CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY

DEPARTMENT OF PESTICIDE REGULATION

HUMAN HEALTH ASSESSMENT BRANCH

Summary of Toxicological Data: Chloropicrin

Original: 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, 11/17/09 and 2/7/23 [redacted] 2/9/2023

Table of Contents

INTRODUCTION

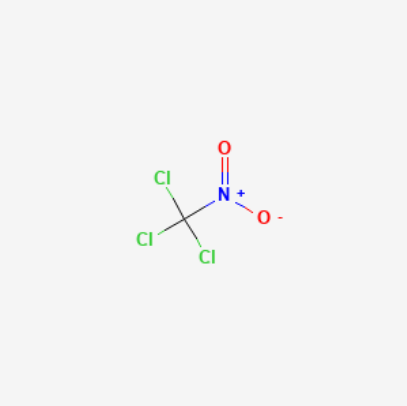
DPR Background

File Name: T230207
DPR Chemical Code: 136
Data Volume Nos.: 199-0001, -0017, -0038, -0041, -0046, -0051, -0055, -0056, -0058, -0064, -0066, -0067, -0074, -0081, -0082, -0088, -0115, -0133, -0134, -0167, -0168
SB 950: 15
Original: T871208
Revised: T230207
About This Document: Toxicology one-liners are attached. All record numbers for the above study types 036210 through 343071, (Data Volume Numbers 199-0001 through 199-0168) were examined. This includes all relevant studies indexed by DPR as of 2/7/23. This record contains summaries of studies. Individual worksheets may be useful for detailed assessment. In the 1-liners below: ** indicates an acceptable study.

Chemical Properties

IUPAC Name: trichloro(nitro)methane
CAS No.: 76-06-2
Description: slightly oily colorless to yellow liquid with a strong irritating odor
Molecular Weight: 164.4
Melting Point: -64 °C
Boiling Point: 112 °C at 757 mm Hg
Density: 1.6448 at 20 °C
Partition Coefficient: log Kow = 2.09
Water Solubility: 0.19 g/100 ml H2O at 20 °C
Vapor Pressure: 24 mm Hg at 25 °C

Chemical Structure



Physical and Chemical Properties and Structure from: Chloropicrin | CCl3NO2 - PubChem (nih.gov)

HAZARD IDENTIFICATION SUMMARY

Chloropicrin is a broad-spectrum soil fumigant. It is a liquid under ambient conditions which is highly volatile with a vapor pressure of 24 mm Hg at 25 °C. It is a highly irritating chemical whose acute toxic profile is Category I for both systemic and localized irritation criteria. There are no dermal sensitization studies on file with DPR. In a mouse single 6-hour exposure study, the Club cell was identified as the target with necrosis noted throughout the extrapulmonary, midlevel and bronchiolar airways at a LOEL of 0.5 ppm.

For the longer-term multiple dosing regimens, either oral dosing or inhalation exposure protocols have been employed. In a non-guideline mouse 5-day exposure, a LOEL of 1 ppm was identified for nasal lesions. In the rat combined chronic oral toxicity and oncogenicity study, the study animals manifested a localized effect of an increased incidence of hyperkeratosis and epithelial hyperplasia in the nonglandular stomach at a treatment level of 10 mg/kg/day. There was a possible oncogenic effect of an increased incidence in mammary fibroadenomas in the females. In the rat subchronic inhalation toxicity study, histological lesions were identified in the nasal cavity and lungs at a LOEL of 1.0 ppm. Decreased survival was noted for the males at exposure levels of 0.5 ppm and above in the rat chronic inhalation toxicity study. An oncogenic potential was not noted. In the mouse inhalation oncogenicity study, the histological lesions were manifested in the nasal cavity and lungs at a LOEL of 0.5 ppm. Absolute and relative lungs weights were increased for both sexes at 0.5 ppm and above. An increase in lung adenoma and carcinomas was reported for the females in the 1.0 ppm group. In the genotoxicity battery, an increase in reverse mutations was noted in two of the studies and negative in a forward mutation assay. One of two *in vitro* chromosomal aberration studies was positive for an increase in aberrations in the absence of activation. Otherwise one *in vitro* and one *in vivo* Unscheduled DNA Synthesis assays did not indicate a positive response.

The rat two-generation reproduction toxicity and rat and rabbit developmental toxicity studies were performed using an inhalation exposure regimen. Exposure for the animals in the reproductive toxicity study was limited to a maximum of 1.5 ppm. For the rat developmental toxicity study exposures up to 3.5 ppm were employed. The maximal exposure level used in the rabbit developmental toxicity study was 2.0 ppm. At those exposure levels there were no apparent effects upon reproduction or fetal development.

At treatment levels for which nasal and pulmonary lesions were evident, there was no manifestation of neurotoxic endpoints. Likewise, tissues/organs pertinent to the functioning of the immune system were not affected by the treatment.

METABOLISM AND PHARMACOKINETICS

No studies on file with DPR.

GUIDELINE ACUTE STUDIES ON ACTIVE INGREDIENT

Acute Oral Toxicity, Rat

199-017 47669; Acute oral toxicity; 811; Male Rats; U.S. Testing Co., Study# not reported; 4/76; Trical Technical Chloropicrin; 10 males/dose, administered by gavage at 25.0, 50.4 and 63.0 mg/kg; mortality: 25.0: 2/10; 50.4: 7/10; 63.0: 9/10; The only major finding reported was the day of death and the resulting oral LD_{50} in male rats (37.5 mg/kg). No other details concerning the study outcome were reported (e.g., no daily

clinical signs or necropsy findings were presented). Reported LD50 (M) = 37.5 mg/kg; (i.e., Toxicity Category I); Study Unacceptable; not upgradeable. [redacted] 8/17/00).

Acute Dermal Toxicity, Rat

199-017 47671; Acute dermal toxicity; 812; Rabbit; U.S. Testing Co., Study# not reported; 4/76; Trical Technical Chloropicrin; 6 rabbits/dose (sex unspecified), administered dermally (with semi-occlusive wrap) at 100 and 140 mg/kg for 24 hours; mortality: 100: 3/6; 140: 5/6; Dermal irritation included moderate edema during the first 24 to 48 hours after bandage removal, with discoloration of the skin; some necrosis appeared on the ventral side on three of the survivors (from gravity induced downward flow of test material); the only other major findings reported were the day of death and the resulting dermal LD_{50} (100 mg/kg). No other details concerning the study outcome were reported (e.g., no daily clinical signs or necropsy findings were presented). Reported LD50 = 100 mg/kg; (i.e., Toxicity Category I); Study Unacceptable; not upgradeable. [redacted] 8/17/00).

Acute Inhalation Toxicity, Rat

199-082 172375; Chloropricrin: An Acute (4-Hour) Inhalation Toxicity Study in the Rat via Whole-Body Exposure; Hoffman, G.; Huntingdon Life Sciences, East Millstone, New Jersey; # 99-5387, 11/11/99; Chloropicrin (purity >99%); 5 rats/sex/group; Exposure Concentrations (analytical): 0.0, 10.5, 18.0 and 23.5 ppm; MMAD (GSD): NA (v.p. of 5.7 mm Hg @ 0°C), 4-hour whole-body exposure; 48-hour observation period; Mortality: 0.0 (M/F: 0/5), 10.5 (M/F: 0/5), 18.0 (M/F: 3/5, 1/5), 23.5 (M/F: 5/5, 4/5); Clinical Observations (during exposure): labored breathing and/or gasping, decreased activity and closed eyes; (soon after exposure and persisting to sacrifice): lacrimation, nasal discharge, salivation, dried brown material on face, labored breathing and/or gasping and moist rales; body weight losses noted during 2 days after exposure; Necropsy: red lungs and fluid in trachea and lungs; Micropathology: lumenal fibrin, congestion of respiratory mucosa, and necrosis/erosions of respiratory epithelium of nasoturbinal tissue; epithelial necrosis, erosions, ulcers and inflammation of nasopharynx; lumenal fibrin and inflammatory cells, vascular congestion, edema and necrosis of larynx and trachea; desquamation/erosion of bronchiolar epithelial cells with vascular congestion, edema, focal hemorrhages, and inflammation (e.g. increased alveolar macrophages) of the lung; no NOEL: respiratory tract effects at all dose levels 2 days after exposure; 48-hour LC50 (M):16.7 ppm (0.12 mg/l at STP); (F): 20.1 ppm (0.15 mg/l at STP); Supplemental study; Toxicity Category not determined. [redacted], 1/13/00).

199-081 172374 Addendum to -082 172375; Chloropicrin: A Sensory Irritation Study in the Mouse via Head-only Exposure; Hoffman, G.; Huntingdon Life Sciences, East Millstone, New Jersey; # 99-5388, 11/11/99; Chloropicrin (purity > 99%); 4 male mice/group; Exposure Concentrations (analytical): 0.99, 3.20, 4.20, 7.25, 10.0 and 14.5 ppm; MMAD (GSD): NA (v.p. of 5.7 mm Hg @ 0°C); potential sensory irritation of chloropicrin (as determined by respiratory rate depression) was assessed when administered for 30 minutes via head-only exposure to Swiss-Webster mice; mortality: none; no abnormal clinical signs; Respiratory rate decrease (%) from pre-exposure level was 30, 55, 65, 72, 73 and 77%, respectively; chloropicrin vapor resulted in respiratory depression in mice with an RD_{50} of 2.34 ppm (0.017 mg/l at STP). Supplemental Study. ([redacted], 1/18/00).

199-017 47670; Acute inhalation toxicity; 813; Rats; U.S. Testing Co., Study# not reported; 4/76; Trical Technical Chloropicrin; 5 rats/sex/dose, administered by inhalation (whole-body) at 21.74, 49.67 and 74.55 ppm for one-hour exposure; mortality (sex of decedents not specified): 21.74: 4/10; 49.67: 7/10; 74.55: 8/10; The only major findings reported post-exposure was the day of death and the resulting one-hour inhalation LC_{50} in rats (25.5 ppm); The animals exhibited gagging response and irritation to the eyes and mucous membranes during exposure (dose response not indicated). This study had major deficiencies, including

inadequate exposure period and the lack of post-exposure clinical signs and necropsy findings. Reported one-hour LC50 = 25.5 ppm (equivalent to approx. 0.2 mg/l); Toxicity Category not determined; Study Unacceptable; not upgradeable. ([redacted], 8/17/00).

Primary Eye Irritation, Rabbit

No study on file with DPR.

Primary Dermal Irritation, Rabbit

199-017 47672; Primary Dermal Irritation; 815; Rabbit; U.S. Testing Co., Study# not reported; 4/76; Trical Technical Chloropicrin; 6 rabbits (sex not specified), administered dermally (0.5 ml) under a patch of surgical gauze and secured with tape (exposure period of 4 hours); The only major finding reported was that the test compound was considered corrosive based on necrosis at 72 hours; (i.e., Toxicity Category I); surrounding erythema was seen; Study Unacceptable (rabbits only observed up to 72 hours); not upgradeable. ([redacted] 8/17/00).

Dermal Sensitization

No studies on file with DPR.

SUBCHRONIC STUDIES

Rat Subchronic Inhalation Toxicity

** 199 - 088 183793 "Chloropicrin: 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 CD® rats (10/sex/dose) and CD-1® 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 $\geq$ 1.0 ppm. Nasal cavity and lung histopathology at $\geq$ 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 $\geq$ 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 ($\geq$ 1.0 ppm) were increased. There was an increase in nasal cavity and lung histopathology at $\geq$ 1.0 ppm.) Possible adverse effect (There was increased mortality (rat), and nasal cavity and lung histopathology in both rat and mouse.) Acceptable. [redacted], 11/15/01.

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 $\geq$ 1.58 ppm. Food consumption and food efficiency were initially lower at $\geq$ 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 and bronchiole) was observed to significantly increase at ≥ 1.58 ppm. Reported NOAEL = 0.67 ppm. The study was performed according to US EPA Guidelines. The data are supplemental. ([redacted] 7/21/92).

CHRONIC STUDIES

Combined Chronic and Carcinogenicity, Rat

** 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 Crl: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 significant 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. [redacted], 10/14/99.

** 067 139750, "Chloropicrin: Vapor Inhalation Oncogenicity Study in CD® 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 (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. ([redacted] and [redacted] 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. (J. Gee, 2/27/85, [redacted] and [redacted] 12/6/88).

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 significantly toxic effect. Acceptable. [redacted], 4/28/94.

Oncogenicity, Mouse

** 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 $\geq$ 0.5 ppm. Food consumption in males at 1.0 ppm and in females at $\geq$ 0.5 ppm was decreased. Absolute and relative lung weights were increased in a dose related manner in both sexes at $\geq$ 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 $\geq$ 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). NOTE: Lung tumor data and non-neoplastic lung pathology from this study were re-examined in response to new submission 00199-0133 249017, below. That re-examination suggested that this study should be re-classified to indicate a "possible adverse effect."

00199-0133 249017 McConnell, E. E. "Comments on the interpretation of CD-1 mouse lung pathology in the Chloropicrin inhalation study" (4 pp.) and Haseman, J. K., "Comments on the statistical evaluation and interpretation of female CD-1 mouse lung tumors in the Chloropicrin inhalation study (4 pages). This record contains comments relating to an existing mouse oncogenicity study, namely DPR Document No. 199-058, Record No. 136552, "Chloropicrin: Vapor Inhalation Oncogenicity Study in CD® Rats," (Burleigh-Flayer, H.D. and C.L. Benson, Bushy Run Research Center (BRRC), Laboratory Project ID 92N1106, July 29, 1995). DPR review was performed on the original report by Silva, 9/28/95. Concerns emerging from a Risk Assessment on Chloropicrin underway at DPR prompted the present submission. The intent of this submission was to address concerns about a modest increase in lung bronchoalveolar adenomas and carcinomas in female CD-1 mice in the cited study. The 1995 review by Silva had tabulated the incidences of bronchoalveolar findings, including tumors, but had not determined that the study indicated an oncogenic response. A DPR Risk Assessment is currently in process for chloropicrin, which has been provided to external state agencies and stakeholders for comment. This draft assessment considers evidence for a meaningful increase in tumors in lungs of 1.0 ppm female mice to treat chloropicrin as an oncogen. The present review by the DPR Data Review Group was provided to reconcile the conclusions of the original DPR reviewers, the DPR Risk Assessment in process, and the responses to the latter by the authors of the two "comments" submissions in Record No. 249017. This reconciliation first considered four concerns in the present record relating to the chloropicrin risk assessment draft concerns about oncogenicity in mouse lungs, namely (1) the relevance of an alternative to Fisher's exact test to compare lung bronchoalveolar tumor incidence in control and high dose females, (2) the relevance of slightly increased multiplicity of such lung tumors in treated vs. control mice, (3) the slight reduction in mean time to tumor in high dose females, and (4) paucity of suitable historical control incidence data for inhalation studies in this mouse strain. This review gives survival data for females, which

show very similar survival patterns in controls and high dose mice, and indicate no need for specialized analytical techniques for tumor incidence analysis. Multiplicity of lung tumors is sometimes evaluated in studies such as NTP rodent bioassays, taking on particular importance when background incidence is high (such as the NTP tetranitromethane rat and mouse cancer bioassays). In the present study, it appears that incidence alone would suffice for group comparisons, and nevertheless multiplicity was not significantly elevated (by Fisher's exact test). The mean time to tumor difference between controls and high dose females was 11 days (based on 3 decedents with tumors in high dose females, vs. 1 such decedent in controls: tumors not considered to be cause of death). This does not appear to reflect a treatment effect. Historical control data in this strain for inhalation studies appear to be rare, but Charles River Laboratories data for the period of this study (same strain, same exposure period, but not same route) indicate that mean bronchoalveolar adenoma incidence in all groups in the present study (including controls of both sexes) were well above historical control means, whereas carcinoma incidences of all groups in the present study were similar to historical norms. McConnell noted that most studies showing clear bronchoalveolar tumor responses (1) have well-defined dose-response patterns, (2) frequently elicit unusual morphological characteristics in treated animals with tumors, and (3) (as also noted by Haseman) typically do not show differential responses between sexes. Items #1 and #3 are generally borne out in the 4 NTP reference studies examined by Aldous from Haseman's analysis. Unusual morphological characteristics of neoplastic lesions were reported for the very potent lung oncogen, tetranitromethane, but were not commonly detailed in the other studies with less profound responses. The present review affirmed that non-neoplastic changes in lungs support the NOEL of 0.1 ppm held by the original investigators, by the original DPR reviewer, and by the author of the DPR draft risk assessment document. Nevertheless, several cases of bronchiectasis in 0.1 ppm males and females, but not in controls of either sex, could justify a lower extrapolated NOEL. The current DPR reviewer (Aldous) concludes that the indications of oncogenicity in the lung are not strong enough to warrant designating as treatment-related. There was ample evidence of local irritation to the nasal and lung epithelia to base a NOEL on chronic local irritant effects, the pivotal findings of this study. The original review of 1995 did not designate a "possible adverse effect." That determination may have reflected the reviewer's judgement that no oncogenicity was evident from the study. This reviewer (Aldous) considers the strong irritant responses evident in the nasal and lung epithelia to warrant designation as a "possible adverse effect." [redacted], 11/16/09.

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. (J. Gee, 2/27/85; Gee and Kishiyama, 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.

GENOTOXICITY

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. ([redacted] and [redacted], 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 µg/plate (initial assay) and 0 (ethanol), 10, 3, 100, 333 and 500 µg/plate (confirmatory assay). Possible significantly toxic effect. An increase in revertant colonies was observed both with and without S9. Acceptable. [redacted] and [redacted], 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 µg/plate, unless the compounds showed toxicity to bacteria. If the compound showed mutagenicity only at doses from 1000-5000 µg/plate, then doses higher than 5000 µg/plate were used to obtain a dose-response. RESULTS: Of the 6 halogenated alkanes tested, all 6 were mutagenic. E. coli (WP2 hcr) and TA98 (no S9) and TA100 (with S9) were mutagenic with chloropicrin. These data are supplemental. [redacted], 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 and 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. ([redacted], 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 thioloprives" 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 and 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. [redacted] 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 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. [redacted], 7/23/92.

Chromosome Damage

** 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 µl/ml (1st assay -S9); 0.0005, 0.00075, 0.001, 0.0015 µl/ml (1st confirmatory assay -S9); 0.0004, 0.0006, 0.0008, 0.001 µg/ml (2nd confirmatory assay -S9) or 0.003, 0.004, 0.005, 0.006 µl/ml (1st assay +S9); 0.002, 0.003, 0.004, 0.005 or 0.006 µl/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 significantly toxic effect: A significant increase in chromosomal aberrations was observed without S9 at $\geq$ 0.0075 µl/ml. Acceptable. ([redacted] and [redacted], 7/15/92).

**199-0134 249858 Mehmood, Z., "Chloropicrin: mouse micronucleus test," Huntingdon Life Sciences Ltd., Huntingdon, England, 11/20/03. Laboratory Study #: RDB 002/023006. Five to 7 male CD-1 mice were dosed once by gavage with 0, 62.5, 125, or 250 mg/kg chloropicrin (technical, 99.9% purity) 24 hrs prior to sacrifice and collection of cell suspensions from femur bone marrow for micronucleus evaluation. Vehicle was corn oil (20 ml/kg b.w.). Positive control was 0.6 mg/kg of Mitomycin C. In addition, similar groups of mice were pre-treated with 0 or 250 mg/kg chloropicrin 48 hrs prior to sacrifice for micronucleus evaluation. Dose levels were based on a preliminary test, showing mortalities and clinical signs such as piloerection, underactive behavior, hunched position, and irregular respiration at 300 mg/kg; and similar signs without mortalities at 250 mg/kg. Three of 14 mice at 250 mg/kg in the main study died prior to scheduled termination, validating adequacy of dose levels used. There was no sex difference

evident in the preliminary studies, hence only males were used in the primary study. There were no increases in polychromatic erythrocytes (PCE's) with micronuclei at any dose level chloropicrin at either pre-treatment period. Positive control was highly effective. Study is acceptable, with no adverse effects. [redacted] 10/26/09.

DNA Damage or Miscellaneous Effects

** 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) µl/ml. A confirmatory assay was performed at the same doses. No increase in UDS was observed. Acceptable. ([redacted] and [redacted] 7/17/92).

**199-0134 249859 Mehmood, Z., "Chloropicrin: rat liver DNA Repair (UDS) test," Huntingdon Life Sciences Ltd., Huntingdon, England, 11/20/03. Laboratory Study #: RDB 003/023007. Groups of 5 male Sprague-Dawley rats were dosed by gavage with single doses of Chloropicrin Technical, Batch No. 001-255F, purity 99.9% either 2 hrs or 14 hrs before sacrifice and collection of hepatocytes for evaluation of DNA damage based on nuclear grain counts following tritiated thymidine exposure. Dose levels of chloropicrin were 0, 85, and 250 mg/kg. The high dose caused clinical signs such as "piloerection, underactivity or overactivity, flattened and hunched posture, abnormal gait, fast and irregular respiration, partially closed eyelids, and thin appearance," verifying that this was a maximum tolerable exposure level. Dimethylnitrosamine was positive control for the 2-hr exposure group, and 2-acetylaminofluorene was used for the 14-hr exposure group. Both gave definitive positive responses. Chloropicrin was uniformly negative in these assays. Study is acceptable, with no adverse effects. [redacted], 11/16/09.

REPRODUCTIVE TOXICITY

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 Crl: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 $\geq$ 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 $\geq$ 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. [redacted] 9/27/95.

199-0115; 217717; "Reproduction Range-Finding Inhalation Study in Rats"; (K. H. Denny; MPI Research, Mattawan, MI; Project ID. No. 656-010; 7/30/96); Ten Crl:CD® VAF/Plus rats/sex/group were exposed whole-body to 0, 0.4, 1.0 or 2.0 ppm of Chloropicrin (Lot no. 920130-1, purity: >99%) for 6 hours/day during a 2-weeks premating period, up to a 15-day mating period, and a 20-day gestation period. No deaths resulted from the exposure. The mean body weights of both sexes in the 2.0 ppm

exposure group were less than the control values during the premating period (NS, $p<0.01$). The mean food consumption of this group was less than that of the control during this time period. For the reproduction indices, the number of implantation sites/dam of the 2.0 ppm dams was less than that of the controls (control: 13.8 sites/dam vs. 2.0 ppm: 9.6 sites/dam). Otherwise, no treatment-related effect was evident in the development of the offspring. No significantly toxic effect indicated. Parental NOEL: (M/F) 1.0 ppm (based upon lower mean body weights and reduced food consumption of both sexes in the 2.0 ppm group); Reproductive NOEL: 1.0 ppm (based upon the lower number of implantation sites per dam of the dams in the 2.0 ppm group; Developmental NOEL: 2.0 ppm (based upon the lack of effect on the development of the offspring in the 2.0 ppm group); Study supplemental (non-guideline study). ([redacted], 4/11/08)

DEVELOPMENTAL TOXICITY

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 Crl:CD VAF/Plus rats (30/group) at 0 (filtered air), 0.4, 1.2 and 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 based on 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 $\geq$ 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. [redacted], 11/15/01.

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 and 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 and food consumption were observed at 2.0 ppm. Increased clinical signs, abortions and mortality occurred at $\geq$ 1.2 ppm.) Developmental NOEL = 1.2 ppm (Increased developmental variations were observed at $\geq$ 2.0 ppm.) ACCEPTABLE. [redacted], 11/19/93.

NEUROTOXICITY

Acute Neurotoxicity, Rat

No study on file with DPR nor required at this time.

90-Day Neurotoxicity, Rat

No study on file with DPR nor required at this time.

Developmental Neurotoxicity, Rat

No study on file with DPR nor required at this time.

IMMUNOTOXICITY

No study on file with DPR nor required at this time.

ENDOCRINE DISRUPTOR STUDIES

No study on file with DPR nor required at this time,

SUPPLEMENTAL STUDIES

199-0167; 343071; "Evaluation of the Effects of Chloropicrin on the Lungs of Mice with the Goal of Creating a Better Understanding of Chloropicrin Mechanism of Cytotoxicity in the Respiratory Tract of Mice Following the Inhalation of Chloropicrin Vapor"; (L.S. Van Winkle; Center for Health and the Environment, University of California, Davis, Davis, CA; Laboratory Project ID. CMA001; 9/2/22). The stated purpose of the initial study was to elucidate the lung target cell type and the region(s) of the lungs affected by exposure to low levels of chloropicrin. A follow-up investigation was undertaken to identify if there was a sex-related difference in response and if glutathione levels were affected and/or if there was oxidative DNA damage. In Study No. 1, 12 female CD-1 mice/group were exposed nose-only to 0 (filtered air), 50, 100, 500 or 1000 ppb (nominal) of Chloropicrin (purity 99.5%) for 6 hours/day for either 1 or 5 days. Respective analytical exposure levels were 44, 96, 439, and 778 ppb for the single day exposure. Mean analytical exposure levels for the 5-day regimen were 51, 111, 391, and 1048 ppb. Six animals/group/time point were euthanized at 2 or 16 hours post-exposure or post-final exposure. The lungs were excised and fixed with Karnovsky's fixative while inflated. The tissues were processed and embedded in Araldite 502 epoxy. A minimum of one block each from extra- and intrapulmonary tissue were prepared and examined by high resolution microscopy. In Study No. 2, part 1, 6 animals/sex/group were exposed for 6 hours to either 0 or 500 ppb of Chloropicrin and euthanized at 2 hours post-exposure. In Study No. 2, part 2, 6 animals/sex/group were likewise exposed for 6 hours to 0 or 500 ppb and euthanized at 16 hours post-exposure. The analytical concentration for both parts of the study was 517 ppb. Samples of lung and trachea tissue from animals euthanized at 2 hours post-exposure were measured for DNA oxidation. DNA was isolated and 8-OHdG was measured using the Oxiselect Oxidative DNA Damage ELISA kit. Glutathione (GSH) and glutathione disulfide (GSSG) levels were also measured in the lung and trachea tissues of these animals, using HPLC. Protein concentrations were determined in these samples to normalize the GSH and GSSG levels. For the animals euthanized at 16 hours the trachea and lung tissues were examined by high resolution microscopy for potential injury. In the first study the histological examination revealed that the Club cell was the target for chloropicrin-mediated effects. These cells demonstrated an exposure-related incidence of swelling and cytoplasmic vacuoles with the hierarchy of severity being greatest in the midlevel airways, followed by the terminal bronchioles and lastly the extrapulmonary airways. This effect was more severe after a single exposure than after the 5-daily exposure regimen. After a single exposure, a lowest effect level (LOEL) of 500 ppb was observed for all

three regions of the lung. For the animals exposed 5 times, the selection of a LOEL was more equivocal due to the diminished response and possible trauma resulting from insertion of the cannula to inflate and fix the lung for histological examination. The 500 ppb exposure level selected for the second study was based upon the LOEL noted for the single 6-hour exposure. In Study No. 2, part 1, after 6 hours of exposure to 500 ppb of the test material, the oxidized DNA assay did not indicate an increased content of 8-OHdG/µg DNA at 2 hours post-exposure. Likewise the normalized GSH content in either the whole lung, trachea, or airways did not demonstrate a substantive alteration at 2 hours post-exposure. The content of GSSG in these tissues was not quantifiable. Histological examination of the midlevel intrapulmonary tissue revealed a more severe response in the males than the females at an exposure level of 500 ppb at 16 hours post-exposure. Overall, the Club cell was the target with the greatest effect being evident in the midlevel airways. A certain degree of adaptation was evident after multiple exposures. The observed effects did not seem to be the result of direct oxidative effect on the DNA. The males actually demonstrated a more severe response to the chloropicrin exposure than did the females. Supplemental study ([redacted] 12/15/22)

199-0168; 345350; "Evaluation of the Effect of Chloropicrin on the Nasal Tissue of Mice with the Goal of Creating a Better Understanding of Chloropicrin Mechanism of Cytotoxicity in the Respiratory Tract of Mice Following the Inhalation of Chloropicrin Vapor"; (L.S. Van Winkle, T.A. Crabbs; Center for Health and the Environment, University of California, Davis, Davis, CA, Experimental Pathology Laboratories, Inc., Durham, NC; Study No. CMA001-SUPP; 1/4/23); In the 1st study nasal tissue recovered from the CD-1 female mice exposed to 0, 50, 100, 500 or 1000 ppb (nominal) of Chloropicrin (purity 99.5%) for 6 hours/day for either 1 or 5 days were histologically examined (respective analytical exposure levels were 0, 44, 96, 439, and 778 ppb for the single day exposure. Mean analytical exposure levels for the 5-day regimen were 0, 51, 111, 391, and 1048 ppb). Six animals/group/time point had been euthanized at 2 or 16 hours post-exposure or post-final exposure. In the 2nd study six animals/sex/group were exposed to 0 or 500 ppm of the test material for 6 hours and euthanized at 16 hours post-exposure. The analytical concentration was 517 ppb. The nasal tissues of these animals were examined histologically as well. Five serial sections from the T2 region (middle section at the level of the incisive papilla of the hard palate in the nasal cavity) of each sample were stained with hematoxylin and eosin and examined. Autolysis of some of the nasal tissue samples limited the number which were available to evaluate. The following lesions were identified in the T2 region: eosinophilic globules in the olfactory and/or respiratory epithelium, atrophy of the olfactory epithelium, and vacuolation in the respiratory and/or transitional epithelium. At two hours post-exposure of the single 6-hour exposure, increased incidences of eosinophilic globules in the olfactory epithelium was evident at an exposure level of 500 ppb. By 16-hours post-exposure, this lesion was no longer evident and no other apparent exposure-related lesions were noted. By 16 hours post-exposure, an increased incidence of vacuolation was noted in the transitional epithelium at 500 ppb and above. After the multiple exposures, at 16-hours post-final exposure, there were increased incidences of eosinophilic globules in the olfactory and respiratory epitheliums and atrophy of the olfactory epithelium for the 1000 ppb exposure group. There were no lesions in the transitional epithelium. In the 2nd study the only lesions identified in the nasal tissue at 16 hours after a single exposure were eosinophilic globules in the olfactory epithelium (3/11, minimal) and vacuolation in the transitional epithelium (1/11, minimal).

Overall, an exposure level of 1000 ppb to chloropicrin resulted in a definitive dose-response. Supplemental Study ([redacted], 2/2/23)

DATA GAP STATUS TABLE

Study Type	Data Gap Status
Combined Toxicity, Rat	No data gap, possible oncogenic effect
Chronic Toxicity, Dog	No data gap, no significantly toxic effect
Oncogenicity, Mouse	No data gap, possible oncogenic effect
Reproduction, Rat	No data gap, no significantly toxic effect
Developmental Toxicity, Rat	No data gap, no significantly toxic effect
Developmental Toxicity, Rabbit	No data gap, no significantly toxic effect
Gene Mutation	No data gap, possible positive mutagenic effect
Chromosome Effects	No data gap, possible chromosomal aberration effect
DNA Damage	No data gap, no significantly toxic effect
Neurotoxicity	No study on file, not required at this time