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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460
August 1, 1988

AUG 5 1988

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Methyl Bromide rebuttal to letter of 10/19/87 from Methyl Bromide Industry Panel regarding their Inhalation Two-generation Reproduction Study CASWELL # 555, Project # 8-09278

FROM: Laurence D. Chitlik, D.A.B.T.
Senior Science Advisor
Toxicology Branch/HED (TS-769c)

TO: Walter C. Francis
PM team # 32
Registration Division

The letter from Dr. L. Vernon White, 10/19/87, took issue with the Agency position on the registant's inhalation reproduction study as stated in the 5/27/87 memo of W. Burnam. The Agency response follows a summary restatement of the registrant's position.

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Registrant position

The study was designed and conducted in accordance with EPA Guidelines (1982) in effect at the time of study initiation. Dr. White then goes on to purportedly quote the Guidelines.... "The guidelines state in Section (4)(c)(ii)(A) and (B) 'All P1 [or F1 in (B)] males should be sacrificed immediately after delivery of the last litter sired or, in cases of infertility, after the conditions of (7)(i)(B) are met.'(emphasis added) Section (7)(i)(B) states 'Those pairs that fail to mate successfully should be evaluated to determine the cause of the apparent infertility. This may involve such procedures as histological examination of the reproductive organs, and examination of the estrus or spermatogenic cycles."(emphasis added The registrant also states that the conditions of the above sections were met since those animals were sacrificed and their reproductive organs were examined. They also indicated that "the protocol" had been reviewed by the Agency prior to the start of the study.

Agency Response

Actually, two proposals (submitted to the Methyl Bromide Committee for a two-generation inhalation study were submitted to the Agency for review. One of these was from Wil Research and the other was from Whittaker Toxigenics, Inc.. The Wil protocol cited earlier

Agency Guidelines of 1978 which were no longer being used by the Agency. The Toxicenics guideline referenced the 1982 Agency Guidelines, but actually did not follow them in a number of important ways (e.g.- no requirement for both a and b matings). In addition, it is not the policy of the Agency to select among various proposals for a registrant, nor to compare details of various protocols to an available published guideline. Therefore, the reviewer just made general reference to the protocols but noticed and apparently commented only on the dosing interruption. Generally, if there are specific questions due to identified protocol deviations, then these should be highlighted by the registrant for discussion by the Agency. This was not done and a line by line comparison of the two proposals was not performed by the reviewer.

Further, the Agency Guideline was grossly mis-quoted by Dr. White. Section (7)(i)(B) actually states, "Those pairs that fail to mate successfully should be evaluated to determine the cause of the apparent infertility. This may involve such procedures as additional opportunities to mate with other sires or dams, histological examination of the reproductive organs, and examination of the estrus or spermatogenic cycles." Please note that the underlined portion was completely left out in the quote by Dr. White. It is the first point raised and among the most important and easily investigated. However, no remating of these animals to obtain b matings was performed in this study. As well, no examination of the estrous or spermatogenic cycles was apparently reported in the study. Therefore, it is our position that the conditions of this section were not fully met as required by sections (4)(c)(ii)(A) and (B). The procedure followed was not desired and could have clearly reduced the sensitivity of this reproduction study by eliminating the more sensitive animals.

However, despite the fact that this remains the Agency position, additional examination of the data has not revealed an increase of animals being eliminated from the study due to infertility on a dose related basis. Therefore, it is less likely that this procedure would have had a major impact upon the conduct of this study although it is still quite possible since effects upon pregnancy status were noted in this study at the second mating of the second generation in the mid and high doses. It was the concern of the Agency that such apparent effects could have extended to the low dose leaving the study without a NOEL. However, in light of the fact that the loss of the non-pregnant animals did not increase with dose, the Agency concerns are at least partially reduced.

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RECOMMENDATION

The study shall be classified as Core Minimum data and the NOEL established at 3 ppm. However, if any other data become available to either the Agency or the registrant which suggest fertility and/or pregnancy effects or any other potential low dose effects, this decision may be reconsidered and a new

reproduction study may be required. It is suggested the the registrant check the literature and verify that no such effects have been noted by other investigators. If at any time such data are noted by the registrant, they should immediately be forewarded to the Agency.

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007939 Caswell 55

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

MAY 27 1987

OFFICE OF
PESTICIDES AND TOXIC SUBSTAN

MEMORANDUM

SUBJECT: Methyl Bromide Reproduction Study via Inhalation
EPA 55644-Q -- Caswell No. 555 -- Record 169307

TO: Walter Frances
Disinfectants Branch
Registration Division (TS-767)

FROM: William L. Burnam, Deputy Chief
Toxicology Branch
Hazard Evaluation Division (TS-769)

WLB 5/27/87

I am attaching a copy of the Dynamac review of the two-generation reproduction study carried out at American Biogenics Corp. for Great Lakes Chemical Corp.

Mr. Chitlik and myself are concerned about the protocol design that included sacrifice of adults that did not reproduce after the first breeding and request comments from the Registrant regarding this procedure. This is stated on p. 4 of the Dynamac review "Adults that did not produce litters after the first breeding were killed and necropsied". On table 4 of page 10, there is a dose-related decrease in percent of pregnant rats during the b matings and this is one of the reasons for selection of the NOEL at 3 ppm for reproductive toxicity. Note also that the number paired and mated is apparently reduced due to the above stated sacrifice procedure. Thus it appears that this procedure could have potentially confounded or reduced the sensitivity of the study to detect fertility effects. The CORE-classification and the acceptability of the study are withheld pending the receipt of the above information.

Attachment

CONFIDENTIAL BUSINESS INFORMATION
DOES NOT CONTAIN
NATIONAL SECURITY INFORMATION (EO 12065)

007939

EPA: 68-02-4225
DYNAMAC No. 234-A
May 13, 1987

DATA EVALUATION RECORD

METHYL BROMIDE

Two-Generation Reproduction Study in Rats

STUDY IDENTIFICATION: Enloe, P.V., Salamon, C.M., and Becker, S.V. Two-generation reproduction study via inhalation in albino rats using methyl bromide. (Unpublished study No. 450-1525 by American Biogenics Corp., Decatur, IL, for Great Lakes Chemical Corp., W. Lafayette, IN; dated February 19, 1986.) Accession Nos. 261736-261742.

APPROVED BY:

I. Cecil Felkner, Ph.D.
Department Manager
Dynamac Corporation

Signature: I. Cecil Felkner

Date: 5-13-87

1. CHEMICAL: Methyl bromide; bromomethane; meth-o-gas.

2. TEST MATERIAL: Methyl bromide gas.

3. STUDY/ACTION TYPE: Two-generation reproduction toxicity study in rats.

4. STUDY IDENTIFICATION: Enloe, P.V., Salamon, C.M., and Becker, S.V. Two-generation reproduction study via inhalation in albino rats using methyl bromide. (Unpublished study No. 450-1525 by American Biogenics Corp., Decatur, IL, for Great Lakes Chemical Corp., W. Lafayette, IN; dated February 19, 1986.) Accession Nos. 261736-261742.

5. REVIEWED BY:

Michael Narotsky, B.A.
Principal Reviewer
Dynamac Corporation

Signature: M. Narotsky
Date: 5-13-87

Guillermo Millicovsky, Ph.D.
Independent Reviewer
Dynamac Corporation

Signature: G. Millicovsky
Date: 5-13-87

6. APPROVED BY:

I. Cecil Felkner, Ph.D.
Teratogenicity & Reproductive Effects
Technical Quality Control
Dynamac Corporation

Signature: I. Cecil Felkner
Date: 5-13-87

William L. Burnam, M.S.
EPA Deputy Chief

Signature: _____
Date: _____

Theodore M. Farber, Ph.D.
EPA Branch Chief

Signature: _____
Date: _____

7. CONCLUSIONS:

A. The NOEL and LOEL for parental toxicity of methyl bromide vapor in rats are 30 and 90 ppm, respectively, based on reduced body weights of F_0 males and females at 90 ppm.

The NOEL and LOEL for reproductive and developmental toxicity are 3 and 30 ppm, respectively, based on reduced pregnancy rates and pup weights at 30 and 90 ppm and reduced pup survival at 90 ppm.

B. This study is classified Core Minimum.

Items 8-10--see footnote 1.

11. MATERIALS AND METHODS (PROTOCOLS):

A. Materials and Methods: (See Appendix A for details.)

1. Test Material: Liquid methyl bromide was supplied by the sponsor in pressurized steel cylinders. Vapor phase methyl bromide was delivered to exposure chambers via a heated three-neck glass flask that was charged with liquid methyl bromide. Chamber concentrations were controlled by needle valves associated with each chamber's rotameter. Atmospheres of the inhalation chambers were sampled and analyzed by gas chromatography at least hourly during exposure. Chamber airflow and temperature were monitored continuously during exposure. Relative humidity of incoming air was determined hourly.

Animals were housed in the exposure chambers 6 hours/day for 5 days/week and exposed to the appropriate concentration of methyl bromide . Food and water were not available during exposure. At the end of each exposure, animals were transferred to a different chamber in the same room. Dams were not exposed from gestation day (GD) 21 through lactation day 4 (inclusive). In subsequent exposures during lactation, dams were separated from their litters. In addition, on nonexposure days (i.e., weekends) dams were also separated from their litters and housed in chambers without food or water for 6 hours/day.

2. Animals and Experimental Design: Charles River CD Sprague-Dawley albino rats were obtained at 42 days of age from Charles River Breeding Laboratories, Inc., Portage, MI, and acclimated for 20 days. Twenty-five animals of each sex were randomly assigned to each of the four treatment groups and designated F_0 parental animals. A high-dose female

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[1]Only items appropriate to this DER are included.

that died after four exposures was replaced with a stock animal starting on the sixth exposure.

After 8 weeks of exposure, each male was paired with one female of the same group for up to 3 weeks to produce F_{1a} litters. The progeny were weaned on lactation day 28; approximately 1 week later, the parents were rebred using different pairs to produce F_{1b} litters. Adults that did not produce litters after the first breeding were killed and necropsied.

Twenty-five F_{1b} weanlings of each sex were randomly selected from each group and designated F_1 parental animals; treatment of these animals began at 29-33 days of age. After 11 weeks of treatment, F_1 adults were bred, using the same procedures as their parents, to produce F_{2a} and F_{2b} litters. Sibling pairings were avoided.

3. Observations and Measurements: All animals were observed at least twice each day for mortality, morbidity, and toxic signs. In addition, animals were individually examined for physical change at least once each week. Body weights and food consumption were determined weekly prior to breeding. Mated females were weighed on GD 0, 6, 15, and 20 and lactation days 0, 4, 7, 14, 21, and 28. In addition, the final body weight of each animal was determined at termination.

All adult animals were necropsied and selected organs were weighed and tissues were preserved. Reproductive tissues from all control and high-dose parental animals and from nonfertile low- and mid-dose animals were examined histologically. In addition, tissues with gross lesions from animals of all groups were examined histologically.

For each litter, the gestation length was recorded and the pups were examined for viability, sex, and weight on the day that parturition was completed. The number of live pups was also determined on day 1. Litters were reduced to a maximum of eight pups (four per sex, when possible) on day 4. Litter sizes and pup weights were recorded on days 4, 7, 14, 21, and 28. Progeny was examined daily for mortality and abnormal behavior and for other developmental abnormalities at birth and at each weighing interval.

One male and one female weanling from each 'b' litter were randomly selected and their tissues were subjected to histological examination; necropsies were performed, organs were weighed, and reproductive tissues and gross lesions were preserved. Tissues from 10 randomly selected weanlings per sex of the control and high-dose groups were examined histologically. Carcasses of pups killed on day 4 and any pups found dead were preserved in 10% formalin; pups with structural abnormalities were necropsied.

4. Statistical Methods: Body weight and food consumption data were evaluated by analysis of variance (ANOVA); significant differences were further evaluated by Tukey's or Scheffe's multiple comparisons. Organ weight ratios were evaluated using Kruskal-Wallis analysis. Reproductive data and progeny abnormality data were evaluated with chi-square analysis. Progeny weights were analyzed on an individual pup basis using ANOVA and Scheffe's multiple comparison as well as on a litter basis using analysis of covariance and Dunnett's t-test.

B. Protocol: A protocol was not included in the study report.

12. REPORTED RESULTS:

A. Test Material Analyses: Time-weighted average concentrations during the F_0 generation were reportedly 0.0, 3.0, 30.0, and 90.2 ppm for the control and low-, mid-, and high-dose groups, respectively. During the F_1 generation, the results were 0.0, 3.0, 30.1, and 90.0 ppm for the respective groups.

B. Parental Data: All F_0 males survived the experimental period; however, one control and two low-dose females died during the F_0 generation. The control female and one of the low-dose females had renal calculi and other urinary tract lesions at necropsy. The stomach and esophagus of the other low-dose female that died were distended with food; signs of cyanosis were also present. The high-dose F_0 female that died after four exposures reportedly had lesions that were apparently not compound related. All F_1 males and females survived the experimental period.

Antemortem observations (e.g., alopecia, crusty eyes) occurred sporadically in all groups and were not attributable to the compound. Necropsy findings (e.g., dilated renal pelvis) of all surviving parental animals and histological findings of control and high-dose animals also did not suggest any compound-related effects.

Organ weight data revealed significantly reduced absolute brain weights in high-dose F_0 males and F_1 males and females. Significantly increased relative liver (to body) weights were evident in high-dose F_0 males and females and increased heart:brain weight ratios were evident in high-dose F_1 females.

Body weights of high-dose F_0 males were, in general, significantly reduced when compared to controls after the third week of the study (Table 1). Premating and total weight gains of these rats also were significantly reduced. No significant differences in body weight data were noted for the F_0 females; however, slightly reduced weights and weight gains were evident in the high-dose group at the initiation of mating and at termination. For the F_1 males, body weights were comparable for all groups throughout the generation. F_1 females had

TABLE 1. Mean Body Weights (g) of Rats Exposed to Methyl Bromide Vapor

	Dose Level (ppm)	Week 0	Week 1	Week 3	End of Premating[a]	Final	Weight Gain Premating	Weight Gain Total
F_0 Males	0	315	346	397	481	617	166	301
	3	316	348	393	462	594	147	280
	30	312	340	386	464	604	152	293
	90	314	338	375*	440**	550**	126**	234**
F_0 Females	0	204	220	244	280	346	76	141
	3	205	224	242	277	347	72	144
	30	205	221	242	276	345	71	139
	90	207	221	242	270	330	63	124
F_1 Males	0	72[b]	125	229	456	598	384	526
	3	71	122	230	476	620	405	547
	30	68	119	229	484	643	416*	574
	90	68	117	224	459	596	390	527
F_1 Females	0	68	112	166	267	340	199	271
	3	67	111	166	277	361	210	294
	30	62	103	162	271	347	209	285
	90	63	103	160	253	322	191	259

[a] End of premating was week 8 for the F_0 generation and week 11 for the F_1 generation.

[b] F_1 generation initial body weights (i.e., at weaning) are presented here under week 0.

*Significantly different from control value ($p < 0.05$).

**Significantly different from control value ($p < 0.01$).

comparable body weights prior to mating for all groups, but high-dose maternal weights were significantly reduced during the F_{2a} gestation and lactation periods (Table 2). Maternal weights were comparable, however, in the F_{2b} interval.

Food consumption values of F_0 males were comparable throughout the premating period although high-dose body weights were decreased (Table 3). For the F_0 females, food consumption was significantly reduced in all three dosed groups during the first week of treatment; these differences, however, were not attributed to differences in animal weight since initial body weights were comparable for all groups. All other significant differences in food consumption occurred sporadically in the F_1 generation and were uncorrelated with body weights.

Reproductive and Developmental Data: Precoital intervals and the numbers of animals mating were generally comparable among all groups. Pregnancy rates were comparable in the first three litter intervals; however, in the F_{2b} interval, mid- and high-dose values were slightly reduced when compared to controls (Table 4). Gestation lengths and the percentages of pregnant females delivering were comparable for all groups.

There were no significant differences in litter size between groups throughout lactation for all litter intervals (Table 5). Pup survival also showed no significant differences between groups; however, slightly reduced survival was evident for F_{1b} and F_{2a} high-dose progeny.

Mean pup weights per litter in the mid- and high-dose F_{1a}, F_{2a}, and F_{2b} intervals during late lactation were significantly reduced when compared to controls (Table 6). In the F_{1b} litters, mid- and high-dose pup weights were slightly reduced but reached significance only when analyzed on an individual pup (rather than litter) basis.

Progeny abnormalities (e.g., runts, hematomas, malformations) and clinical observations occurred sporadically in all groups. Absent or short tail was observed in one pup each from the F_{1a} mid-dose, F_{1b} low-dose, and F_{1b} mid-dose litters. Other malformations noted were exencephaly in one F_{2b} control pup and spina bifida in one F_{2b} mid-dose pup.

Organ weight data of 'b' litter weanlings revealed significantly reduced absolute brain, heart, and kidney weights in high-dose females and reduced absolute liver weights and liver:brain weight ratios in mid- and high-dose females from the F_{2b} litters.

13. STUDY AUTHORS' CONCLUSIONS/QUALITY ASSURANCE MEASURES:

A. Although the study authors did not explicitly state any overall conclusions, they noted reduced parental body weights in F_0 males and F_1 dams at 90 ppm and reduced food consumption in

TABLE 2. Mean Maternal Body Weights (g) of Rats Exposed to Methyl Bromide Vapor

	Dose Level (ppm)	Gestation Day 0	Gestation Day 20	Lactation Day 0	Lactation Day 14	Lactation Day 28
F_0 Females						
F_{1a} Interval	0	284	404	308	343	313
	3	279	402	310	344	310
	30	277	396	304	338	311
	90	275	394	302	338	310
F_{1b} Interval	0	321	439	346	373	344
	3	323	448	355	371	344
	30	319	442	347	368	337
	90	314	430	336	355	333
F_1 Females						
F_{2a} Interval	0	265	385	295	331	296
	3	279	400	312	342	311
	30	267	376	300	331	297
	90	252	349*	282	310*	282
F_{2b} Interval	0	304	410	326	359	320
	3	331*	450*	359*	375	347**
	30	323	425	348	366	339
	90	294	400	316	348	317

*Significantly different from control value ($p < 0.05$).

**Significantly different from control value ($p < 0.01$).

TABLE 3. Mean Food Consumption (g/rat/day) of Rats Exposed to Methyl Bromide Vapor

	Dose Level (ppm)	Week 1	2	6	9	11
F_0 Males	0	21.0	23.9	28.0	26.0	
	3	21.3	22.2	27.0	24.7	
	30	20.8	24.2	26.4	25.8	
	90	20.8	23.8	26.7	25.7	
F_0 Females	0	18.3	17.2	19.4	18.2	
	3	14.7**	17.5	19.6	18.9	
	30	15.2**	17.9	19.7	18.7	
	90	14.7**	18.0	19.9	18.6	
F_1 Males	0	17.5	20.0	29.5	26.2	25.2
	3	17.4	21.0	27.8	27.6	25.4
	30	16.4	22.4**	29.1	28.0	26.8
	90	18.2	22.9**	28.2	28.2	25.6
F_1 Females	0	15.3	16.6	20.6	18.3	17.6
	3	15.4	16.5	19.6	18.6	18.0
	30	15.2	17.4	19.2	18.1	18.1
	90	15.6	18.2*	18.7*	18.1	17.2

*Significantly different from control value ($p < 0.05$).

**Significantly different from control value ($p < 0.01$).

TABLE 4. Summary of Reproduction Data of Rats Exposed to Methyl Bromide Vapor

	Dose Level (ppm)	No. Cohabited	Copulated No.	Copulated %[a]	Pregnant No.	Pregnant %[b]	Delivering No.	Delivering %[c]
F_0 Females	0	25	24	96	22	92	22	100
F_{1a} Interval	3	25	25	100	24	96	24	100
	30	25	25	100	22	88	22	100
	90	25	24	96	22	92	22	100
F_{1b} Interval	0	22	22	100	22	100	20	91
	3	24	24	100	24	100	24	100
	30	22	22	100	19	86	19	100
	90	22	22	100	21	95	21	100
F_1 Females								
F_{2a} Interval	0	25	24	96	23	96	23	100
	3	25	25	100	22	88	22	100
	30	25	24	96	22	92	21	95
	90	25	25	100	23	92	21	91
F_{2b} Interval	0	23	22	96	20	91	19	95
	3	22	22	100	19	86	19	100
	30	22	20	91	14	70	14	100
	90	23	22	96	15	68	15	100

[a](No. copulated/No. cohabited) x 100.

[b](No. pregnant/No. copulated) x 100. Corresponds to "fertility index" in the study report.

[c](No. delivering/No. pregnant) x 100. Corresponds to "gestation index" in the study report.

TABLE 5. Mean Litter Population Data of Rats Exposed to Methyl Bromide Vapor

	Dose Level (ppm)	No. Live Pups			Percent Survival[a]	
		Birth	Day 4	Day 28	Birth-Day 4	Days 4-28
F_{1a} Litters	0	13.6	13.4	7.6	99	95
	3	13.1	12.9	7.1	94	92
	30	13.4	13.4	7.6	100	95
	90	14.0	13.7	8.0	98	100
F_{1b} Litters	0	14.0	13.7	7.2	98	91
	3	13.8	13.5	7.4	98	94
	30	13.7	13.5	7.6	99	97
	90	13.2	13.1	6.3	99	79
F_{2a} Litters	0	12.0	11.9	7.9	100	98
	3	12.1	12.0	7.3	100	92
	30	12.4	11.5	6.4	92	84
	90	10.9	10.7	6.3	98	82
F_{2b} Litters	0	11.8	11.6	7.9	99	99
	3	12.6	12.6	7.9	100	99
	30	11.5	11.4	7.6	99	99
	90	11.5	11.0	7.5	96	101[b]

[a] Litter-based survival data are presented by the study authors in the statistical summaries of the report appendices.

[b] Reviewers' calculations indicate 98.

TABLE 6. Mean Pup Weights (g) Per Litter[a] of Rats Exposed to Methyl Bromide Vapor

	Dose Level (ppm)	Lactation Day 0	4	21
F_{1a} Litters	0	6.1	9.6	38
	3	6.2	9.4	37
	30	6.2	9.3	34*
	90	6.0	9.3	34*
F_{1b} Litters	0	6.2	9.4	39
	3	6.4	9.9	39
	30	6.3	9.7	36
	90	6.5	9.8	35
F_{2a} Litters	0	5.7	8.2	35
	3	6.2*	8.4	36
	30	5.6	7.8	31**
	90	5.6	7.6	29**
F_{2b} Litters	0	6.5	10.2	40
	3	6.7	10.0	40
	30	6.3	9.5	32**
	90	6.4	9.5	32**

[a] Litter-based pup weight data are presented by the study authors as "mean litter body weight values" in the statistical summaries of the report appendices.

*Significantly different from control value ($p < 0.05$).

**Significantly different from control value ($p < 0.01$).

F_0 females during the first week of the study at 3, 30, and 90 ppm. They also noted reduced absolute brain weights, increased relative liver weights, and increased heart:brain weight ratios in parental animals at 90 ppm. Observations noted in progeny were decreased pup weights, absolute liver weights, and liver:brain weight ratios at 30 and 90 ppm and decreased absolute brain, heart, and kidney weights at 90 ppm.

B. A quality assurance statement was signed and dated February 19, 1986.

14. REVIEWERS' DISCUSSION AND INTERPRETATION OF STUDY RESULTS:

A. Test Material Exposure Data: Our review of the exposure procedures and of the daily data from chamber concentration analyses indicates that the exposure methods and concentrations in this study were acceptable.

Experimental Design: Exposure was interrupted from GD 21 through lactation day 4, as well as on weekends. Although this design is different from that generally followed in non-inhalation protocols, we regard this procedure to be appropriate for inhalation studies. Separating the neonates from their dam in order that the dam be exposed would excessively disrupt maternal care of the litter and possibly lead to cannibalism or neonatal mortality which would mask effects of the compound.

After 'a' litter intervals, infertile animals were killed "in an attempt to determine the possible reason for their apparent infertility." This provided more complete data for 'a' matings since subsequent mating and conception would have precluded detection of fully resorbed 'a' litters. Although the reduced numbers of animals available for breeding may have slightly reduced the sensitivity of data from 'b' matings, there were relatively few infertile animals after the first matings and they were evenly distributed among all groups. We therefore assess that it is unlikely that this procedure introduced bias into the study or altered the interpretation of the results.

Parental Data: Deaths occurred in low frequency and were only observed in females of the F_0 generation. Necropsy findings did not indicate compound effects. We also do not consider the antemortem observations or necropsy findings of the surviving animals to be indicative of compound toxicity.

We attribute the increased relative liver weights and decreased absolute brain weights of F_0 high-dose adults to the compound-related body weight reductions of these animals. We do not regard the other changes in organ weight data to indicate overt toxicity; however, the biological meaning of these findings is unclear.

We regard the significantly reduced body weights of males and the nonsignificantly reduced weights of females in the F_0 generation (Table 1) to be indicative of parental toxicity at 90 ppm. The significantly reduced F_1 maternal weights noted for the high-dose group during the F_{2a} gestation and lactation periods (Table 2) may have been related to slightly reduced litter sizes rather than parental toxicity; maternal weights of these dams in the F_{2b} interval were comparable to controls.

We consider the significantly reduced food intake of the F_0 females from all groups dosed with the test material during the first week of the study (Table 3) to indicate a transient effect of compound inhalation. However, we do not consider this finding to be indicative of frank toxicity since these animals apparently adapted to the exposures--subsequent food consumption values were comparable to controls.

Reproductive and Developmental Data: We regard the slightly decreased pregnancy rates in the F_{2b} interval (Table 4) to indicate reproductive toxicity at 30 and 90 ppm.

We consider the reduced pup weights seen in late lactation (Table 6) to indicate consistent developmental toxicity in all four litter intervals at 30 and 90 ppm. In addition, slight, but nonsignificant, reductions in survival of the F_{1b} and F_{2a} progeny (Table 5) also suggested developmental toxicity at 90 ppm.

The incidences of runts and pups with hematomas, malformations, or other antemortem or postmortem observations did not indicate a compound-related effect. We attribute reductions in absolute organ weights in mid- and high-dose F_{2b} female weanlings to the reduced body weights of these animals; relative organ weights were comparable for all groups.

B. All differences in interpretation between the reviewers and the study authors were minor. We assess that the NOELs and LOELs set by the authors' interpretations are appropriate. Unlike the study authors, we consider the reduced F_{2b} pregnancy rates at 30 and 90 ppm and reduced F_{1b} and F_{2a} pup survival at 90 ppm to be below expected ranges and, therefore, compound related.

Although we generally concur with the authors on the remaining data, they did not discuss the toxicological meaning of the reduced food consumption during the first week of the study, reduced maternal body weights, or differences in organ weight data.

C. We noted a deficiency regarding the food consumption data in the study report. Food consumption was reportedly determined for 8

weeks prior to breeding in the F_0 generation; however, data for 9 weeks are presented in the individual data and Table 6 of the study report.

Item 15--see footnote 1.

16. CBI APPENDIX: Appendix A, Materials and Methods, CBI pp. 6-22.

APPENDIX A

Materials and Methods

Methyl bromide toxicology review

Page _____ is not included in this copy.

Pages 21 through 37 are not included in this copy.

The material not included contains the following type of information:

___ Identity of product inert ingredients

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___ Description of the product manufacturing process

___ Description of product quality control procedures

___ Identity of the source of product ingredients

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The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.