

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
CHLOROPICRIN

SB 950-015, Tolerance # 199
Chemical Code #: 000136

October 8, 1987

Revised: 12/8/88, 8/6/92, 11/24/93, 4/28/94, 1/20/95, 10/6/95, 4/22/97, 10/20/99, 11/15/01

I. DATA GAP STATUS

Chronic rat :	No data gap, possible adverse effect
Chronic dog :	No data gap, no adverse effect
Oncogenicity rat :	No data gap, no adverse effect
Oncogenicity mouse :	No data gap, no adverse effect
Reproduction rat :	No data gap, no adverse effect
Teratology rat :	No data gap, no adverse effect
Teratology rabbit :	No data gap, no adverse effect
Gene mutation :	No data gap, possible adverse effect
Chromosome :	No data gap, possible adverse effect
DNA damage :	No data gap, no adverse effect
Neurotoxicity :	Not required at this time

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Note, Toxicology one-liners are attached

** indicates acceptable study

Bold face indicates possible adverse effect

File name : T011115

Revised: Green & Silva, 8/6/92; Silva, 11/24/93, 4/28/94 & 1/20/95; Silva & Kishiyama, 10/6/95; Silva,
4/22/97; 10/20/99, 11/15/01.

Reconciled with library listing through volume # 088 & record # 183793.

The one-liners in this document contain summary information only. Please refer to individual worksheets for detailed reviews.

I. TOXICOLOGY SUMMARY

CHRONIC, RAT

Subchronic Study:

**** 199 - 088 183793** AChloropicrin: Ninety-Day Inhalation Toxicology Study in Rats and Mice,@(Chun, J.S., Kintigh, W.J.; Union Carbide, Bushy Run Research Center, Export, PA; Laboratory Project ID#: 91N0098; 12/14/93). Chloropicrin (99.6% pure) was administered by inhalation to CD⁷ rats (10/sex/dose) and CD-1⁷ mice (10/sex/dose) at 0 (filtered air), 0.3, 1.0 and 3.0 ppm (6 hours/day, 5 days/week) for 13 weeks (Analytical Concentration 0.3, 1.03, 2.89 ppm; Nominal Concentration 0.65, 1.31, 3.49 ppm). Rat NOEL = 0.3 ppm (There was increased mortality, decreased body weight and food consumption, hematologic changes and changes in clinical chemistry parameters at 3.0 ppm. There was a decrease in liver and kidney and an increase in spleen absolute and relative weights at 3.0 ppm. Lung absolute and relative weights were increased at ≥ 1.0 ppm. Nasal cavity and lung histopathology at ≥ 1.0 ppm were increased. Female rats had increased lung goblet cell hyperplasia at all doses, however the report stated that this was a sign of irritation and was not toxicologically important.) Mouse NOEL = 0.3 ppm (There was decreased body weight (3.0 ppm) and food consumption, hematologic changes and clinical chemistry parameters at ≥ 1.0 ppm. There was a decrease in liver and kidney and an increase in spleen absolute and relative weights at 3.0 ppm. Lung absolute (3.0 ppm) and relative weights (≥ 1.0 ppm) were increased. There was an increase in nasal cavity and lung histopathology at ≥ 1.0 ppm.) Possible adverse effect (There was increased mortality (rat), and nasal cavity and lung histopathology in both rat and mouse.) Acceptable. M. Silva, 11/15/01.

Definitive Study:

**** 066, 074 138871, 161345** "Two Year Oral (Gavage) Chronic Toxicity Study of Chloropicrin in Rats," (Slauter, R.W., IRDC, Mattawan, MI; Laboratory ID #: 656-003, 6/27/95) and "Chronic Toxicity in Rats,@ (Swenberg, J.A.;The Chloropicrin Manufacturers Task Force, Niklor Chemical Co., Long Beach, CA; IRDC, Mattawan, MI; 6/27/95; Rebuttal Document: 5/6/98). Chloropicrin technical (99% pure) was administered by gavage to Charles River CrI:CD BR, VAF/Plus rats at 0 (corn oil), 0.1, 1.0 and 10 mg/kg/day for 2 years. Chronic NOEL < 0.1 mg/kg; NOAEL = 0.1 (Increased salivation was observed in both sexes at 10 mg/kg. Male body weights at ≥ 1.0 mg/kg were decreased. Periportal vacuolization of hepatocytes were increased at all doses in both sexes. Hyperkeratosis at ≥ 1.0 mg/kg and epithelial hyperplasia at 10 mg/kg (of the nonglandular stomach) were increased in both sexes.) **Possible adverse effect:** Oncogenicity NOEL = 1.0 mg/kg (A male at 10 mg/kg had a stomach papilloma which the report stated to be possibly treatment-related. Females showed an increase in mammary fibroadenomas (14/30) which was significant at 10 mg/kg.) Acceptable. Volume 199-074, record #: 161345 was a re-evaluation of the pathology data. No change in status. M. Silva, 10/14/99.

052 122676 A letter from J.H. Butala (Technical Advisor Chloropicrin Manufacturers Task Force) dated 4/12/93 discussed results of "Three Month Oral (gavage) Range-Finding Toxicity Study of Chloropicrin in CD Rats," performed by IRDC. The results of this preliminary study were used to estimate dose levels for the two year oral (gavage) toxicity study. No worksheet. M. Silva, 11/23/93.

A letter from J.H. Butala (Technical Advisor Chloropicrin Manufacturers Task Force) dated 3/25/95 was a report for possible adverse effects (liver periportal vacuolation) of chloropicrin in rats from the two-year oral (gavage) chronic toxicity study (DPR volume/record #: 199-066/133871). No worksheet. M. Silva, 9/28/95.

070 146359 A letter from J.H. Butala (Technical Advisor Chloropicrin Manufacturers Task Force) dated 3/25/96 was a request to remove the "possible adverse effect" indication related to the nonglandular

stomach papillomas and mammary fibroadenomas. M. Silva, 4/22/97.

CHRONIC, DOG

** 055 129614 "Evaluation of Chloropicrin in a One Year Oral (Capsule) Toxicity Study in Dogs," (Wisler, J.A., IRDC, Mattawan, MI, Study #: 656-005, 4/1/94). Chloropicrin (purity = 99%) was administered by capsule to Beagle dogs (4/sex/dose) at 0 (corn oil), 0.1, 1.0 and 5.0 mg/kg for one year. NOEL = 1.0 mg/kg (Decreased body weight (males), MCV, MCH, total protein and albumin were observed at 5.0 mg/kg.) **No adverse effect.** Acceptable. M. Silva, 4/28/94.

052 122677 A letter from J.H. Butala (Technical Advisor Chloropicrin Manufacturers Task Force) dated 4/8/93 discussed results of "Evaluation of Chloropicrin in an Eight-Week Oral (capsule) Range-Finding Toxicity Study in Dogs," performed by IRDC, Study #: 656-004. The results of this preliminary study will be used to estimate dose levels for a one year oral (capsule) toxicity study in dogs. No worksheet. M. Silva, 11/23/93.

A letter from J.H. Butala (Technical Advisor Chloropicrin Manufacturers Task Force) dated 11/29/93 was an adverse health report for chloropicrin after evaluating the one year chronic dog study. There was no information beyond that observed by DPR in the definitive study (DPR volume/record #: 199-055/129614). No worksheet. M. Silva, 9/29/95.

ONCOGENICITY, RAT

** 067 139750, "Chloropicrin: Vapor Inhalation Oncogenicity Study in CD7 Rats," (Burleigh-Flayer, H.D. and C.L. Benson, Bushy Run Research Center (BRRC), Laboratory Project ID 92N1106, July 29, 1995). Chloropicrin (99.6% pure, technical) vapor was administered in air to CD* rats (50/sex/dose) at 0 (air), 0.1, 0.5 or 1.0 ppm for 6 hours/day (5 consecutive days/week) for at least 107 weeks. NOEL = 0.1 ppm/day (Mortality in males was increased in both sexes at ≥ 0.5 ppm (significant in males only). Clinical signs were increased in both sexes, primarily at 1.0 ppm. Absolute and relative (brain) lung and liver weights were increased at 1.0 ppm in both sexes. Nasal rhinitis was increased in both sexes, primarily at 1.0 ppm.) Oncogenicity NOEL = greater than 1.0 ppm (No oncogenicity was observed at any dose.) ACCEPTABLE. (Silva & Kishiyama, 9/28/95).

001 036211, "Bioassay of Chloropicrin for Possible Carcinogenicity", (Hazleton Laboratories America, Inc., Vienna, Virginia, NCI-CG-TR-65, 1978). Chloropicrin, purity 98%, administered dosages (time-weighted averages) of 25 and 26 mg/kg/day to 50 Osborne-Mendel male rats/group; 20 and 22 mg/kg/day to 50 Osborne-Mendel female rats/group (initial doses to males and females were 23 and 46 mg/kg/day in low and high dose groups but doses were changed during study including cyclical dosing); twenty untreated and twenty vehicle (corn oil) treated rats/sex served as controls. NOEL = < 20 mg/kg/day (based on mortality). Evaluation of Chloropicrin for carcinogenicity was not possible due to high mortality of dosed rats (both sexes). UNACCEPTABLE. Not upgradeable. (JSK, 12/6/88 and J. Gee, 2/27/85 and 12/6/88).

021 058190 Exact duplicate of 001 036211.

038 090206 Duplicate of 001 036211.

053 122678 A letter from J.H. Butala (Technical Advisor Chloropicrin Manufacturers Task Force) dated 4/12/93 discussed results of "Chloropicrin: Ninety-Day Inhalation Toxicology Study in Rats and Mice," performed at Bushy Run Research Center, Export, PA (Study #: 91N0098). Chloropicrin was administered by whole body inhalation for 6 h/day, 5 days/week to both sexes of rats & mice at 0, 0.3, 1.0 & 3.0 ppm for 3 months. Results of this preliminary study were used to estimate dose levels for the two-year inhalation study in rats & mice. No worksheet. M. Silva, 11/23/93.

ONCOGENICITY, MOUSE (See Chronic, rat for a Subchronic Inhalation Study in mice)

** 058 136552 "Chloropicrin: Vapor Inhalation Oncogenicity Study in CD-1 Mice," (Burleigh-Flayer, H.D., Kintigh, W.J. and Benson, C.L.; Union Carbide, Bushy Run Research Center, Export, PA; Laboratory Project ID #: 92N1105; 4/20/95). CD-1 mice (50/sex/dose) were exposed to chloropicrin (99.6% pure) vapor at 0 (air), 0.1, 0.5 or 1.0 ppm for 6 hours/day, 5 consecutive days/week for at least 78 weeks. Chronic NOEL = 0.1 ppm (Body weights and body weight gains were significantly decreased in both sexes at ≥ 0.5 ppm. Food consumption in males at 1.0 ppm and in females at ≥ 0.5 ppm was decreased. Absolute and relative lung weights were increased in a dose related manner in both sexes at ≥ 0.5 ppm. Macroscopic pathology at 1.0 ppm was increased in lung and kidney (increased lung nodules, kidney cysts, size decrease and color change) in males and in females (lung color change, hyperinflation and masses and kidney cysts--0.5 ppm). Microscopic pathology showed increased nasal cavity (serous exudate, hyaline epithelial inclusions, rhinitis, olfactory epithelial atrophy) and lung (alveolar protein deposits, alveolar histiocytosis, hemorrhage, peribronchiolar lymphocytic infiltrate, bronchiectasis, bronchial submucosal fibrosis, peribronchiolar smooth muscle hyperplasia) pathology, in addition to kidney cysts at ≥ 0.5 ppm.) Oncogenicity NOEL > 1.0 ppm (An increase in oncogenicity was not observed at any dose). No adverse effect. Acceptable. (M. Silva, 9/18/95).

001 036210, "Bioassay of Chloropicrin for Possible Carcinogenicity", (Hazleton Laboratories America, Inc., Vienna, Virginia, NCI-CG-TR-65, 1978). Chloropicrin, purity 98%, administered dosages (time-weighted averages) of 33 and 66 mg/kg/day to 50 B6C3F1 mice/sex/group for 78 weeks; twenty untreated and twenty vehicle (corn oil) treated mice served as controls. Chronic and oncogenic NOEL = <33 mg/kg/day, stomach changes in males and females. Number of dose levels (2) and number of control animals are inadequate. Report lacks data on the analysis of dosing solution, individual body weight, food consumption and clinical data. UNACCEPTABLE. Not upgradeable. (JSK, 12/6/88 and J. Gee, 2/27/85, 12/6/88).

EPA one-liner: No core grade, oncogenic NOEL > 70 mg/kg (HDT). No increase incidence of neoplasms at 50 to 70 mg/kg. Shortened survival time prevented definitive conclusions.

021 058190 Exact duplicate of 001 036210.

038 090206 Duplicate of 001 036210.

053 122678 A letter from J.H. Butala (Technical Advisor Chloropicrin Manufacturers Task Force) dated 4/12/93 discussed results of "Chloropicrin: Ninety-Day Inhalation Toxicology Study in Rats and Mice," performed at Bushy Run Research Center, Export, PA (Study #: 91N0098). Chloropicrin was administered by whole body inhalation for 6 h/day, 5 days/week to both sexes of rats & mice at 0, 0.3, 1.0 & 3.0 ppm for 3 months. Results of this preliminary study were used to estimate dose levels for the two-year inhalation study in rats & mice. No worksheet. M. Silva, 11/23/94.

REPRODUCTION, RAT

** 056, 064 132463, 138326 "Two Generation Inhalation Reproduction/Fertility Study in Rats," (Schardein, J.L., IRDC Mattawan, MI, ID #: 656-011, 9/28/94). A composite of chloropicrin (purity = 99%) was administered 6 hours/day (7 days/week) in filtered air to Charles River CrI:CD VAF/Plus rats (26/sex/dose; whole body exposure) at 0 (filtered air), 0.5, 1.0 and 1.5 ppm for 2 generations (through weaning of F2 pups). Systemic NOEL = 0.5 ppm (Both generations of females and F1 males showed transitory body weight decreases at ≥ 1.0 ppm. F1 females showed a significant decrease in food consumption at 1.5 ppm (days 0-20). Females (primarily F0) showed macro and microscopic pulmonary pathology at ≥ 1.0 ppm.) Pup NOEL > 1.5 ppm (No treatment-related effects were observed at any dose.) Reproductive NOEL > 1.5 ppm (No reproductive effects observed at any dose.) Previously

reviewed as unacceptable (Silva, 1/18/95), upon submission of the requested historical controls and data regarding genetic drift in Charles River CD rats, the study is upgraded to acceptable. M. Silva, 9/27/95.

A letter from J.H. Butala (Technical Advisor, Chloropicrin Manufacturers Task Force), dated 12/4/92 regards test results for "Reproduction Rangefinding Inhalation Study in Rats," performed by IRDC (Study #: 656-010). The letter discusses preliminary results. No volume or record number (no worksheet) accompanied the letter. M. Silva, 11/23/93.

A letter from J.H. Butala (Technical Advisor, Chloropicrin Manufacturers Task Force), dated 7/15/94 contains an adverse health effect report for the definitive rat reproduction study (DPR volume/record #: 199-056, 064 132463, 138326). It was stated that although it appeared there may be adverse effects for pulmonary inflammation (based on the rangefinding study), this was not observed in the definitive study. No worksheet. M. Silva, 9/29/95.

TERATOLOGY, RAT

** 051 122503 "Inhalation Developmental Toxicity Study in Rats," (Schardein, J.L., IRDC, MI, Project #: 656-007, 4/9/93). Chloropicrin technical (purity = 99%) was administered to mated Charles River CrI:CD VAF/Plus rats (30/group) at 0 (filtered air), 0.4, 1.2 & 3.5 ppm by whole body inhalation exposure daily (6 h/day) during days 6-15 of gestation. Cesarean sections were performed on day 20 of gestation (day 0 = evidence of mating--copulatory plug). Maternal NOEL = 1.2 ppm (Decreased body weight, body weight gain and food consumption and increased clinical signs were reported at 3.5 ppm. Developmental NOEL = 0.4 ppm: Previously reviewed as having a possible adverse effect (Silva, 11/19/93) based on a statistically significant increase in total fetal skeletal variations at ≥ 1.2 ppm, however there was no statistically significant increase when data were examined on a per litter basis.) The study status has been changed to acceptable, with no adverse effect. Silva, 11/15/01.

A letter from J.H. Butala (Technical Advisor, Chloropicrin Manufacturers Task Force), dated 6/29/92 regards possible adverse effects in the "Range-Finding Inhalation Developmental Toxicity Study in Rats," performed by IRDC (Study #: 656-006). It was stated that the dose levels for the definitive study were based on findings from this investigation (no adverse effects in this preliminary study). There was no volume or record number (no worksheet). M. Silva, 11/23/93.

A letter from J.H. Butala (Technical Advisor, Chloropicrin Manufacturers Task Force), dated 12/4/92 regards the results of the "Inhalation Developmental Toxicity Study in Rats," performed by IRDC. Information in the letter was stated to be unaudited (draft of the final report would follow). The final report was reviewed at DPR (volume record #: 051/122503). No volume or record number (no worksheet) was included with the letter. M. Silva, 11/23/93.

070 146363 A letter from J.H. Butala (Technical Advisor, Chloropicrin Manufacturers Task Force), dated 3/25/96 regards the results of the "Inhalation Developmental Toxicity Study in Rats," performed by IRDC. An appeal was made to remove the "adverse effect indication", due to increased fetal effects compared to maternal toxicity. M. Silva, 4/22/97.

TERATOLOGY, RABBIT

** 051 122504 "Inhalation Developmental Toxicity Study in New Zealand White Rabbits," (York, R.G., IRDC, MI, Project #: 656-009, 4/9/93). Chloropicrin technical (purity = 99%) was administered to artificially inseminated New Zealand White Rabbits SPF (20/group) at 0 (filtered air), 0.4, 1.2 & 2.0 ppm by whole body inhalation exposure daily (6 h/day) during days 7-20 of gestation. Cesarean sections were performed on day 29 of gestation (day 0 = day of insemination). **Maternal NOEL = 0.4 ppm**

(Decreased body weight, body weight gain & food consumption were observed at 2.0 ppm. Increased clinical signs, abortions & mortality occurred at ≥ 1.2 ppm.) **Developmental NOEL = 1.2 ppm**
(Increased developmental variations were observed at ≥ 2.0 ppm.) **ACCEPTABLE.** M. Silva, 11/19/93.

A letter from J.H. Butala (Technical Advisor, Chloropicrin Manufacturers Task Force), dated 12/4/92 regards the results of the "Inhalation Developmental Toxicity Study in New Zealand White Rabbits," performed by IRDC. Information in the letter was stated to be unaudited (draft of the final report would follow). The final report was reviewed at DPR (volume record #: 051/122504). No volume or record number (no worksheet) was included with the letter. M. Silva, 11/23/93.

GENE MUTATION

** 041 086982, "L5178Y TK +/- Mouse Lymphoma Mutagenesis Assay with Confirmation", (Richard H. C. San, Cynthia I. Sigler, Microbiological Associates, Inc., Rockville, MD., Study # T9152.701020, 4/26/90). Chloropicrin Technical (99.5% pure) was used in a forward mutation assay with L5178Y mouse lymphoma cells at 0, 0.038, 0.05, 0.067, 0.089, 0.12, 0.16, 0.21, 0.28, 0.38 or 0.50 nl/ml (-S9, initial trial) and 0, 0.89, 1.2, 1.6, 2.1, 2.8, 3.8, 5.0, 6.7, 8.9, 12, 16 or 21 nl/ml (+S9, initial trial) with 3 cultures/dose. S9 was from induced livers of adult male Sprague-Dawley rats (500 mg/kg of a 2:1 mixture of Aroclor 1242 and Aroclor 1254). A confirmatory test was performed (in duplicate) at 0, 0.36, 0.46, 0.56, 0.65 or 0.75 nl/ml (-S9) and 0, 9, 10, 12, 14, or 16 nl/ml (+S9). **No increase in forward mutation frequency** was reported. **Acceptable.** (H. Green & M. Silva, 7/15/92)

** **046 088717**, "Salmonella/Mammalian-Microsome Plate Incorporation Mutagenicity Assay (Ames Test) with a Confirmatory Assay", (Richard H. C. San, and Valentine O. Wagner, III, Microbiological Associates, Inc., Rockville, MD., Study # T9152.501014, 6/21/90). Chloropicrin Technical (99.5% pure) was tested with Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538 (triplicate plates) in the presence and absence of S9 activation from Aroclor 1254 induced male Sprague-Dawley rat livers at 0 (ethanol), 10, 33, 100, 333 or 1000 ug/plate (initial assay) and 0 (ethanol), 10, 3, 100, 333 and 500 ug/plate (confirmatory assay). **Possible adverse effect.** An increase in revertant colonies was observed both with and without S9. **Acceptable.** (H. Green & M. Silva, 7/15/92.)

038 090207, "Further Mutagenicity Studies on Pesticides in Bacterial Reversion Assay Systems", (Moriya, M., Ohta, T., Watanabe, K., Miyazawa, T., Kato, K. and Shirasu, Y., Institute of Environmental Toxicology, Tokyo, Japan, Mutation Research, 116:185-216, 1983). The assay was performed to test the mutagenicity of 228 pesticides (one of which was chloropicrin) on Escherichia coli (WP2 hcr) and Salmonella typhimurium strains TA100, TA98, TA1535, TA1537, and TA1538. Doses were stated to be tested up to 5000 ug/plate, unless the compounds showed toxicity to bacteria. If the compound showed mutagenicity only at doses from 1000-5000 ug/plate, then doses higher than 5000 ug/plate were used to obtain a dose-response. **RESULTS:** Of the 6 halogenated alkanes tested, all 6 were mutagenic. E. coli (WP2 hcr) & TA98 (no S9) and TA100 (with S9) were mutagenic with chloropicrin. These data are supplemental. M. Silva, 7/22/92.

038 090208, "Chemical Mutagenesis Testing in Drosophila. III. Results of 48 Coded Compounds Tested for the National Toxicology Program", (Department of Zoology, University of Wisconsin, Madison, WI; National Institute of Environmental Health Sciences, Research Triangle Park, NC; Department of Biological Sciences, Bowling Green State University, Bowling Green, OH and Division of Biology and Medical Sciences, Brown University, Providence, RI. Environmental Mutagenesis 7:325-348, 1985). Chloropicrin (91% pure) was used in a sex-linked recessive lethal test (SLRL) with Drosophila melanogaster Canton-S wild-type males were fed with 0 and 100 ppm (4 hour exposure) or injected with 0 and 150 ppm, then mated individually to 3 harems of Basc virgin females to produce 3 broods of 3, 2 & 2 days (so that primarily post-meiotic germ cells were tested. 40 or fewer F1 females were mated from each brood of each male (decrease the chances of recovering several lethals from the same male). Therefore, no more than 120 chromosomes were tested from each P1 male. Lethality in F2 was

scored as positive if the number of male wild-types recovered was $\leq 5\%$ of the number of Basc males (or Basc/+ females). The report considered the results to be questionable or equivocal. The data are considered supplemental. (M. Silva, 7/22/92)

038 090209, Auerbach, C., Experientia, 6:17-18, 1950. Brief Reports: This study was performed to determine the mechanism of mutagenicity of mustard gas. Mustard gas is on a list of "substances thioloпрives" whose toxic effects are primarily induced by reaction with -SH groups on enzymes. The toxicity of mustard gas, may be due to inactivation of hexokinase, and other phosphate-transferring, -SH containing enzymes (phosphokinases). Arsine gas also reacts with -SH groups and hexokinase, but unlike mustard gas is not mutagenic in Drosophila. Therefore, mustard gas mutagenicity is probably not caused by -SH blocking or phosphokinase inhibition. Chloropicrin was selected for this study since it is a potent -SH poison (blocks 50% of -SH groups in denatured ovalbumin in less than 1 minute; irreversibly blocks -SH groups on native ovalbumin and inactivates papaine; activity on phosphokinases is unknown). In this study, 3 series of tests were performed: **TEST #1:** Young Drosophila melanogaster males were exposed to chloropicrin (dose unspecified) for as long as they could tolerate it (the longest was 3 minutes). Then the survivors were used in a test for sex-linked lethals (from exposures of 2, 2.5 & 3 min). Results = 1 lethal/1318 X-linked chromosomes. **TEST #2:** Exposure was prolonged (6-9 min) by passing air through a mixture of chloropicrin and liquid paraffin. By altering the proportion of the 2 fluids, the tolerance threshold of exposure could be shifted. Results = 2 sex-linked lethals/463 chromosomes. It was therefore concluded that -SH poisoning does not produce mutations in mature sperm. **TEST #3:** Males were treated as in experiment #2 (5-7 min exposure), then they were mated with a new series of virgin females every 3-4 days (4 broods total) and lethals were scored/brood. Results = No increase in lethals over untreated controls. Therefore, the author concluded that -SH poisoning is not linked with the mutagenic action of mustard gas. These data are supplemental. M. Silva, 7/23/92.

CONCLUSION: Chloropicrin is mutagenic in more than one Salmonella strain (both with and without S9) and in one E. Coli strain (data obtained from both an acceptable FIFRA Guideline study and a study obtained from the open literature). On the other hand, chloropicrin was not mutagenic in L5178Y TK+/- Mouse Lymphoma cells (acceptable FIFRA Guideline study). The results of tests with Drosophila were equivocal (weakly positive/equivocal or negative). Valencia, et al., considered chloropicrin to be weakly mutagenic but Auerbach did not (sex-linked recessive lethal test reported in the open literature, neither were acceptable according to FIFRA Guidelines). When considering the structure of chloropicrin, an alkylating agent, one might expect it to be mutagenic, as it would bind non-specifically to macromolecules. However it is so non-specifically toxic that it functions only as a weak a mutagen and only in systems which can tolerate relatively high concentrations (high enough to allow sufficient chloropicrin to get to the DNA and mutate it). The high doses used in the bacterial tests were cytotoxic to mouse lymphoma cells. By weight of evidence, however, although weak, chloropicrin is mutagenic in certain test systems. M. Silva, 7/23/92.

CHROMOSOME ABERRATIONS:

**** 041 086983**, "Chromosome Aberrations in Chinese Hamster Ovary (CHO) Cells with Confirmatory Assay", (Donald L. Putman, Marcia J. Morris, Microbiological Associates, Inc., Rockville, MD., Study # T9152.337001, 5/31/90). Chloropicrin Technical (99.5% pure) was used with Chinese Hamster Ovary (CHO-K1) cells (2 cultures/dose) at: untreated (culture media only), 0 (ethanol), 0.0002, 0.0004, 0.0008, 0.0015, 0.003 ul/ml (1st assay -S9); 0.0005, 0.00075, 0.001, 0.0015 ul/ml (1st confirmatory assay -S9); 0.0004, 0.0006, 0.0008, 0.001 ug/ml (2nd confirmatory assay -S9) or 0.003, 0.004, 0.005, 0.006 ul/ml (1st assay +S9); 0.002, 0.003, 0.004, 0.005 or 0.006 ul/ml (1st confirmatory assay +S9). S9 was from livers of Aroclor 1254 (500 mg/kg) induced male Sprague-Dawley rats. Cells were exposed for 10 hours (non-activated) and 2 hours (activated). A minimum of 100 metaphase spreads were scored (50/duplicate flask). **Possible adverse effect:** A significant increase in chromosomal aberrations was

observed without S9 at ≥ 0.0075 ul/ml. **Acceptable.** (H. Green & M. Silva, 7/15/92).

DNA DAMAGE

** 046 088718, "Unscheduled DNA Synthesis in Rat Primary Hepatocytes with a Confirmatory Assay", (Roger D. Curren, Microbiological Associates, Inc., 9900 Blackwell Road, Rockville, MD., Study # T9152.380009, 6/28/90). Chloropicrin Technical (99.5% pure) was used in an unscheduled DNA synthesis assay with adult male Fischer 344 rat primary hepatocytes (triplicate plates) at untreated, 0 (ethanol), 0.0003, 0.001, 0.003, 0.004, 0.005, 0.006 and 0.009 (initial assay) ul/ml. A confirmatory assay was performed at the same doses. No increase in UDS was observed. **Acceptable.** (H. Green & M. Silva, 7/17/92).

NEUROTOXICITY

Not required at this time.

SUPPLEMENTAL STUDIES

038 090204, "Acute Inhalation Toxicity of Chloropicrin Vapor in Rats", (Yoshida, M., Ikeda, T., Iwasaki, M., Tsuda, S. and Shirasu, Y., Mitsukaido Laboratories, Institute of Environmental Toxicology, Japan, J. Pesticide Sci. **12**:237-244 (1987)). Chloropicrin (99.6% pure) was used in a whole-body inhalation exposure of male Fischer 344 rats (6/group) at mean analytical concentrations of 8.8, 11.0, 11.4, 12.1, 13.6, or 16.0 ppm or a 30 minute exposure at 21.7 and 45.5 ppm (analytical dose; 7 & 6 rats/group, respectively). Rats were observed frequently during the exposure for signs of toxicity, 2 hours after exposure and at least once/day for 14 days post exposure. Body weights were measured before exposure, weekly thereafter and at termination. Necropsies were performed and organ weights were measured on all rats (brain, lungs, liver, kidneys and testes). Analysis of chloropicrin doses were within 15% of nominal. # deaths/# exposed at 4 hours with increasing dose: 0/8, 2/8, 3/8, 5/8, 7/8, and 8/8 respectively. # deaths/# exposed at 30 minutes with increasing dose: 0/7 and 6/6 respectively. Development of deaths was biphasic: 1st phase was within 24 hours post-exposure and the 2nd phase was between days 8 and 10 post-exposure. **NECROPSY RESULTS: 4-Hour Exposure:** Animals that died in the first 24 hours showed body weight loss, diffuse pulmonary edema & emphysema, hydrothorax, gastric gaseous distension and a large increase in absolute lung weight. Rats which died between days 8 & 10 showed similar effects with scattered red patches in the lungs and a large increase in absolute lung weights. Animals which survived to termination showed diffuse emphysema, focal pulmonary edema, scattered dark red patches in the lungs and gastric gaseous distension. Significant increases were: lung weight at 12.1 ppm, lung/body weight at ≥ 11.0 ppm (due to decreased terminal body weights) and lung/brain weight at 11.0 and 12.1 ppm. **30-Minute Exposure:** All rats at 45.5 ppm died on day 6 or 7 but no deaths occurred at 21.7 ppm. Shortly after exposure was initiated, eyelid closure, decrease in spontaneous motor activities and labored breathing were observed in all rats at ≥ 21.7 ppm. Eyelid closure and decrease in spontaneous motor activities disappeared immediately after the exposure was discontinued. Although rhinorrhea decreased within 2 hours, labored breathing remained for 1-2 days. Many rats at 45.5 ppm showed labored breathing and/or blood-like red stains on the fur around the nose and mouth from day 5 until death. At 45.5 ppm, there was an increase in absolute lung weight. Body weights were significantly decreased 1 week after exposure for all groups at both time periods. LC50 = 11.9 ppm. **These data are supplemental.** (M. Silva, 7/21/92.)

038 090205, "Subchronic Inhalation Toxicity of Chloropicrin Vapor in Rats", (Yoshida, M., Ikeda, T., Iwasaki, M., Ikeda, M., Harada, T., Ebino, K., Tsuda, S. and Shirasu, Y., Mitsukaido Laboratories, Institute of Environmental Toxicology, Japan, J. Pesticide Sci. **12**, 673-681 (1987)). Chloropicrin (99.7% pure) was used on male Fischer 344 rats (12/group) in a whole body exposure (6 hrs/day, 5 days/week)

for 13 weeks at mean analytical rates of 0, 0.37, 0.67, 1.58, or 2.93 ppm. All animals were observed daily. Body and organ (brain, pituitary, lungs, heart, kidneys, liver, spleen, adrenals, testes) weights, urinalysis, hematology and serum biochemistry were measured and necropsies were performed.

RESULTS: No deaths occurred. Eyelid closure and decreased motor activity occurred at all doses. Reduced mean bodyweights throughout treatment was observed at ≥ 1.58 ppm. Food consumption and food efficiency were initially lower at ≥ 1.58 ppm. No effects on ophthalmology or urinalysis. Significantly increased terminal red blood cell count, hematocrit, hemoglobin, alkaline phosphatase and BUN and decreased total cholesterol were observed at 2.93 ppm. Significantly increased lung weights occurred at ≥ 1.58 ppm. Histopathology revealed Catarrhal inflammation of the nasal cavity (respiratory region), thickening of the epithelial layer (larynx), epithelial hypertrophy (trachea), epithelial degeneration/necrosis/desquamation, hypertrophy of bronchial gland and thickening of bronchial wall (bronchus) and epithelial degeneration/necrosis and thickening of bronchiolar wall (bronchiole) occurred at 2.93 ppm. Epithelial hypertrophy (bronchus & bronchiole) was observed to significantly increase at ≥ 1.58 ppm. Reported NOAEL = 0.67 ppm. The study was performed according to USEPA Guidelines. **The data are supplemental.** (M. Silva, 7/21/92).