developmental toxicity study in rabbits, methyl bromide (99.5 percent) was dissolved in corn oil and administered by gavage at (absorbed) dose levels of 0, 1, 3, or 10 mg/kg-day during days 6 to 18 of gestation (DPR's Summary of Toxicological Data, page 19). In this study " ... the only fetal finding of interest was the observation that each of the three methyl bromide-treated groups had more fetuses with skeletal malformations than what was observed in the negative-control group. Skeletal malformations involving 2-3 litters in at least one methyl bromide-treated group included: splitting of the nasal/frontal/parietal bones; hemivertebra; fusion of the ribs/stembrae; and absence of the metacarpal and phalangeal bones." Nevertheless, the Summary states " ... the difference between the negative control and methyl bromide-treated groups appear too small to warrant further concern." However, it should be noted that highest absorbed dose used in the oral study is approximately the same as the NOAEL of 10.5 mg/kg-day (absorbed) identified from the inhalation study. Based on the comparison of doses, the highest dose used in the oral study is a NOAEL and therefore a similar effect would not have been expected in the oral study. In fact, some evidence for developmental toxicity, although not statistically significant, was reported in the oral developmental toxicity study even at the lower dose levels. Our approach is consistent with the National Academy of Sciences recommendation "to better be able to compare inhalation with the oral developmental

studies, it would be useful to calculate the estimated absorbed doses for these studies" (NAS, 2000).

The draft RCDs do not present data showing that the mechanism of toxicity for absorbed methyl bromide is different depending on the route of exposure. Likewise, we were not able to locate any data in the open literature that demonstrate the mechanism of action for developmental toxicity is exclusively related to inhalation of methyl bromide.

In summary, there is enough scientific support or there exist data gaps so that the following assumptions for acute exposure to methyl bromide are reasonable:

1. There is a greater variability in inhalation than dietary exposure for the two major groups of exposed individuals (i.e., workers and residents).
2. For occupational aggregate dose levels, the contribution from inhalation exposure is proportionately higher than dietary exposure for upper-end exposures (approximately 99 percent) but about the same for lower end exposures (approximately 50 percent).
3. For residential aggregate dose levels, the contribution from inhalation exposure is also proportionately higher than dietary exposure for upper-end exposures (approximately 77 percent) but lower or about the same for lower end exposures (approximately 25 to 50 percent).
4. The existing oral developmental toxicity study used absorbed dose levels that were at or below the NOAEL for absorbed methyl bromide determined from the inhalation developmental toxicity study.
5. The results of the oral toxicity study present some limited evidence of adverse developmental effects.
6. Developmental toxicity caused by methyl bromide exposure is systemic in nature.
7. Because neither DPR nor OEHHA were able to identify any studies that demonstrate differences, it is reasonable to assume that the mechanism of action of the developmental toxicity of methyl bromide is the same for oral and inhalation exposure.

Based on these assumptions, we recommend that the acute exposures estimated for methyl bromide from inhalation and ingestion be added and compared to the existing NOAEL for developmental toxicity from the inhalation study. As noted previously, we believe this approach is consistent with the recommendation of the National Academy of Sciences (NAS, 2000).

The situation for chronic toxicity from methyl bromide exposure is a little more complicated. The common toxicological endpoint used in the draft RCD for aggregate exposure to oral and inhaled methyl bromide is reduced body weight. The NOAELs (as absorbed doses) were 10 mg/kg-day (chronic inhalation study in rats) and 2.2 mg/kg-day (chronic oral study in rats) for inhalation and oral exposures, respectively. For chronic exposure to methyl bromide through inhalation alone, the critical endpoint is nasal cavity lesions in rats, yielding a NOAEL of 0.067 mg/kg-day (expressed as an absorbed dose). This NOAEL is 150-fold lower than the NOAEL of 10 mg/kg-day used for aggregate exposure. The NOAEL of 2.2 mg/kg-day for chronic oral exposure was used in both the aggregate RCD and the dietary RCD.

Unlike the acute toxicity data for developmental toxicity, the effects of long-term repeated inhalation of methyl bromide on the nasal cavity might be the result of a localized effect. Therefore, although the other assumptions we present above for acute exposure would likely also apply for chronic exposure to methyl bromide, further research should be conducted to ascertain the nature of the most sensitive toxicological endpoint from chronic exposure.

For chronic exposure to methyl bromide, we recommend that aggregate risks be estimated separately for different exposure scenarios based on the toxicological endpoints most sensitive for the prevalent route of exposure for each scenario. This approach is recommended by U.S. EPA (1999, 2001) for situations where there is more than one critical toxicological endpoint for a single chemical and where toxicological effects via different routes of exposure are not the same. Alternatively, the aggregate risk RCD should not include an aggregate risk assessment for chronic oral and inhalation exposure because the results in the draft RCD are confusing and not useful. If the latter option is chosen, then DPR should use the results of the inhalation RCD for methyl bromide in developing mitigation options as proposed in the draft RCD.

In reference to the aggregate risk estimate for chronic exposures, on pages 3 and 30 of the draft RCD the toxicological significance of animal weight loss is questioned due to a failure of the magnitude of the weight loss to increase with continued exposure. For methyl bromide (chronic rat study) the maximum reduction in high dose animals occurred during the first weeks of testing while "a further reduction in bodyweight relative to the controls did not occur despite continued exposure." However, in chronic studies, it is often the case that the magnitude of the body weight loss does not increase with increased time of exposure. Examples of chronic studies where weight loss in treated animals did not increase relative to controls with continued exposure include:¹

¹ Source of information: **DPR** Website, Available Toxicology Summaries.

1. Mecoprop (chronic dog study): NOAEL based on "reduced bodyweight and bodyweight gain." Group mean body weight gains in high dose males were decreased 75 percent relative to controls between days 0 to 49, but decreased only 15 percent during days 0 to 364; group mean body weight gains in high dose females were decreased 25 percent relative to controls only between days 1 to 49.
2. Quinclorac (combined rat study): NOAEL is based on reduced body weight in females. The body weights were only lower than controls between days 518 to 658 (study went from 0 to 730 days).
3. Chlorpyrifos (combined rat): non-cholinesterase NOAEL based on body weight decreases in males; high dose males had reductions in body weights of "7-9% throughout study."
4. Diflufenzopyr (oncogenicity mouse): chronic NOAEL based on reduced body weight; mean body weight of high dose males were significantly lower than controls over 12 of the first 21 weeks, then no significant differences from controls.

We recommend the discussion on the toxicological insignificance of the reductions in body weight from chronic methyl bromide exposure be reconsidered in light of the examples where **DPR** has selected NOAELs based on the same endpoint for other active ingredients.

Thank you for the opportunity to review the draft risk characterization document for aggregate exposure to methyl bromide. If you have any questions regarding our comments, feel free to contact me or Dr. Michael DiBartolomeis at (510) 622-3200.

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cc: See next page

Gary Patterson, Ph.D, Chief
August 26, 2002
Page 6

cc: Val F. Siebal
Chief Deputy Director
Office of Environmental Health Hazard Assessment

George V. Alexeeff, Ph.D., D.A.B.T.
Deputy Director for Scientific Affairs
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Michael J. DiBartolomeis, Ph.D., Chief
Pesticide and Food Toxicology Unit
Pesticide and Environmental Toxicology Section
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Department of Pesticide Regulation



Paul Helliiker
Director

MEMORANDUM

Gray Davis
Governor
Winston H. Hickox
Secretary, California
Environmental
Protection Agency

TO: Gary Patterson, Supervising Toxicologist
Medical Toxicology Branch

FROM: Lori O. Lim, Staff Toxicologist *[original signed by Lori Lim]*
(916) 324-3515

DATE: October 24, 2002

SUBJECT: RESPONSE TO COMMENTS FOR METHYL BROMIDE RISK
CHARACTERIZATION DOCUMENT FOR AGGREGATE EXPOSURE
FROM OFFICE OF ENVIRONMENTAL HEALTH ASSESSMENT

This memorandum addresses comments from the Office of Environmental Health Assessment (OEHHA, August 26, 2002) regarding the draft Methyl Bromide Risk Characterization Document for Aggregate Exposure (February 22, 2002).

Pages 1-4: For acute exposure, OEHHA was concerned that the endpoint used to estimate the aggregate risk resulted in lower risks than those for individual routes alone. They proposed using the NOEL for developmental toxicity from a rabbit inhalation study for aggregate exposure.

Response: The OEHHA proposal was based on the assumption that, in the absence of conclusive evidence, the mechanism of action for developmental toxicity was the same for both inhalation and oral exposures. OEHHA supported the assumption with the results from the oral developmental toxicity studies (Kaneda *et al.*, 1998) in which the data were interpreted to show limited evidence of adverse developmental effects. OEHHA was also concerned that the doses tested were at or lower than those used for the inhalation developmental toxicity studies.

DPR considers the OEHHA proposal to have limited application. The developmental toxicity endpoint can only be applicable for women of childbearing age. In comparison, the neurotoxicity endpoint used in the draft aggregate RCD is applicable for all population subgroups. Furthermore, there are more uncertainties associated with the use of developmental toxicity than for neurotoxicity as the critical endpoint. Clinical signs associated with neurotoxicity have been reported for oral and inhalation routes whereas developmental toxicity has not been observed with the oral route. DPR disagrees with OEHHA's position that developmental toxicity was demonstrated in the oral developmental toxicity studies. DPR considers the effects reported not treatment related; they were not statistically significant from the control and they were not dose-related. The rabbits in the oral study may or may not have been adequately tested since comparison of absorbed doses only provides a limited estimation of the target tissue doses. Pharmacokinetic studies with methyl bromide show differences in the disposition of methyl bromide when given by inhalation compared to gavage route of administration. These differences are expected especially since inhalation exposure involved continuous exposure at the same dose for several hours compared to a single one-time bolus



dosing with gavage administration. Furthermore, it is unlikely that the oral dose could be increased much higher than 10 mg/kg/day since 30 mg/kg/day caused severe erosion of the stomach lining of the pregnant rats (Kaneda *et al.*, 1998).

DPR will include the above discussion in the Risk Appraisal section. The overall assessment, however, remains the same using the neurotoxicity as the endpoint since it is applicable for all population subgroups, including children.

Page 4: For chronic exposure, OEHHA recommended that “aggregate risks be estimated separately for different exposure scenarios based on the toxicological endpoints most sensitive for the prevalent route of exposure for each scenario”, or aggregate chronic risk assessment should not be performed since the results were confusing and not useful.

Response: The chronic aggregate risk was performed using the common endpoint approach as recommended by the U.S. EPA. The risks for individual route exposures were determined in the inhalation and dietary risk characterization documents. DPR disagrees with OEHHA’s comment that the aggregate risks should not be performed. DPR considers the analysis useful in that it points out the limitations of the database and the need for the risk management to consider risks mainly from the individual routes.

Pages 4-5: OEHHA commented that the toxicological insignificance of body weight reduction discussed on page 3 and 30 of the draft RCD should be reconsidered.

Response: In the draft RCD, the toxicological significance of the body weight reduction was discussed in the Risk Appraisal section in the context of uncertainty of the endpoint. The significance of the effect was considered “uncertain” because the reduction varied little with continued exposure and was about 10% of control values for both routes of exposure. Furthermore, the effect was observed at some time points and not throughout the study. The discussion was not intended to dismiss its usefulness as a toxicological endpoint in the determination of a study NOEL.