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

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MAR 24 1994

MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: Chloropicrin (CP): Submissions: Rat Developmental Study (MRID 42740602) and Rabbit Developmental Study (MRID 42740601). BC# D193220.
Chemical ID #081501
Chemical No. 214

TO: Larry Schnaubelt/Susan Jennings (PM 72)
Reregistration Review Branch
Registration Division (H7508W)

FROM: Stanley B. Gross, PhD, DABT, CIH
Toxicologist/Hygienist
Toxicology Branch I
Health Effects Division (H7509C)

12/10/93

THRU: Joycelyn E. Stewart, PhD
Head, Section II, Toxicology Branch I
Health Effects Division (H7509C)

3/21/94

THRU: Karl P. Baetcke, PhD
Chief, Toxicology Branch I
Health Effects Division (H7509C)

3/22/94

A. SUBMISSIONS FOR REVIEW:

1) Inhalation Developmental Toxicity Study in Rats. International Research and Development Corporation report dated 4/9/93. (MRID 42740602). GLN 83-3a
2) Inhalation Developmental Toxicity Study in New Zealand Rabbits. International Research and Development Corporation report dated 4/9/93. (MRID 42740601). GLN 83-3b

B. CONCLUSIONS.

1. RAT DEVELOPMENTAL STUDY:

Pregnant female rats (30/sex/group) were exposed in inhalation chambers to concentrations of 0.0, 0.4, 1.2 and 3.5 ppm CP, 6 hours per day during gestation days 6 through 15. Four mortalities, clinical signs of dyspnea, nasal staining, decreased activity and emaciation were seen in the 3.5 ppm group. There was an increase in total numbers of developmental variations (primarily unossified sternebrae); however, when the data were evaluated statistically by

Toxicology Branch I, there were no significant differences between the control and treated groups.

Conclusions: Maternal NOEL = 0.4 ppm (LDT); Maternal LOEL = 1.2 ppm based on mortality, decreased BW and FC and signs consistent with CP toxicity. Developmental Toxicity NOEL = 1.2 ppm and LEL = 3.5 ppm based on decreased pup body weights.

Core Classification: Core Minimum study. No flagging trigger found.

2. RABBIT DEVELOPMENTAL STUDY:

Pregnant rabbits (20/sex/group) were exposed in inhalation chambers to concentrations of 0.0, 0.4, 1.2 and 2.0 ppm CP 6 hours per day during gestation days 7 through 29. Two mortalities in the from the 1.2 ppm group and 10 mortalities from the 2.0 ppm group were observed. The deaths were due primarily to pulmonary edema. Dose related toxic signs in all of the treated animal groups included included dyspnea, nasal staining, decreased activity and emaciation, yellow anogenital staining and salivation. One dam from the MDT group and 2 dams from the HDT group aborted. Post dose implantation losses were increased in all treated animals. Fetal weights for both sexes and uterine weights were reduced in the MDT and HDT groups.

Conclusions: Maternal NOEL =0.4 ppm (LDT); Maternal LOEL =1.2 ppm based on body weight and food consumption reduction. The HDT level of 2.0 ppm produced mortality, BW reduction and FC reduction as well as toxic signs. Developmental Toxicity NOEL = 0.4 ppm. Developmental Toxicity LEL = 1.2 ppm due to increased abortions and reduced fetal and uterine weights.

Classification: Core Minimum. No flagging trigger found.

cp193220.m3 E-3 3/14/94

Reviewed by: Stanley B. Gross, PhD, DABT, CIH
Section 2, Tox. Branch 1 (H7509C)
Secondary Reviewer: Joycelyn E. Stewart, PhD, Head
Section 2, Toxicology Branch 1, (H7509C)

12/10/93

3/21/94

DATA EVALUATION REPORT

STUDY TYPE: Rat Developmental Study TOX. CHEM. NO.: 214

ACCESSION NUMBER: D193220 MRID NO.: 42740602

TEST MATERIAL: Chlorpicrin

STUDY NUMBER(S): GLN 83-3a

SPONSOR: Chlorpicrin Manufacturing Task Force.

TESTING FACILITY: International Research and Development Corporation, Mattawan, MI. (IRDC)

TITLE OF REPORT: Inhalation Developmental Toxicity Study Rats.

AUTHOR(S): James L. Scharadein, MS, ATS

REPORT ISSUED: April 9, 1993

*A. EXECUTIVE SUMMARY:

Pregnant female rats (30/sex/group) were exposed in inhalation chambers to concentrations of 0.0, 0.4, 1.2 and 3.5 ppm CP, 6 hours per day during gestation days 6 through 15. Four mortalities, clinical signs of dyspnea, nasal staining, decreased activity and emaciation were seen in the 3.5 ppm group. There was an increase in total numbers of developmental variations (primarily unossified sternebrae); however, when the data were evaluated statistically by Toxicology Branch I, there were no significant differences between the control and treated groups.

Conclusions: Maternal NOEL = 0.4 ppm (LDT); Maternal LOEL = 1.2 ppm based on mortality, decreased BW and FC and signs consistent with CP toxicity. Developmental Toxicity NOEL = 1.2 ppm and LEL = 3.5 ppm based on decreased pup body weights.

Core Classification: Core Minimum study. No flagging trigger found.

*B. STUDY DESIGN:

Study Groups. Pregnant Charles River Cr/:CD female rats (30 per group) were assigned to groups as shown in **Table 1.** and exposed in whole body exposure chambers to 0, 0.4, 1.2 and 3.5 ppm, 6 hours/day through gestation days 6 to 15.

TABLE 1: ANIMAL ASSIGNMENT

Test Group	Dose Level (ppm)	Number Assigned
Control	0.0	30
Low Dose (LDT)	0.4	30
Mid Dose (MDT)	1.2	30
High Dose (HDT)	3.5	30

The rat specie was selected because rats provided an acceptable test model and the laboratory had historical control data for comparison.

Dosing Rationale. The rationale for dosing was based on a preliminary developmental toxicity study, IRDC study no. 656-006 "Range-Finding Inhalation Developmental Toxicity Study in Rats". In that study, ten mated Charles River Crl:CD VAF/Plus female rats each in one control and three exposure groups were administered target exposure levels of 0.4, 1.2 and 3.5 ppm of CP by whole-body inhalation exposure daily for 6-hour periods during gestation days 6 through 15. Significant maternal body weight gain differences were observed in the 3.5 ppm test group.

Statistical analysis: All statistical tests were performed by a VAX computer; SAS statistical software, as well as inhouse software. Mean maternal body weights and body weight changes, food consumption, mean numbers of corpora lutea, total implantations, live fetuses, mean fetal body weights and mean crown-rump lengths were compared by analysis of variance, Bartlett's test for homogeneity of variance and the appropriate t-test as described by Steel and Torrie using Dunnett's multiple comparison table or pairwise comparisons with a Bonferroni correction to determine significance of differences.

Male and female sex ratios and proportions of litters with malformations and developmental variations were compared using the Chi-square test with Yeate's correction for 2x2 contingency tables and/or Fisher's exact probability test as described by Siegel to determine the significance of differences. The proportions of resorbed and dead fetuses and postimplantation losses were compared using the Kruskal-Wallis test described by Siegel.

Quality Assurance: A quality assurance statement dated 14/9/93 and signed by Margery J. Wirth was included in the report. A negative flagging statement was also included.

*C. MATERIALS

Test compound: Clear liquid chlorpicrin, greater than 99% pure was obtained from Niklor Chemical Co., Inc., Long Beach California. Lot No. 920130-1 (IRDC No. 10848).

Test animals: Species: Rat. Strain: Sprague-Dawley-derived Charles River Crl:CD VAP/Plus, 147 females obtained from Charles River Laboratories, Portage, MI. Age: 12.5 weeks, weighing 221 to 285 gm at mating time.

*D. EXPOSURE METHODS.

Exposure Chambers. Exposures were carried out using glass/metal chambers, 16 cu.meters in volume. Air was supplied to the chambers by an HVAC filter system (99.9% ≤3μm). The animals were housed individually in cages stacked near the bottom of the chamber. Exhaust air was removed from the around the bottom of the chamber and passed through charcoal filter to remove the remaining CP.

Generation of CP Atmospheres. Pure CP was first diluted in Tedlar gas bags and these dilutions metered (Fluid Metering System) into the chamber inlet over the 6 hour exposure period to achieve the target test concentrations.

Chamber Concentrations Analyses. Preliminary chamber concentration analyses involved triplicate sampling of the chamber at 4 different locations, two at the top (one front and one back) and two at the bottom (one front and one in the back) of the chamber cage location areas. CP concentrations were determined using gas chromatography (GC) with an electron capture detector (ECD) interfaced with a Hewlett-Packard Model 3396 Series II laboratory computer which sampled the chamber concentrations at approximately hourly intervals. CP vapor standard curves were made by devolving 1% CP vapor in hexane at four concentrations to bracket the chamber concentrations.

Chamber Temperature and Humidity. Building air was filtered and metered into the chamber to maintain temperature and humidity conditions. There was no descriptions of the any monitoring devices used to monitor the chamber temperature or humidity.

*E. TREATMENT OF ANIMALS.

Husbandry. Animals were acclimatized for 11 days before being placed on test. When not in exposure chambers, the animals were housed under standardized laboratory conditions in stainless steel, wire mesh cages; temperatures ranging between 65-70°F (mean 70 ± 1.2 °F; humidity ranging between 40% and 72% (mean 56 ±14.8%. The animals were fed Certified Rodent Chow #5002 (Purina Mills, St. Louis, MO. libitum except during the 6 hour chamber exposure period. Water was available ad libitum throughout.

Mating. At the end of the acclimation period, the females were subjected to a detailed physical examination and were then

cohabitated with stock males of the same stock and source used exclusively for this purpose. One female and one male were placed together for mating. Females were inspected daily for a copulatory plug. The day the plug was detected was designated as gestation day 0, and the female was returned to an individual cage, assigned an animal number and identified by an ear tag. Mated females were assigned consecutively in a block design to either a control or to one of three exposure groups consisting of the 30 rats each.

Observations. The pregnant females were checked twice daily for mortality and once daily for abnormal condition during the course of the study. They were weighed prior to the start of the chamber exposures and on days 6, 9, 12, 16 and 20. Food consumption weighings were made on body weighing days and calculated for the following intervals: 0-6, 6-9, 9-12, 12-16, 16-20 and 6-16 and 0-20 days.

Necropsy. Animals which died prior to schedule were euthenized and the maternal tissues were preserved in 10% neutral buffered formalin for future histopathological examination as deemed necessary by the gross findings.

Cesarean Section Examinations. On gestation day 20, all surviving females were euthanized by carbon dioxide inhalation; the uterus and ovaries exposed through abdominal incisions and the pregnancy status determined. The uterus was excised and the gravid uterus was weighed. The location of viable and nonviable fetuses, early and late resorptions and the number of total implantations and corpora luteas were recorded. The abdominal and thoracic cavities and organs of the females were examined for gross morphological changes and the carcasses discarded. Maternal tissues were preserved for possible future histopathological examination. Uteri from females that appeared non-gravid were opened and placed in 10% ammonium sulfide solution for detections of implantations.

Fetal Examinations. Individual fetuses were weighed, sexed, tagged and examined for external malformations and variations. Crow-rump lengths were measured and recorded for all fetuses. Approximately one-half of the fetuses were placed in Bouin's solution for subsequent soft-tissue examination using the Wilson razor-blade sections technique. The remaining one-half of the fetuses were fixed in alcohol, macerated with potassium hydroxide, stained with Alizarin Red S and cleared with glycerin in a method similar to that described by Dawson and examined for skeletal abnormalities.

Historical control data were provided for 33 different studies ranging in time from 2/90 to 7/91.

* F. RESULTS

Exposure Concentrations. The chamber concentrations achieved the targeted concentrations with a 15% variation -- SD's were 0.02, 0.06 and 0.08 ppm for LDT, MDT and HDT groups, respectively.

Maternal Mortality/Toxicity. There were four mortalities in 3.5 ppm test group. Clinical signs in these animals included labored breathing, coldness to touch, red material (blood) around nose; decreased activity and emaciation consistent with severe lung irritation due to the toxicity of CP. No mortality and no CP related clinical signs were reported for other dose groups.

High dose maternal body weight and body weight gains were significantly reduced ($p<0.05$) throughout the dosing period. For mid-dose dams, maternal body weight gain was significantly reduced during early dosing (gestation days 6-9). In addition, for the entire dosing period, dam body weights were 18% lower than controls.

Body Weight.

Table 2: BODY WEIGHT GAINS (GRAMS)

Group:	Prior to Dosing Period	Dosing Period	Post Dosing Period	Entire Gestation Period	Corrected Body Weight Gains Entire P.*
	BW			GAINS	
Control	251	34	58	122	50
LDT	254	39	54	122	53
MDT	251	28	57	115	44
HDT	250	3	64	103*	34*

* Corrected body weight gain for entire gestation period = body weight gain for entire gestation period minus gravid uterus weight.
** Statistically significant from control. weight gain for entire gestation period minus gravid uterus weight.

Food consumption was reduced in both mid and high dose dams. The reduction paralleled the body weight decrements in these groups.

Food Consumption.

Table II: FOOD CONSUMPTION DATA (gm/animal)

Group:	Prior to Dosing Period	Dosing Period	Post-Dosing Period	Entire Gestation Period
Control	20.6	23.7	26.9	23.4
LDT	20.9	24.1	26.2	23.6
MDT	20.1	22.7	25.7	22.6
HDT	20.6	17.0**	25.4	19.6**

** Statistically significant from control ($p<0.01$).

Cesarean Section Observations. These observations are provided in the attached **Table 4** taken from the study report. Biologically significant reductions in mean fetal body weight were observed in the HDT group compared to the control group. Mean fetal body weights in the low- and mid-exposure groups were comparable to controls. No exposure-related differences were observed for other parameters: corpora lutea, total implantations and live and dead fetuses; pre- and post implantation loss, fetal sex distribution and gravid uterine weights.

Fetal Malformations. These observations are summarized in the attached **Table 5** taken from the study report. There were no compound related changes observed. The malformations observed occurred in single or low incidences. Total malformations for fetuses (litters) were 3 (3), 3 (3), 4 (4) and 2 (2) for the control, LDT, MDT and HDT groups, respectively.

Fetal Developmental Variations. These results are summarized in the attached **Table 6** taken from the study report. There was an increase in total number of developmental variations seen in the total number of fetuses (total litters): 49 (19), 47 (17), 75 (26) and 65 (25) for the control, LDT, MDT and HDT groups. The high dose group [65 (25)] was statistically significant at the 0.01 level. The MDT group [75 (26)] appears also to be significant. Although most of the developmental variations presented in Table 6 of the report have low incidence rates, the unossification of the sternebrae #5 and/or #6 were increased for the exposure groups: 29 (13), 33 (14), 56 (23) and 41 (18) for the control, LDT, MDT and HDT groups, respectively. However, when the data were evaluated statistically by Toxicology Branch I, there were no significant differences between the control and treated groups.

*G. DISCUSSION.

Study Design. The study was well designed and reported and met guideline requirements. Pregnancy rates were high at greater than 90% (ranging from 90 to 100%). The HDT group demonstrated definite and severe toxicity. Females that survived exposures to CP had a low abortion rate (1-3), not relatable to CP exposure rates.

Maternal Findings. The HDT and MDT levels reflected decreases in body weights and food consumption and expected toxicity from CP a highly toxic and irritating vapor which produced pulmonary damage. All maternal and fetal reproductive parameters were not adversely effected by the CP exposures.

Developmental Findings. Although the study director concluded that the NOAEL for both maternal systemic toxicity was 0.4 ppm, statistical evaluation by Toxicology Branch by the Chi Square analysis of the developmental variations (unossified sternebrae)

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developmental toxicity is 1.2 ppm based on decreased fetal body weights at 3.5 ppm, the HDT. The LOEL is 3.5 ppm.

Historical Control Comparisons. The range of developmental findings in this study were consistent with those found in the historical control data.

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Subsequent Review

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Reviewed by: Stanley B. Gross, PhD, DABT, CIH
Section 2, Tox. Branch 1 (H7509C)
Secondary Reviewer: Joycelyn E. Stewart, PhD, Head
Section 2, Toxicology Branch 1, (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: Rabbit Developmental Study TOX. CHEM. NO.: 214

ACCESSION NUMBER: D193220 MRID NO.: 42740601

TEST MATERIAL: Chlorpicrin

STUDY NUMBER(S): GLN 83-3b

SPONSOR: Chlorpicrin Manufacturing Task Force.

TESTING FACILITY: International Research and Development Corporation, Mattawan, MI. (IRDC)

TITLE OF REPORT: Inhalation Developmental Toxicity Study in New Zealand Rabbits.

AUTHOR(S): Raymond G. York, PhD.

REPORT ISSUED: April 9, 1993

*A. EXECUTIVE SUMMARY:

Pregnant rabbits (20/sex/group) were exposed in inhalation chambers to concentrations of 0.0, 0.4, 1.2 and 2.0 ppm CP, 6 hours per day during gestation days 7 through 29. Mortalities (two in the from the 1.2 ppp and 10 from the 2.0 ppm groups). Deaths were due primarily to pulmonary edema. Toxic signs included dyspnea, nasal staining, decreased acivity and ematiation, yellow anogenital staining and salivation were dose related. One doe from the MDT group and 2 does from the HDT group aborted. Post dose implantation losses were increased in treated animals. Fetal weights for both sexes and uterine weights were reduced in the MDT and HDT groups.

Conclusions: Maternal NOEL =0.4 ppm (LDT); Maternal LOEL =1.2 ppm based on body weight and food consumption reduction. The HDT level of 2.0 ppm produced mortality, BW reduction and FC reduction as well as toxic signs. Developmental Toxicity NOEL = 0.4 ppm. Developmental Toxicity LEL = 1.2 ppm due to increased abortions and reduced fetal and uterine weights.

Classification: Core Minimum. No flagging trigger found.

*B. MATERIALS

Test compound: Clear liquid chlorpicrin, greater than 99% pure was obtained from Niklor Chemical Co., Inc., Long Beach California. Lot No. 920130-1 (IRDC No. 10848).

Test animals: Species: Rabbits. Strain: New Zealand White. Source: Hazleton Research Products, Kalamazoo, MI. Sexually mature virgin females, approx. 4.5 months of age.

*C. STUDY DESIGN.

This study was designed to assess the developmental toxicity potential of rabbits when administered by inhalation on gestation days 7 through 20, inclusive. Pregnant females were randomly assigned by computer to the following groups:

TABLE 1: ANIMAL ASSIGNMENT

Test Group	Dose Level (mg/kg/day)	Number Assigned
Control	0.0	20
Low Dose (LDT)	0.4	20
Mid Dose (MDT)	1.2	20
High Dose (HDT)	2.0	20

The rabbit species was selected because rabbit provided an acceptable test model and the laboratory had historical control data for comparison.

Dosing Rationale. The rationale for dosing was based on a preliminary developmental toxicity study was performed for dose selection IRDC study no. 656-008 "Range-Finding Inhalation Developmental Toxicity Study in New Zealand Rabbits". In that study, ten mated rabbits each in one control and three exposure groups were administered target exposure levels of 0.4, 1.2 and 3.5 ppm of CP by whole-body inhalation exposure daily for a 6-hour period on gestation days 7 through 29. Mortality, toxicity and maternal body weight losses were observed in the 3.5 ppm test group. Slight maternal toxicity was observed at the two lower dose levels. Minimal fetal body weight losses were observed in the 1.2 ppm test group.

Husbandry. Animals were acclimatized for 78 days before being place on test. When not in exposure chambers, the animals were housed under standardized laboratory conditions in stainless steel, wire mesh cages; temperatures ranging between 68-78°F (mean 71 ± 1.9 °F; humidity ranging between 35% and 74% (mean 49 ±13.9%). The animals were fed Certified Rabbit Chow (Purina Mills, St. Louis, MO) libitum except during the 6 hour chamber exposure periods. Tap water was also available ad libitum.

Statistical analysis: All statistical tests were performed by a VAX computer; SAS statistical software, as well as inhouse software. Mean maternal body weights and body weight changes, food consumption, mean numbers of corpora lutea, total implantations, live fetuses, mean fetal body weights and mean crown-rump lengths were compared by analysis of variance, Bartlett's test for homogeneity of variance and the appropriate t-test as described by Steel and Torrie using Dunnett's multiple comparison table or pairwise comparisons with a Bonferroni correction to determine significance of differences.

Male and female sex ratios and proportions of litters with malformations and developmental variations were compared using the Chi-square test with Yeate's correction for 2x2 contingency tables and/or Fisher's exact probability test as described by Siegel to determine the significance of differences. The proportions of resorbed and dead fetuses and postimplantation losses were compared using the Kruskal-Wallis test described by Siegel.

Quality Assurance: A quality assurance statement dated 4/9/93 and signed by Margery J. Wirth was included in the report. A negative flagging statement was also included.

Mating. At the end of the 78 day acclimation period, the females were injected with human chorionic gonadotropin to induce ovulation 3 weeks before being artificially inseminated with sperm from proven male rabbits from the same source and strain. Sperm with greater that 60% motility was used. The inseminated females were again treated with gonadotropin to help assure maintenence of pregnancy.

Maternal Animal Observations. The pregnant females were checked twice daily for mortality and daily for abnormal condition during the course of the study. They were weighed prior to the start of the chamber exposures and on days 7, 13, 20, 24 and 29. Food consumption weighing were made on body weighing days and calculated for the intervals of 0-7, 7-13, 13-20, 20-29, 24-29, 7-20 and 0-20 days.

Necropsy: Animals which died prior to scheduled necropsy were euthanized and the maternal tissues preserved in 10% neutral buffered formalin for future histopathological examination as deemed necessary by the gross findings.

Cesarean Section Examinations. On gestation day 20, all surviving females were euthanized by sodium pentobarbital injection; the uterus and ovaries exposed by abdominal incisions and the pregnancy status determined. The uterus was excised and weighed. Viable and nonviable fetuses, early and late resorptions and the number of total implantations and corpora

luteae were recorded. The abdominal and thoracic cavities and organs of the dams were examined for grossly morphological changes and the carcasses discarded. Maternal tissues were preserved for possible future histopathological examination. Uteri from females that appeared non-gravid were opened and placed in 10% ammonium sulfide solution for detections of implantation.

Fetal Examinations. Individual fetuses were weighed, sexed, tagged and examined for external malformations and variations. Crown-rump lengths were measured and recorded for all fetuses. Each fetus was dissected, internally sexed and examined for visceral malformations and variations. The heart of each fetus was examined (Staples method). Each fetus was eviscerated and stained with Alizarin Red S for visceral morphology; and cleared with glycerin (Dawson method) for skeletal examination.

Historical Controls. Historical control data were provided for 56 studies over a period of time ranging from 5/85 to 8/90.

*D. EXPOSURE METHODS.

Exposure Chambers. The chambers were cuboidal, glass/metal, 16 cu.meters in volume. Air was supplied to the chambers by an HVAC filter system (99.9% $\leq 3\mu m$). The animals were housed individually in cages stacked near the bottom of the chamber. Exhaust air was removed from the around the bottom of the chamber and passed through charcoal filter to remove the remaining CP. Building air was filtered and metered into the chamber to maintain temperature and humidity conditions. There was no descriptions of the any monitoring devices used to monitor the chamber temperature or humidity.

Generation of CP Atmospheres. Pure CP was first diluted in Tedlar gas bags and these dilutions metered (Fluid Metering System) into the chamber inlet over the 6 hour exposure period to achieve the target test concentrations.

Chamber Concentrations Analyses. Preliminary chamber concentration analyses involved triplicate sampling of the chamber at 4 different locations, two at the top (one front and one back) and two at the bottom (one front and one in the back) of the chamber cage location areas. CP concentrations were determined using gas chromatography (GC) with an electron capture detector (ECD) interfaced with a Hewlett-Packard Model 3396 Series II laboratory computer which sampled the chamber concentrations at approximately hourly intervals. CP vapor standard curves were made by dissolving 1% CP vapor in hexane at four concentrations to bracket the chamber concentrations.

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* F. RESULTS

Exposure Concentrations. The chamber concentrations achieve met the targeted concentrations with a SD = 0.005, 0.00, 0.05 ppm for the LDT, MDT and HDT exposure groups respectively.

Maternal Observations. Two does from MDT and 10 from the HDT exposure groups died during the study. 70% of the animals in the HD group died of pulmonary edema. Clinical toxic signs in all animals that died on study included labored breathing, coldness to touch, red material (blood) around nose; decreased activity and emaciation, yellow anogenital staining, increased salivation, dose related. One doe from the MDT group and 2 does from the HDT group aborted. None of the abortions were in animals that died.

Maternal Body Weights and Gains.

Table 2: Body Weighs and Gains (grams)

Group:	Prior to Dosing Period	Dosing Period	Entire Gestation Period	Corrected Body Weight Gains Entire[1]
	BW	----------Gain/Loss----------		
Control	3852	51	269	-148
LDT	3974	142	335	-87
MDT	3928	-119*	137	-263
HDT	3975	-320*	-59*	-364

[1] = corrected body weight gain for entire gestation period = body weight gain for dosing period minus gravid uterus weight.
* Statistically significant (0.05 level).

Food Consumption.

Table 3. : Maternal Food Consumption Data (gm/animal/day)

Group:	Prior to Dosing Period	Dosing Period	Post-Dosing Period	Entire Gestation Period
Control	167	135	86	133
LDT	166	149	101	144
MDT	169	93*	112	123
HDT	169	42*	102	118

Cesarean Section Observations. These observations are provided in the attached **Table 5** taken from the study report. One female from the MDT and 2 from the HDT aborted. These abortions were not related to the animals who had died. The number of females with viable fetuses was reduced in the MDT (16)

and HDT (8) groups compared to the control (18) and LDT (19) groups. Post dose implantation losses were increased (0.6 to 1.0 per litter) for treated animals compared to the control animal (0.2). Fetal weights for both sexes and uterine weights were reduced in the MDT and HDT groups compared to the controls and LDT groups.

Other parameters were not effected by CP administration including: animals with resorptions, number of implantation sites, resorptions, dead fetuses, live fetuses and sex ratios.

Fetal Malformations. These observations are summarized in the attached **Table 6** taken from the study report. None of the malformations were apparently or statistically effected by the CP exposures. This included anencephaly, ablepharia, aortic arch stenosis and skeletal development. Total fetal (litter) malformations found included 7 (4), 1 (1), 1 (1) and 3 (2) for the controls, low, mid and high exposure groups, respectively.

Fetal Developmental Variations. These results are summarized in the attached **Table 7** taken from the study report. The investigators concluded that there were "slight increases" in the developmental variations observed in the mid- and high-exposure groups compared to the controls. There were not of "significance". However, it is difficult to see this in Table 7 because of the 10% mortality and 50% losses in the higher exposure groups.

*G. DISCUSSION.

Study Design. The design and reporting of the study was adequate. Pregnancy rates were high at greater than 90% (ranging from 90 to 100%). Females that survived exposures to CP had a low abortion rate (1-3), not relatable to CP exposure rates. The maternal and fetal findings in the control animals were within ranges of historical controls.

Maternal Effects. The HDT and MDT levels reflected decreases in body weights and food consumption and expected toxicity from CP a highly toxic and irritating vapor which produced pulmonary damage (pulmonary edema). None of the reproductive parameters (Table 5) were effected by the CP exposures.

Fetal Toxicity. In spite of severe maternal toxicity, there were no morphological abnormalities attributable to CP exposure. The only fetal toxicity which might be ascribed to the CP exposures were a non-statistically reduce fetal weight and increased variability of the skeleton, seen more prominently in the sternebra at the high dose. .

Chlorpyrifos Review

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and HDT (8) groups compared to the control (18) and LDT (19) groups. Post dose implantation losses were increased (0.6 to 1.0 per litter) for treated animals compared to the control animal (0.2). Fetal weights for both sexes and uterine weights were reduced in the MDT and HDT groups compared to the controls and LDT groups.

Other parameters were not effected by CP administration including: animals with resorptions, number of implantation sites, resorptions, dead fetuses, live fetuses and sex ratios.

Fetal Malformations. These observations are summarized in the attached **Table 6** taken from the study report. None of the malformations were apparently or statistically effected by the CP exposures. This included anencephaly, ablepharia, aortic arch stenosis and skeletal development. Total fetal (litter) malformations found included 7 (4), 1 (1), 1 (1) and 3 (2) for the controls, low, mid and high exposure groups, respectively.

Fetal Developmental Variations. These results are summarized in the attached **Table 7** taken from the study report. The investigators concluded that there were "slight increases" in the developmental variations observed in the mid- and high-exposure groups compared to the controls. There were not of "significance". However, it is difficult to see this in Table 7 because of the 10% mortality and 50% losses in the higher exposure groups.

*G. DISCUSSION.

Study Design. The design and reporting of the study was adequate. Pregnancy rates were high at greater than 90% (ranging from 90 to 100%). Females that survived exposures to CP had a low abortion rate (1-3), not relatable to CP exposure rates. The maternal and fetal findings in the control animals were within ranges of historical controls.

Maternal Effects. The HDT and MDT levels reflected decreases in body weights and food consumption and expected toxicity from CP a highly toxic and irritating vapor which produced pulmonary damage (pulmonary edema). None of the reproductive parameters (Table 5) were effected by the CP exposures.

Fetal Toxicity. In spite of severe maternal toxicity, there were no morphological abnormalities attributable to CP exposure. The only fetal toxicity which might be ascribed to the CP exposures were a non-statistically reduce fetal weight and increased variability of the skeleton, seen more prominently in the sternebra at the high dose. .