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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Chloropicrin (CP): Submissions: 90 day inhalation studies in the rat and mouse. (MRID 43063201). BC# D199838
Chemical ID #081501
Chemical No. 214

TO: Larry Schnaubelt/Susan Jennings (PM 72)
Reregistration Review Branch
Registration Division (7508W)

FROM: Stanley B. Gross, PhD, DABT, CIH
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6/28/94
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THRU: Joycelyn E. Stewart, PhD
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THRU: Karl P. Baetcke, PhD
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7/19/94

A. SUBMISSIONS.

STUDY : Chloropicrin: Ninety- day inhalation toxicity study in Rats and Mice. Bushy Run Research Center (BRRC), Export PA. #91N0098. J.S. Chun and W. J. Kintigh, Dec. 14, 1993. Sponsor: The Chloropicrin Manufacturer's Task Force, Northbrook, IL. (MRID 43063201).

B. EXECUTIVE SUMMARIES.

1) **Rat Study.:** Groups of CD rats (10 per sex/group) were exposed 6 hours per day, 5 days per week for 13 weeks to air controls or CP vapor at concentrations of 0.3 (LD), 1.0 (MD) and 3.0 (HD) ppm. The animals were monitored for toxicity, clinical chemistry, hematology, urinalyses, body weight, food consumption, ophthalmological examination and gross and histological changes.

Three males from the HD group died with signs related to CP toxicity including labored breathing and non-specific findings of emaciation, dehydration, urine stains, hunched posture, urogenital

area wetness. One female control died of lymphosarcoma, not related to the CP exposures. during the study. The only clinical sign consistently seen in the animals from the HD and MD groups was blepharospasm.

Body weight losses were observed in male and female rats from the HD groups. At the end of the study, the percent decreases in body weight gain for males were 17% (body weight) and 41% (body weight gain) for the males; and for females, The decrease in weight was 6% and a 15% for body weight gain.

Clinical chemistry changes were limited to increased hemoglobin concentrations, hematocrit, and total RBCs observed in male rats from the 3.0 ppm group. There were no effects ophthamologically and by urinalysis in any of the test groups.

Absolute and relative lung weights were increased in the HD and MD groups of males and females. Lesions in the nose (rhinitis) and of the pulmonary epithelia (hyperplasia/dysplasia) and pulmonary histiocytosis were seen in the HD and MD groups. Increased goblet cell hyperplasia of the nasal epithelia was seen in all exposure groups and sexes.

Conclusions. NOEL = 0.3 ppm. LOEL = 1.0 ppm based on decreased body weight and food consumption, histopathological effects on the nose and lung.

Classification: Core minimum: The study meets the guideline 82-4 requirements of 90 day inhalation study in rodents.

2) **Mouse Study:** Groups of CD-1 mice (10 per sex/group) were exposed 6 hours per day, 5 days per week for 13 weeks to air controls or CP at concentrations of 0.3, 1.0 and 3.0 ppm. The animals were monitored for toxicity, clinical chemistry, hematology, urinalyses, body weight, food consumption, ophthalmological examination and gross and histological changes.

One male (1.0 ppm group) and one female control were found dead. Death was due to trauma or urinary tract obstruction, not to CP exposures. Clinical signs observed at 3.0 ppm included discoloration of skin; dehydration and body weight losses and blepharospasms. There were no clinical signs in the 0.3 and 1.0 ppm groups, except blepharospasms. Decreases in body weight and/or body weight gain and food consumption were observed in the animals from the 1.0 and 3.0 ppm exposure groups.

Total serum protein, albumin, and calcium were increased in males (not females) from the 3.0 ppm group. Clinical chemistries in the 0.3 and 1.0 ppm groups were unremarkable. Statistically significant increases in nasal findings (rhinitis; hyperplasia, dysplasia, hyaline inclusion bodies) and pulmonary findings (bronchial and pulmonary fibrosis and hypelasia; and alveolar histiocytosis) were see in the males and females of the 3.0 ppm

group and in the females of the 1.0 ppm group.

CORE GRADE: NOEL = 0.3 ppm. LOEL = 1.0 ppm based on decreased body weight and food consumption; and pathological lesions of the nasal and pulmonary regions.

Classification: CORE MINIMUM. The study meets the guideline 82-4 requirements of 90 day inhalation study in rodents.

cp199838.mmo E2 June 30, 1994

Primary reviewer: Stanley B. Gross, PhD, DABT, CIH.
Secondary Reviewer: Joycelyn E. Stewart, PhD.
Section II, Toxicology Branch I (H7509C).

DATA EVALUATION REPORT

STUDY TYPE: 90 Day rat inhalation toxicity study.

TOX. CHEM. No.: 214

MRID No.: 430632-01

TEST MATERIAL: Chloropicrin

SPONSOR: The Chloropicrin Manufacturer's Task Force, Northbrook, IL.

TESTING FACILITY: Bushy Run Research Center (BRRC), Export PA.

STUDY NO.: 91N0098.

REPORT TITLE: Chloropicrin: Ninety-Day Inhalation Toxicity Study in Rats.

AUTHOR(S): J.S. Chun and W. J. Kintigh

REPORT ISSUED: Dec. 14, 1993.

Quality Assurance statment was included: signed by Linda J. Calisti, dated 12/13/93.

I. EXECUTIVE SUMMARY.

Groups of CD rats (10 per sex/group) were exposed 6 hours per day, 5 days per week for 13 weeks to air controls or CP vapor at concentrations of 0.3 (LD), 1.0 (MD) and 3.0 (HD) ppm. The animals were monitored for toxicity, clinical chemistry, hematology, urinalyses, body weight, food consumption, ophthalmological examination and gross and histological changes.

Three males from the HD group died with signs related to CP toxicity including labored breathing and non-specific findings of emaciation, dehydration, urine stains, hunched posture, urogenital area wetness. One female control died of lymphosarcoma, not related to the CP exposures. during the study. The only clinical sign consistently seen in the animals from the HD and MD groups was blepharospasm.

Body weight losses were observed in male and female rats from the HD groups. At the end of the study, the percent decreases in body weight gain for males were 17% (body weight) and 41% (body weight gain) for the males; and for females, The decrease in weight was 6% and 15% for body weight gain.

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Clinical chemistry changes were limited to increased hemoglobin concentrations, hematocrit, and total RBCs observed in male rats from the 3.0 ppm group. There were no effects ophthamologically and by urinalysis in any of the test groups.

Absolute and relative lung weights were increased in the HD and MD groups of males and females. Lesions in the nose (rhinitis) and of the pulmonary epithelia (hyperplasia/dysplasia) and pulmonary histiocytosis were seen in the HD and MD groups. Increased goblet cell hyperplasia of the nasal epithelia was seen in all exposure groups and sexes.

Conclusions. NOEL = 0.3 ppm. LOEL = 1.0 ppm based on decreased body weight and food consumption, histopathological effects on the nose and lung.

Classification: Core minimum: The study meets the guideline requirements of 90 day inhalation study in rodents.

II. STUDY DESIGN:

Ten animals/sex were exposed by whole body inhalation for 6 hours/day, 5 days/week for 13 weeks to zero, 0.3, 1.0 and 3.0 ppm CP. The animals were monitored for toxicity, clinical chemistry, hematology, urinalyses, body weight, food consumption, ophthalmological examination and gross and histological changes.

III. MATERIALS

A. Test compound: Chloropicrin (99.6% a.i.) obtained from Niklor Chemical Co., , Long Beach, CA. Lot Nos. 920130-2 and 31291-A. Clear, colorless, oily liquid with extremely strong odor.

B. Test animals: Male and female CD rats from Charles River Laboratories (Portage, MI. Age: Weight: males 252 to 319 gm, females 169 to 223 gm at the start of the study. Animals were acclimated for approximately 3 weeks under standard laboratory conditions prior to the start of the study.

IV. METHODS.

A. Exposure Chambers: Cubic stainless steel and glass whole body exposure chambers with pyramidal shaped top and bottom obtained from Wahmann Manufacturing Co., Timonium, MD. The chambers were approximately 900 L. in volume, air flow through the chamber was approximately 200 L/min (13 air changes per hour). Chamber temperature and relative humidly were recorded every 2 hours using a Fisherbrand dial type thermometer (Fisher

Scientific, Pittsburgh, PA) and a Air glide humidity indicator (Airguide Instrument Co., Chicago, IL).

B. Generating System: Liquid CP was metered from a syringe by means of a pump (Sage Instruments, Cambridge, MA) into a heated glass evaporator similar to one described by Snellings and Dodd (1990). The temperature of the evaporator was enough to completely vaporize the liquid CP which was then fed into the chamber intake air steam.

C. Chamber Concentration Monitoring: Chamber concentrations of CP were analyzed by flame ionization gas chromatography at approximately 11 times over each exposure period and averaged to obtain an overall concentration.

D. Clinical Observations Clinical observations were made daily. Body weights were obtained initially and on a weekly basis throughout 13 week exposure period. Food consumption was measured weekly during the study.

E. Hematology. Blood was collected by retroorbital bleeding from methoxyflurane-anesthetized animals during terminal sacrifice. The CHECKED (X) parameters were examined.

X Hematocrit (HCT)*	
X Hemoglobin (HGB)*	X Leukocyte differential count
X Leukocyte count (WBC)*	X Mean corpuscular HGB (MCH)
X Erythrocyte count (RBC)*	X Mean corpuscular HGB conc.(MCHC)
X Platelet count*	X Mean corpuscular volume (MCV)

F. Urinalysis - Urine specimens were collected during exposure week 13 by placing the animals individually in metabolic cages (Nalgene Co., Rochester, NY). The urine was examined for the following. The CHECKED (X) parameters were examined.

X		X	
x	Appearance*	X	Glucose*
X	Volume*	X	Ketones*
	Specific gravity*	X	Bilirubin*
X	pH	X	Blood*
X	Sediment (microscopic)*		Nitrate
X	Protein*	X	Urobilinogen
X	Osmolality		

^Not required for subchronic studies
* Required for chronic studies

G. Clinical Chemistry. Blood was collected by retroorbital bleeding from methoxyflurane-anesthetized animals during terminal sacrifice. The following CHECKED (X) analyses were carried out:

Electrolytes:	Other:
X Calcium*	X Albumin*
X Chloride*	X Blood creatinine*
X Magnesium*	X Blood urea nitrogen*
X Phosphorus*	X Cholesterol*
X Potassium*	X Globulins
X Sodium*	X Glucose*
ENZYMES:	X Total bilirubin*
X Alkaline Phosphatase (AP)	X Total plasma protein*
- Cholinesterase (CHE)	- Triglycerides (TG)
- Creatinine phosphokinase* (CP)	
Lactic acid dehydrogenase (LDH)	
X Serum alanine aminotransferase (also SGPT)	
X Serum aspartate aminotransferase (also SGOT)	

H. Ophthalmological examinations. A veterinary ophthalmologist examined the animals prior to the study and during week 14 using indirect ophthalmoscopy and biomicroscopy following dilation of the eyes with Mydriacyl 1% (tropicamide 1.0%) Ophthalmic Solution.

I. Sacrifice and Pathology - At the end of the exposures, all surviving animals were anesthetized with methoxyflurane and were euthanized by severing their brachial vessels to permit exsanquination. Terminal sacrifice involved the gross and histological examination of the following organs.

DIGESTIVE SYSTEM	CARDIVASC./HEMAT.	NEUROLOGIC
Tongue	Aorta*	W Brain*
Salivary glands*	W Heart*	Periph nerve*
Esophagus*	Bone marrow*	Spinal cord (3 levels)
Stomach*	Lymph nodes*	Pituitary*
Duodenum*	Spleen*	Eyes(optic nerve)
Jejunum*	Thymus*	GLANDULAR
Ileum*	UROGENITAL	Adrenal*
Cecum*	W Kidneys*	Lacrimal gland*
Colon*	Urinary bladder*	Mammary gland*
Rectum*	W Testes*	Parathyroids*
W Liver*	Epididymides*	Thyroids*
Gall bladder*	Prostate	OTHER
Pancreas*	Seminal Vesicle	Bone*
RESPIRATORY	Ovaries	Skeletal musc.*
Trachea*	Uterus*	All gross lesions & masses.
Lungs*		

The above organs marked with W (brain, heart, liver, kidneys and testes) were weighed and compared to body weight changes.

J. Statistical Methods. Data for continuous and parametric variables were compared using Levene's test of homogeneity of variances, ANOVA and t-tests. Frequency data was compared using the Fisher's exact test. Minimal biological significance was assumed for the 0.05% level.

V. RESULTS:

Selected dose-related data are presented in TABLE I (page 7).

A. Exposures Concentrations/Conditions. The analytical chamber concentrations were close to the target concentrations: LD: 0.30 ± 0.024 ppm; MD: 1.03 ± 0.069 ppm and HD 2.89 ± 0.141 ppm. Mean chamber humidity ranged from 45 to 55% and mean temperatures ranged from 21 to 23 degrees C.

B. Toxicity. Three males from the HD group died with signs related to CP toxicity including labored breathing and non-specific findings of emaciation, dehydration, urine stains, hunched posture, urogenital area wetness. One female control died of lymphosarcoma, not related to the CP exposures. during the study. The only clinical sign consistently seen in the animals from the HD and MD groups was blepharospasm.

C. Body Weight. Body weight losses were observed in male and female rats from the HD groups. At the end of the study, the percent decreases in body weight gain for males were 17% (body weight) and 41% (body weight gain) for the males; and for females, The decrease in weight was 6% and a 15% for body weight gain.

D. Food consumption. Food consumption was proportional to the BW decreases and was significantly reduced in the HD males (-85 gm., $p<0.01$) Body weight in the HD females was reduced (-19 gm) but was only significant in decreased body weight gain (-18 gm, $p < 0.05$)

E. Hematology. None of the hematological findings were relatable to CP exposures. Increases in hemoglobin concentration (statistically inceased), hematocrit, and total erythrocyte count were observed for male rats (not females) of the HD group.

F. Urinalysis There were no agent related changes in the urinalysis parameters.

G. Clinical Chemistry. No agent related clinical chemistry findings were observed in any of the exposure groups.

H. Ophthalmological examinations. There were no agent related findings.

I. Gross Pathology The only gross lesion related to CP exposures were hyperinflation of the lungs in both sexes from the HD group.

J. Organ weights Increases in absolute and relative lung weights and the brain were observed in the males of the MD and HD groups: increased relative lung weights for males were 14% and 56% for the MD and HD respectively; 9% and 27% increases for the females of the MD and HD respectively.

K. Microscopic pathology Primary exposure-related lesions were observed in the nasal cavity and the lungs of the HD and MD groups (TABLE I). Statistically significant increases in nasal findings (rhinitis; hyperplasia, dysplasia, hyaline inclusion bodies) and pulmonary findings (bronchial and pulmonary fibrosis and hypelasia; and alveolar histiocytosis) were seen in the males and females of the 3.0 ppm group and in the females of the 1.0 ppm group.

There was an increased incidence of goblet cell hyperplasia (non-specific sign of local irritation of the nasal cavities of all CP exposure groups.

VI. DISCUSSION.

A. The study was well executed and reported.

B. The animals in the MD and HD groups were generally effected adversely by their CP exposures by decreased body weight and body weight gain; by toxicity of the nasal and pulmonary systems which lead to death in three HD males and consistent histopathology in the MD and HD males and females. Changes in LD test groups were minimal and/or inconsistent.

C. The study is suitable to meet the requirements for a 90 day subchronic rodent inhalation study.

cp9838rt.inh June 30, 1994

TABLE I. SELECTED DOSE-RESPONSE DATA .

	Controls	0.3 ppm	1.0 ppm	3.0 ppm
(MALE RATS)				
BW (gm)	488	489	500	403**
BW gain (gm)	209	205	217	102**
Mortality	0/10	0/10	0/10	3/10
Nasal Pathology:				
Rhinitis-	2/10	2/10	4/10	10/10**
Hyperplasia/ Dysplasia-	1/10	0/10	2/10	10/10
Pulmonary Pathology:				
Fibrosis/hyperplasia	0/10	0/10	2-4/10	10/10
(FEMALE RATS).				
BW (gm)	325	330	316	306
BW gain (gm)	122	127	117	104*
Mortality	1/10	0/10	0/10	0/10
Nasal Pathology:				
Rhinitis-	1/10	1/10	7/10*	8/10**
Hyperplasia/ Dysplasia-	0/10	0/10	0/10	9/10**
Pulmonary Pathology:				
Fibrosis/hyperplasia	0/10	0/10	5 /10	8/10**

* Significant at the 0.05 per level.
** Significant at the 0.01 level.

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Primary reviewer: Stanley B. Gross, PhD, DABT, CIH.
Secondary Reviewer: Joycelyn E. Stewart, PhD,
Section II, Toxicology Branch I (H7509C).

DATA EVALUATION REPORT

STUDY TYPE: 90 Day mouse inhalation toxicity study.

TOX. CHEM. No.: 214

MRID No.: 430632-01

TEST MATERIAL: Chloropicrin

SPONSOR: The Chloropicrin Manufacturer's Task Force, Northbrook, IL.

TESTING FACILITY: Bushy Run Research Center (BRRC), Export PA.

STUDY NO.: 91N0098.

REPORT TITLE: Chloropicrin: Ninety-Day Inhalation Toxicity Study in Rats and Mice.

AUTHOR(S): J.S. Chun and W. J. Kintigh

REPORT ISSUED: Dec. 14, 1993.

Quality Assurance statement was signed by Linda J. Calisti, dated 12/13/93.

I. EXECUTIVE SUMMARY.

Groups of CD-1 mice (10 per sex/group) were exposed 6 hours per day, 5 days per week for 13 weeks to air controls or CP at concentrations of 0.3, 1.0 and 3.0 ppm. The animals were monitored for toxicity, clinical chemistry, hematology, urinalyses, body weight, food consumption, ophthalmological examination and gross and histological changes.

One male (1.0 ppm group) and one female control were found dead. The causes of death death was not determined by was assumed to be due to trauma or urinary tract obstruction. not to CP exposures. Clinical signs observed at 3.0 ppm included discoloration of skin; dehydration and body weight losses and blepharospasms. There were no clinical signs in the 0.3 and 1.0 ppm groups, except blepharospasms. Decreases in body weight and/or body weight gain and food consumption were observed in the animals from the 1.0 and 3.0 ppm exposure groups.

Total serum protein, albumin, and calcium were increased in males (not females) from the 3.0 ppm group. Clinical chemistries in the 0.3 and 1.0 ppm groups were unremarkable. Statistically significant increases in nasal findings (rhinitis; hyperplasia,

dysplasia, hyaline inclusion bodies) and pulmonary findings (bronchial and pulmonary fibrosis and hypelasia; and alveolar histiocytosis) were see in the males and females of the 3.0 ppm group and in the females of the 1.0 ppm group.

CORE GRADE: NOEL = 0.3 ppm. LOEL = 1.0 ppm based on decreased body weight and food consumption; and pathological lesions of the nasal and pulmonary regions.

Classification: CORE MINIMUM. The study meets the guideline requirements of 90 day inhalation study in rodents.

II. STUDY DESIGN:

Ten animals/sex were exposed by whole body inhalation for 6 hours/day, 5 days/week for 13 weeks to zero, 0.3, 1.0 and 3.0 ppm CP. The animals were monitored for toxicity, clinical chemistry, hematology, body weight, food consumption, ophthalmological examination and gross and histological changes.

III. MATERIALS

A. Test compound: Chloropicrin (99.6% a.i.) obtained from Niklor Chemical Co., , Long Beach, CA. Lot Nos. 920130-2 and 31291-A. Clear, colorless, oily liquid with extremely strong odor.

B. Test animals: Male and female CD-1 mice from Charles River Canada, St. Constant, Canada. Weight: means apprx. 31±1.5 gm (males); 24± 1.3 gm (females). Age: approximately 35 days. The animals were acclimated (2-3/cage) for approximately 7 days weeks under standard laboratory conditions prior to the start of the study and then housed individually for the rest of the study.

IV. METHODS.

A. Exposure Chambers: The animals were exposed in 900 L. cubic stainless steel whole body exposure chambers with pyramidal shaped top and bottom obtained from Wahmann Manufacturing Co., Timonium, MD. Air flow was approximately 200 L/min (13 air changes per hour). Chamber temperature and relative humidity were recorded every 2 hours using a Fisherbrand dial type thermometer (Fisher Scientific, Pittsburgh, PA) and a Air glide humidity indicator (Airguide Instrument Co., Chicago, IL).

B. Generating System: Liquid CP was metered from a syringe pump (Sage Instruments, Cambridge, MA) into a heated glass evaporator similar to one described by Snellings and Dodd (1990). The temperature of the evaporator was enough to vaporize

the liquid CP which was then fed into the chamber intake air stream.

C. Chamber Monitoring: Analytical chamber concentrations of CP were analyzed by flame ionization gas chromatography at approximately 11 times over each exposure period and averaged to determine the daily concentration.

D. Clinical Observations Clinical observations were made daily. Body weights were obtained initially and on a weekly basis throughout 13 week exposure period. Food consumption was measured weekly during the study.

E. Hematology. Blood was collected by retroorbital bleeding from methoxyflurane-anesthetized animals during terminal sacrifice. The CHECKED (X) parameters were examined.

X Hematocrit (HCT)*
X Hemoglobin (HGB)*
X Leukocyte count (WBC)*
X Erythrocyte count (RBC)*
X Platelet count*
X Leukocyte differential count
X Mean corpuscular HGB (MCH)
X Mean corpuscular HGB conc.(MCHC)
X Mean corpuscular volume (MCV)

F. Clinical Chemistry. Blood was collected by retroorbital bleeding from methoxyflurane-anesthetized animals prior to the terminal sacrifice. The following CHECKED (X) analyses were carried out:

Electrolytes:

X Calcium*
X Chloride*
X Magnesium*
X Phosphorus*
X Potassium*
X Sodium*

Other:

X Albumin*
X Blood creatinine*
X Blood urea nitrogen*
X Cholesterol*
X Globulins
X Glucose*
X Total bilirubin*
X Total plasma protein*
- Triglycerides (TG)

ENZYMES:
X Alkaline Phosphatase (AP)
- Cholinesterase (CHE)
- Creatinine phosphokinase* (CP)
Lactic acid dehydrogenase (LDH)
X Serum alanine aminotransferase (also SGPT)
X Serum aspartate aminotransferase (also SGOT)

G. Ophthalmological examinations. A veterinary ophthalmologist examined the animals prior to the study and during week 14 using indirect ophthalmoscopy and biomicroscopy following dilation of the eyes with MYDRIACYL 1% (tropicamide 1.0%) Ophthalmic Solution.

H. Sacrifice and Pathology - At the end of the exposures,

all surviving animals were anesthetized with methoxyflurane and were euthanized by severing their brachial vessels to permit exsanquination. Terminal sacrifice involved the gross and histological examination of the following organs in the control and high dose groups.

DIGESTIVE SYSTEM	CARDIVASC./HEMAT.	NEUROLOGIC
Tongue	Aorta*	W Brain*
Salivary glands*	W Heart*	Periph nerve*
Esophagus*	Bone marrow*	Spinal cord (3 levels)
Stomach*	Lymph nodes*	Pituitary*
Duodenum*	Spleen*	Eyes(optic nerve)
Jejunum*	Thymus*	GLANDULAR
Ileum*	UROGENITAL	Adrenal*
Cecum*	W Kidneys*	Lacrimal gland*
Colon*	Urinary bladder*	Mammary gland*
Rectum*	W Testes*	Parathyroids*
W Liver*	Epididymides*	Thyroids*
Gall bladder*	Prostate	OTHER
Pancreas*	Seminal Vesicle	Bone*
RESPIRATORY	Ovaries	Skeletal musc.*
Trachea*	Uterus*	All gross lesions & masses.
Lungs*		

The above organs marked with W (brain, heart, liver, kidneys and testes) were weighed and compared to body weight changes.

I. Statistical Methods. Data for continuous and parametric variables were compared using Levene's test of homogeneity of variances, ANOVA and t-tests. Frequency data was compared using the Fisher's exact test. Minimal biological significance was assumed for the 0.05% level.

V. RESULTS:

TABLE I contains selected data which supports a number of the observations discussed below (page 6).

A. Exposures Concentrations/Conditions. The analytical chamber concentrations were close to the target concentrations: LD: 0.30 ± 0.024 ppm; MD: 1.03 ± 0.069 ppm and HD 2.89 ± 0.141 ppm. Mean chamber humidity ranged from 45 to 55% and mean temperatures ranged from 21 to 23 degrees C.

B. Toxicity. One male (week 5) from the LD group and 1 female (week 10) control died during the study. The cause of death was not obvious and was assumed to be due to trauma or renal blockage. None of the other animals died as a result of CP

exposures. The only clinical sign seen in the animals was blepharospasm in the HD and MD group animals.

C. Body Weight. The BW weight losses were observed in male and female mice from the MD and HD groups. At the end of the study, the percent decreases in body weight gain for males were 44% and 95% for the MD and HD groups, respectively. The decrease in weight gains for females for the HD group was 58%. Decreases in body weight and body weight gain were inconsistently decreased for the LD males (only).

D. Food consumption. Food consumption was proportional to the BW decreases and was statistically decreased in all three treatment groups for both males and female animals (TABLE I).

E. Hematology. There were no agent related changes in hematological parameters.

F. Clinical Chemistry. Total serum protein, albumin and calcium were increased in male mice from the HD group. No agent related findings were observed in any of the other exposure groups.

G. Ophthalmological examinations. There were no agent related findings.

H. Gross Pathology There were no gross pathological lesions attributable to CP exposures.

I. Organ weights Increases in absolute and relative lung weights were observed in the males of the MD and HD groups: increased relative weights in males were 17% and 68% for the MD and HD respectively; 21% and 58% increases for the females of the MD and HD respectively. The spleen weight was decreased in the 3.0 ppm group, without any related histological changes. Other relative organ weights due to decreased BW (dehydration??) without any D/R relationships.

J. Microscopic pathology Primary exposure-related lesions were observed in the nasal cavity and the lungs of the HD and MD groups. Selected lesions are shown in TABLE I. Statistically significant increases in nasal findings (rhinitis; hyperplasia, dysplasia, hyaline inclusion bodies) and pulmonary findings (bronchial and pulmonary fibrosis and hypelasia; and alveolar histiocytosis) were see in the males and females of the 3.0 ppm group and in the females of the 1.0 ppm group.

There was an increased incidence of goblet cell hyperplasia (non-specific sign of local irritation of the nasal cavities of all CP exposure groups.

VI. DISCUSSION.

A. The study was well executed and reported and will meet the requirements for subchronic inhalation study in mice.

ap9838ms.inh June 28, 1994

TABLE I. SELECTED DOSE-RESPONSE DATA (MALE MICE).

	Controls	0.3 ppm	1.0 ppm	3.0 ppm
Mortality died day 27	0/10	0/10	1/10	0/10
BW (gm)	40	37	37*	32**
BW gain (gm) gm	7.9	5.8*	4.4**	0.4**
FC (gm)	6.4	5.9*	5.8*	5.3*
Nasal Pathology:				
Rhinitis-	1/10	0/10	0/9	10/10**
Hyperplasia/ Dysplasia-	0/10	0/10	1/9	7/10**
Hyaline Inclusion bodies--	0/10	0/10	3/9	10/10**
Pulmonary Pathology:				
Fibrosis/hyperplasia (bronchial/bronchiolar)	0/10	0/10	1 /10	8/10**
Alveolar histio-cytosis-	2/10	1/10	5/9	9/10**
(FEMALE MICE).				
Mortality	1/10	0/10	0/10	0/10
BW (gm)	28	28	27	26*
BW gain (gm)	3.8	4.1	3.2	1.6**
FC	6.9	6.2	6.0*	5.2**
Nasal Pathology:				
Rhinitis-	0/9	0/10	4/10	9/10**
Hyperplasia/ Dysplasia-	0/10	0/10	1/9	7/10**
Hyaline Inclusion bodies--	0/9	2/10	6/10*	10/10**
Pulmonary Pathology:				
Fibrosis/Hyperplasia (bronchial/bronchiolar)	0/10	0/10	1 /10	8/10**
Alveolar histio-cytosis:	2/9	2/10	8/9**	10/10**

* Significant at the 0.05 % level.
** Significant at the 0.01 % level.