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

MAY 5 1992

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM Expidite

SUBJECT: ID No. 053201. Methyl Bromide, technical. Validation of developmental toxicity study of methyl bromide in rats (US NIOSH report).

Tox. Chem. No.:	555
PC No.:	053201
Barcode Nos.:	D177199
	D177253
Submission No.:	S416426

FROM: Linnea J. Hansen, Ph.D. Linnea J. Hansen 4-29-92
Section IV, Tox. Branch I
Health Effects Division (H7509C)

TO: Larry Schnaubelt, Manager, PM Team 72
Don Mackey, Reviewer, PM Team 72
Special Review and Reregistration Division (H7508W)

THRU: Marion P. Copley, D.V.M., D.A.B.T., Section Head
Section IV, Tox. Branch I
Health Effects Division (H7509C) Marion Copley 5/30/92 KB 6/3/92

CONCLUSIONS:

The rat developmental toxicity study of methyl bromide (NIOSH study) was found to be acceptable and the conclusions of the original review valid. The DER for this study, along with the original review, is attached to this memo.

Reports on the carcinogenic effects of methyl bromide in rat forestomach and on intracellular penetration of bromide as a feature in toxicity of alkyl bromides were received and will be evaluated at a later time.

TB-I agreed with the original review of the developmental toxicity study that methyl bromide was not a developmental toxicant or teratogen in pregnant Wistar rats at doses of 20 and 70 ppm (19 and 65 mg/kg/day) administered by inhalation during Days 1 - 19 of gestation. TB-I also agreed that no significant maternal toxicity was observed at 70 ppm but unlike the original review, considered a slight increase in the incidence and severity of interstitial

nephritis compared to controls (6/8 vs 4/8 animals affected) to be treatment-related.

Dams treated with 70 ppm methyl bromide for 3 weeks prior to mating and during Days 1 - 19 of gestation showed a slight but statistically significant decrease in maternal body weight and an increased incidence of interstitial nephritis (8/8 animals affected). Dams treated with 70 ppm methyl bromide for 3 weeks prior to mating also showed increased incidence of interstitial nephritis (8/8). The NOEL for maternal and developmental toxicity (gestational exposure only) was $\geq$ 70 ppm but an LEL could not be determined.

Classification: Core-Minimum (acceptable for regulatory purposes).

ACTION REQUESTED:

A review of a US NIOSH developmental toxicity study of methyl bromide in Wistar rats (NIOSH Publication No. 81-124) and validation of the original review of this study (non-HED; in "Assessment of the Reproductive and Developmental Toxicity of Carbon Disulfide, Carbon Tetrachloride, Ethylene Dichloride, Methylene Chloride and Methyl Bromide", prepared by the Reproductive Effects Assessment Group; memo from Gary L. Kimmel to Amy Rispin dated January 11, 1985) was requested from TB-I. This information is used to support reregistration of methyl bromide.

DISCUSSION:

Maternal and developmental NOEL and LEL for methyl bromide in rats were set based only on the data from dams treated during gestation as per Guidelines for developmental toxicity studies. Data on pregestational and pregestational plus gestational exposure was valuable for determining the adequacy of dosing.

Since the incidence/severity of interstitial nephritis increased with dose and/or with duration of dosing and affected all animals treated at 70 ppm both before and during gestation, TB-I considered this effect to be treatment-related. Although the effect at 70 ppm was not significant enough for setting the LEL, it was considered a possible threshold effect since the longer exposures at 70 ppm resulted in apparent maternal toxicity. The high dose of 70 ppm was therefore believed to approach the LEL and the study was classified as Minimum and acceptable for regulatory purposes. The original review did not consider the incidence of interstitial nephritis to be treatment-related but was otherwise in accord with this review.

GUIDELINE: 83-3

Primary Review: Linnea J. Hansen, Ph.D.
Review Section IV, Tox. Branch I
Secondary Review: Marion P. Copley, D.V.M., D.A.B.T.
Review Section IV, Tox. Branch I

Linnea J. Hansen 4-29-92
Marion Copley 4/29/92

DATA EVALUATION RECORD

STUDY TYPE: Teratology-Developmental Toxicity
Species: Rat
Guideline: 83-3 (a)

TOX. CHEM. NO.: 555 PC NO.: 053201

TEST MATERIAL: Methyl bromide, technical

SYNONYMS: Bromomethane, Brom-O-Gas®, Celfume®, Dowfume®, Meth-O-Gas®, Terr-O-Gas®; CAS No. 74-83-9

SPONSOR: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, Experimental Toxicology Branch, Cincinnati, OH

STUDY NUMBER: Contract No. 210-78-0025

TESTING FACILITY: Battelle, Pacific Northwest Laboratory, Richland, WA

TITLE OF REPORT: Teratologic Assessment of Butylene Oxide, Styrene Oxide and Methyl Bromide

AUTHORS: Melvin R. Sikov, William C. Cannon, Daniel B. Carr, Rodney A. Miller, Linda F. Montgomery, Daniel W. Phelps

REPORT ISSUED: July, 1981

BIBLIGRAPHIC CITATION: NIOSH Technical Report, NIOSH Publication No. 81-124

CONCLUSIONS:

Doses tested: 0, 20 and 70 ppm (0, 19 and 65 mg/kg/day) administered via inhalation to female Wistar rats, (1) during entire gestation period (Days 1 - 19) only, (2) for 3 weeks prior to mating AND (3) for 3 weeks prior to mating plus entire gestation period; exposure for 7 hr/day, 5 days/week.

Maternal NOEL (gestational exposure only): $\geq$ 70 ppm. LEL: > 70 ppm. Slightly increased incidence/severity of interstitial nephritis at 70 ppm may represent threshold effect.

At pregestational/gestational exposure of 70 ppm, slight decrease in maternal weight (statistically significant) and increased incidence/severity of interstitial nephritis were observed. At 70 ppm pregestational exposure only, increased incidence/severity of interstitial nephritis was observed.

Developmental NOEL (gestational exposure only): $\geq$ 70 ppm. LEL: > 70 ppm. No evidence of fetal toxicity/ teratogenicity was observed at any treatment level.

TB-I agrees in general with the conclusions of the original review of this study but believes that the increased incidence/severity of interstitial nephritis at pregestational and pregestational/gestational exposure to 70 ppm represented a possible treatment-related effect. Although an LEL cannot be determined for maternal effects, the study is considered Minimum and acceptable for regulatory purposes based on the probability that gestational exposure to 70 ppm may have caused threshold renal toxicity and therefore approached an LEL.

NOTE: Only the data on treatment of rats with methyl bromide is evaluated in this review. Treatment of rabbits with methyl bromide is not reviewed here because the study was previously considered unacceptable due to high mortality at high dose. Teratologic assessments of butylene oxide and styrene oxide are also not reviewed.

Core Classification: Minimum

A signed Quality Assurance Statement was not present (study was not submitted to EPA as part of reregistration).

A. VALIDATION OF REVIEW:

This DER is intended to validate and to supplement details of a previous review of this study (non-HED; in Reproductive Effects Assessment Group's "Assessment of Reproductive and Developmental Toxicity of Carbon Disulfide, Carbon Tetrachloride, Ethylene Dichloride, Methylene Chloride and Methyl Bromide"; memo from Gary L. Kimmel, REAG, to Amy Rispin, Science Integration Staff, HED; dated January 11, 1985). The study was evaluated here according to the Guidelines for developmental toxicity studies (83-3) and the report prepared in the standard manner. A copy of the original review is appended to this document (Appendix 1).

B. MATERIALS

Test Compound:	Purity:	99.5%
	Description:	gas
	Lot No.:	Cylinder Nos. B02777, B02778, Matheson Gas Products
	Contaminant:	Not described

Test Animal:	Species:	Rat
	Strain:	Wistar
	Source:	Hilltop Lab Animals, Inc., Scottdale, PA
	Age:	4 - 5 weeks, females; 8 weeks, males (at receipt)
	Weight:	100 - 125 g, females; 300 - 324 g, males

C. STUDY DESIGN

This study was designed to assess the developmental toxicity potential of methyl bromide when administered by inhalation to female Wistar rats on gestation days 1 through 19, inclusive, with/without 3 weeks of pregestational exposure.

Group Arrangement:

Female rats were assigned to the following treatment groups:

TABLE 1: ASSIGNMENT OF ANIMALS

Test Group	Dose Level (ppm)	Number Assigned (pregnant)
Control	0/0[1]	42
Air/Low	0/20	40
Air/High	0/70	40
Low/Air	20/0	38
Low/Low	20/20	40
High/Air	70/0	39
High/High	70/70	40

1 pregestation exposure/gestation exposure

D. METHODS

Mating:

Animals were acclimated at least 10 days prior to initiation of experiments. Females were caged with males 2:1 on the Monday following completion of the pregestational exposure period. Females in which sperm were detected on the next day were randomly assigned to gestational exposure groups (Day 1 of gestation). Females were then placed in individual cages within the exposure chambers. Matings were continued for a total of 7 - 9 days until enough positive females were assigned to each treatment group. Food (Wayne Lab-Blox) and tap water were supplied ad libitum throughout the study except during each 7 hr exposure period.

Dosing:

Rationale for Dosing: Previous testing of methyl bromide in

rats showed that 6 months exposure (7 hrs/day, 5 days/week) to 66 ppm was tolerated and that exposure to 100 ppm produced severe pneumonia in some rats but no effects in others. A preliminary range-finding developmental toxicity study was not performed for this study.

Administration of Compound: Animals were exposed to the test compound in custom-built stainless steel chambers (described in Moss et al, 1980, Am. Ind. Hyg. Assoc. J., submitted at time of this study for publication). Total volume was 2.3m^3 (1.7 m^3 animal volume) and up to 192 rats could be accomodated at one time. After introduction of aerosol uranine dye (1 μm diameter) equilibrium was reached in 15-20 min and 3-5% variation of concentration above the six catch pans was observed. Separate chambers were used: one each for control, low and high dose treatments.

Air flow through HEPA filters was supplied continuously to the exposure chambers at 10 cfm (7 changes/hr) and methyl bromide was introduced via filtered air streams to give the appropriate concentration.

For each chamber, a methyl bromide gas bottle (13 psig) was attached to a manual control valve, shut-off valve, double pattern metering valve and flow meter. Gas was mixed with 2 liters air/minute and conducted to top of each chamber in 1/4" stainless steel tubing. The mixture was introduced downstream of the inlet HEPA filter at the top of the chamber. A transvector pump with flow and pressure monitors was used to exhaust the chambers into the building exhaust. Methyl bromide degraded seals in valves during the study.

A photoionization detector with an 8-port stream selection valve was used to monitor methyl bromide in each chamber. Standards were prepared by serial dilutions of pure gas. Samples were drawn from the one of the 8 sample lines every 5 minutes and ppm per sample were determined. Methyl bromide coated the UV lamp during the study and monitors had to be calibrated every few days. Concentration of methyl bromide was monitored at least 4 times (usually 12 or more times) per day, and adjustments were made when necessary.

Time-weighted average concentrations were 19.6 $\pm$ 0.9 and 68.5 $\pm$ 1.7 ppm for pregestational rat exposures and 20.0 $\pm$ 1.5 and 68.8 $\pm$ 1.9 ppm for gestational exposures.

Observations:

Animals were checked for mortality or abnormal condition throughout the study. Dams were sacrificed on Day 21 of gestation. Examinations at sacrifice by CO_2 consisted of: examination for gross abnormalities of internal organs,

weighing of liver, lung and kidneys, examination of uteri and ovaries (corpora lutea, implantation sites and resorptions determined), preservation of ovaries, uterus, liver, lungs with trachea and kidneys in 10% neutral buf-fered formalin and histological examination of 25% of all dams.

Fetuses were examined in the following manner: uteri were opened and fetuses were identified as live or dead. Each fetus was weighed, sexed and crown-rump length measured. Fetuses were examined under a stereomicroscope for external abnormalities and randomly assigned to two groups: (1) heads were removed and fixed in Bouin's fluid for sectioning (Wilson, 1965, Teratology Principles and Techniques, U. of Chicago Press) and examined for internal abnormalities, or (2) eviscerated, fixed in alcohol and stained with Alizarin Red S for skeletal examination (Dawson, 1926, Stain Tech. 1:123) under low power magnification (remaining skeletons from group 1 also examined).

Historical control data were not provided to allow comparison with concurrent controls.

Statistical analysis:

The following statistical analysis methods were employed: ANOVA was performed on continuous data using the "Statistical Package for the Social Sciences" software. Where the test for equal variance indicated significant differences, Dunnett's test was performed. For variances that were not significantly different, pooled mean square error was calculated using ANOVA and Dunnett's procedure for equal variances was then applied. Differences between proportions for maternal and fetal data were tested using Fisher's Exact Probability Test and Bonferroni's method adjusted for multiple comparisons against a control group.

Orthogonal polynomial equations were used along with multivariate analysis of variance to identify differences data where missing observations were present among exposure groups. The Randomization Test using t criterion (Edgington) was used to evaluate food consumption values.

E. RESULTS

The results of this study are summarized in the previous evaluation. Additional details are added below.

Maternal Toxicity

Mortality:

No mortality occurred among rats in any of the treatment

groups.

Clinical Observations:

No clinical observations of significance were reported by the study authors.

Body Weight:

Mean maternal body weights during pregestational and gestational periods are presented below in Table 2:

TABLE 2: MEAN MATERNAL BODY WEIGHTS[1]

Days of Exposure	Exposure Level (ppm)		
Pre-gestation	0	20	70
Pre-exposure[2]	157	157	157*
1	171	174	179*
3	177	181*	186*
8	194	201*	204*
10	200	205*	207*
15	209	216*	217*
17	220	220	220

Gestation	0	0/20	0/70	20/0	70/0	20/20	70/70
1	239	239	237	247	240	237	230*
7	269	270	266*	273	268	258	257*
14	303	303	292*	303	307	295	290*
21	372	366	359	376	384	377	368

1 Data taken from Tables 4 and 5 of study
2 Weights determined at time of randomization
* $p < 0.05$

Statistically significant but small (~3.5%) decreases in mean body weight were observed only in the high/high dose group between Days 1 - 14 of gestation. These mean body weights were low primarily because of decreased weight gain that occurred between Days 17 - 21 of pre-gestational treatment; weight gain as % of gestation Day 1 weight was similar to that of controls during gestation. Small but statistically significant increases in body weight in low/low and high/high pregestational treatment groups were not considered treatment-related. Dams treated at high dose only during gestation showed a small, statistically significant decrease in body weight at Day 14 of gestation and a non-statistically significant decrease at termination.

TB-I agrees with the original review that a marginal decrease in maternal body weight was observed at the high/high dose only and not in animals treated only during

gestation.

Food Consumption:

There were no significant differences in food consumption among any of the treatment groups before or during gestation. TB-I does not agree with the original review that the high/high dose dams had slightly increased food consumption. Food consumption data for high/high and air/high animals was not distinguished in the study tables.

Gross and Histological Pathological Observations:

Liver, kidney, lung and placental weights were not affected by administration of methyl bromide. Lung histopathology is described in the original report.

The incidence of interstitial nephritis among treatment groups is presented below in Table 3:

TABLE 3: INCIDENCE OF INTERSTITIAL NEPHRITIS IN DAMS[1]

Dose, ppm:	# Animals affected/total # animals
Pregestational exp.:	
0	4/8 (0.5)[2]
20	5/8 (0.6)
70	8/8 (1.0)
Gestational exp.:	
20	4/8 (0.5)
70	6/8 (0.8)
Pregest./Gest. exp.:	
20/20	6/8 (0.8)
70/70	8/8 (1.0)

1 Data taken from Table 14 of study
2 Value in parentheses is mean severity of all rats examined, scale of 1 to 4; 1 = slight to 4 = severe

The incidence and overall severity of interstitial nephritis was increased relative to controls in animals treated at 70 ppm prior to gestation and prior to/during gestation (100%, mean severity = 1 vs. 50%, mean severity = 0.5). Incidences among animals treated at 70 ppm only during gestation and animals treated at 20 ppm before and after gestation showed intermediate increases relative to controls (80%, vs 50%). No individual animal data was available. Single incidences

of hydronephrosis in all dose groups treated at 70 ppm (1/8; 2/8 for 0/70 animals; all slight) were probably not treatment-related.

TB-I disagrees with the original review that the incidence of interstitial nephritis at 70 ppm pregestational/ gestational exposure was not treatment-related. However, the increased incidence at 70 ppm gestational exposure is not considered significant enough to determine an LEL but is considered a possible threshold effect.

Cesarean Section Observations:

No differences were observed among any of the cesarean parameters for any treatment group (Table from study included in Appendix 2).

2. Developmental Toxicity

No significant differences were noted between controls and treatment groups for fetal external, soft tissues or skeletal findings. A few bones showed slight increases in delayed ossification at higher doses and are shown below in Table 4:

TABLE 4: SKELETAL EXAMINATIONS[1]

	Dose, ppm, pregestational/gestational						
Finding	0/0	0/20	0/70	20/0	20/20	70/0	70/70
# Fetuses	426	378	461	432	483	464	464
# Litters	37	31	36	34	38	36	36
Ossific. defects:							
Supraoccipital	1/1[2] (2.7)	2/2 (6.5)	10/7 (19.4)	4/4 (11.8)	2/2 (5.3)	0/0 (0.0)	20/7 (19.4)
Interparietal	6/5 (13.5)	13/9 (29.0)	9/7 (19.4)	5/5 (14.7)	9/8 (21.1)	5/5 (13.9)	20/14 (38.9)

1 Data taken from Table 32 of study
2 # fetuses/# litter affected (% litters affected)

Slight increases in delayed ossification of the supraoccipital and interparietal bones was noted in animals treated with high dose before and during gestation. TB-I agrees with the original review that these increases were not statistically significant and probably not treatment-related.

F. DISCUSSION/CONCLUSIONS

From this study it can be concluded that methyl bromide did

not produce significant fetal toxicity at doses up to 70 ppm. Slight maternal toxicity (slightly decreased maternal body weight, increased incidence of interstitial nephritis) was noted only among dams treated both before and during gestation, not among those treated only during gestation.

Since there appeared to be a correlation between the dose/length of exposure time and the incidence/severity of interstitial nephritis, TB-I believes that this effect may have been treatment-related. The increase over controls observed in the 70 ppm gestational exposure group was considered a possible threshold response, based on the greater increase at 70 ppm pregestational/gestational exposure and at 70 ppm pregestational exposure. This effect was not significant enough to determine an LEL for maternal toxicity at 70 ppm gestational exposure, but appeared to approach an LEL; therefore the study was classified as Minimum.

Study Deficiencies: No individual animal data and no historical control data was included, NOEL and LEL could not be determined using the data from rats treated only during gestation, developmental range-finding study not performed.

Core Classification: Core Minimum Data.

Taken from:
"Assessment of the Reproductive and Developmental Toxicity of Carbon Disulfide, Carbon Tetrachloride, Ethyl Dichloride, Methylene Chloride and Methyl Bromide", prepared by the Reproductive Effects Assessment Group; Final draft from Gary L. Kimmel to Amy Rispin with memo dated January 11, 1985.

APPENDIX 1

6. DEVELOPMENTAL EFFECTS OF METHYL BROMIDE
Prepared by Carol Sakai, Ph.D.

6.1 Developmental Toxicity

Only one study has been conducted on the teratogenic potential of methyl bromide. This study has been published in full (Sikov et al., 1981), and in summarized form (Hardin et al., 1981). This study was conducted for the National Institute of Occupational Safety and Health by Battelle Pacific Northwest Laboratory. Methyl bromide was one of three chemicals evaluated additional to butylene oxide and styene oxide.

Female Wistar rats and New Zealand white rabbits were exposed to methyl bromide (99.5% minimum purity) by inhalation (7 hrs/day). The rats were divided into six exposure groups and one control group; air-low (filtered air given for 3 weeks pregestationally, 20 ppm methyl bromide given on days 1-19 of gestation), air-high (filtered air given for 3 weeks pregestationally, 70 ppm methyl bromide given on days 1-19 of gestation), low-air (20 ppm methyl bromide given for 3 weeks pregestationally, filtered air given on days 1-19 of gestation), low-low (20 ppm methyl bromide given for 3 weeks pregestationally, 20 ppm methyl bromide given on days 1-19 of gestation), high-air (70 ppm methyl bromide given for 3 week pregestationally, filtered air given on days 1-19 of gestation), high-high, (70 ppm methyl bromide given for 3 weeks pregestationally, 70 ppm given on days 1-19 of gestation), control (filtered air 3 week pregestationally, filtered air on days 1-19 of gestation). Twenty-eight to thirty-six rats were used per group. Rabbits were divided into two exposure groups and one control group; low (20 ppm methyl bromide given on days 1-24 of gestation), and high (70 ppm methyl bromide given on days 1-24 of gestation) and control (filtered air on days 1-24 of gestation. Seventeen and thirteen does were in the low and high groups, respectively.

All pregnant animals animals were sacrificed on the day before term (day 21 for rats, day 30 for rabbits) and the uterine contents examined. Individual fetuses were weighed, measured for crown-rump length, sexed and examined for externally visible malformations. One-half to two-thirds of each litter was preserved in Bouin's fluid for internal examination by the Wilson method of free-hand razor blade sectioning, and the balance of each litter was preserved in ethanol for clearing and skeletal staining with alizarin red. The internal organs of the maternal rats were examined grossly, and the brain, heart, lungs, liver, spleen, kidneys, adrenals and ovaries were weighed and then preserved in 10% formalin for histopathological examination.

In the rats, maternal body weights in the high-high group were significantly decreased as compared to control animals in most periods of gestation. This effect was also reflected in reduced food intake observed in the high-high group. No effect was seen on liver or other organ weights except for a pulmonary infection (diagnosed as Corynebacterium kutcheri) in a few animals that were not used in the final calculations. No effect was seen on endpoints related to pregnancy or effects on the conceptus. Sporadic increases in unossified sternebrae were reported, however these were not dose-related.

In rabbits, after 1 week of exposure to the high (70 ppm) dose of methyl bromide, the animals showed signs of generalized distress which worsened until convulsions and hind-limb paresis occurred. Because of this toxic response, the treatment was terminated in all groups on day 15. At the time of scheduled sacrifice on day 30 of gestation, only 1 out of 25 rabbits was still alive in this group. In the low (20 ppm) group, a toxic effect was not observed and there were no treatment-related effects on maternal body or organ weights. No effect was reported on endpoints related to pregnancy in the low (20 ppm) group, and no adverse effect was observed in the fetal endpoints in this group.

In summary, only one study could be found that evaluated the teratogenic potential of methyl bromide. In this study (Sikov et al., 1981), both rats and rabbits were evaluated. No adverse effects were observed in maternal or fetal rats. In the rabbits, severe toxicity was observed in the does which had been exposed to 70 ppm, with almost all the animals dying by the time of sacrifice (day 30). No adverse effect was observed on the fetas in the low dose (20 ppm) group.

From this study, it appears that methyl bromide is not overtly toxic to the fetus even at doses which were toxic to the maternal animal. However, since this is the only study which has been conducted on this chemical, this conclusion is made tentatively and needs confirmation to strengthen confidence in these results.

6.2 References

Hardin, B.D., G.P. Bond, M.R. Sikov, F.D. Andrew, R.P. Beliles, and R.W. Niemeier. 1981. Testing of selected workplace chemicals for teratogenic potential. Scand. J. Work Environ. Health 7:suppl 4, 66-75.

Sikov, M.R., W.C. Cannon, D.B. Carr, R.A. Miller, L.F. Montgomery, and D.W. Phelps. 1981. Teratogenic assessment of butylene oxide, styrene oxide and methyl bromide. DHHSC (NIOSH) Publication No. 81-124.

APPENDIX 2

TABLE 24. Fecundity, Embryotoxicity and Fetal Viability in Pregnant Rats Exposed Pregestationally and Gestationally to Methyl Bromide and/or Filtered Air. Results are expressed as mean ± S.D., except as noted.

Measure	Pregestational-Gestational Exposure Level						
	Air-Air	Air-Low	Air-High	Low-Air	Low-Low	High-Air	High-High
Number of Litters	37	31	36	34	38	36	36
Corpora Lutea/Dam	14.9 ± 2.7	14.0 ± 2.3	15.0 ± 2.8	14.9 ± 2.6	16.4 ± 3.4	14.5 ± 2.6	14.8 ± 2.8
Number of Implants/Litter	12.2 ± 3.0	12.7 ± 2.1	12.9 ± 1.6	13.3 ± 2.3	13.4 ± 3.0	13.3 ± 2.1	13.2 ± 2.3
Implants/Corpus Luteum	0.83 ± 0.22	0.93 ± 0.18	0.88 ± 0.14	0.90 ± 0.14	0.83 ± 0.19	0.92 ± 0.11	0.90 ± 0.14
Number of Live Fetuses	427	379	456	430	484	466	466
Number of Dead Fetuses	1	0	0	1	0	0	0
Number of Resorptions	24	16	8	20	25	12	8
Live Fetuses/Litter	11.5 ± 3.2	12.2 ± 2.4	12.8 ± 1.6	12.7 ± 2.2	12.7 ± 2.8	12.9 ± 2.1	12.9 ± 2.4
Dead Fetuses/Litter	0.03 ± 0.16	0.0	0.0	0.03 ± 0.17	0.0	0.0	0.0
Resorptions/Litter	0.65 ± 1.4	0.52 ± 0.93	0.22 ± 0.42	0.56 ± 0.75	0.63 ± 1.2	0.33 ± 0.54	0.22 ± 0.54
% Early*	3.8	2.8	1.1	3.1	3.0	1.7	1.3
% Mid*	1.5	1.3	0.43	0.89	1.6	0.63	0.43
% Late*	0.0	0.0	0.22	0.22	0.20	0.0	0.0
Total %	5.3	4.1	1.8	4.2	4.8	2.3	1.7
Number of Litters with Resorptions	14	10	8	14	13	11	6
% Litters with Resorptions	37.8	32.3	22.2	41.2	34.2	30.6	16.7
Resorptions/Litters with Resorptions	1.7 ± 1.9	1.6 ± 1.0	1.0 ± 0.0	1.4 ± 0.50	1.9 ± 1.4	1.1 ± 0.30	1.3 ± 0.52

* Calculated as percent of total implants.

v Denotes statistically significant ($P \leq 0.05$) differences in group variances for indicated measure.