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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

June 7, 2006

MEMORANDUM

SUBJECT: **Human Studies Review Board:** Weight of Evidence Discussion for Trichloronitromethane (Chloropicrin).

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This document describes the scientific support for deriving a point of departure for trichloronitromethane (chloropicrin) using an available benchmark concentration analysis (MRID no. 46614801) from a human sensory irritation study (MRID no. 46443801). This point of departure is applicable for use in acute (1-day) risk assessments to by-standers and occupational workers exposed to chloropicrin in air.

1. Background and Introduction:

Chloropicrin (trichloronitromethane) is a non-selective soil fumigant with fungicidal, herbicidal, insecticidal, and nematicidal properties. Pesticidal uses of chloropicrin include agricultural settings, commercial greenhouse settings, spot treatment for tree replant sites, in-situ telephone pole applications, and empty grain and potato storage house/cellar fumigations. Chloropicrin is a unique soil fumigant in that it is also used as an indicator chemical or warning agent (2% or less by weight in formulations) in methyl bromide and sulfuryl fluoride applications. When used in this capacity, chloropicrin serves to warn of possible hazardous concentrations of odorless methyl bromide and sulfuryl fluoride vapors. Pre-plant soil use in agricultural settings accounts for most of the current use of chloropicrin in the United States.

Chloropicrin, like the other soil fumigants, has the potential to move off site following field applications, resulting in exposure to bystanders near treated areas and to people far away from treated areas through ambient air. Exposure to chloropicrin may also occur to those handling the pesticide or working in treated fields. Acute inhalation exposures to bystanders and workers appear to present the greatest risk concern. Due to the extensive use as a soil fumigant, the major pathway of exposure to chloropicrin is acute inhalation exposure from the off-gassing following application.

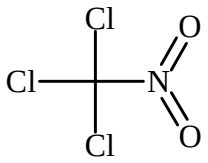

Figure 1. Chemical Structure of chloropicrin

The Agency has received a human sensory irritation study and a corresponding benchmark concentration and categorical regression analysis. The human sensory irritation study provides odor (phase 1) and irritation responses (phase 1, 2, 3) to varying concentration and duration scenarios that may inform the acute inhalation point of departure. In accordance with the human studies rule, the Agency is asking the Human Studies Review Board to review the ethical and scientific conduct and design of the sensory irritation study and its potential utility in assessing human health risk.

2. Hazard Characterization and Database Summary

Chloropicrin is a sensory irritant which stimulates free nerve endings that mediate sensations in the nose, eyes, throat, and upper respiratory tract. As such, chloropicrin is expected to result in port-of-entry related toxic effects (Alarie, 1973[1], Buckley et al., 1984[2], Shusterman 2002[3]). Responses from a sensory irritant are distinct from that of

[1]Alarie, Y. 1973. Sensory irritation by airborne chemicals. CRC Crit. Rev. Toxicol. 2: 299-363.
[2]Buckley et al., 1984. Respiratory tract lesions induced by sensory irritants at the RD50 concentration. Toxicology and Applied Pharmacology. 74: 417-429.
[3]Shusterman D 2002. Review:Individual factors in nasal chemesthesis. Chem. Senses 27: 551-564.

chemical stimulation (specialized olfactory or taste receptor cells). Irritation responses from a sensory irritant may include localized chemosensations such as burning, itching, and stinging, as well as associated physiologic (e.g., secretory) responses resulting from surrounding tissues (e.g., eyelid).

Chloropicrin was first discovered in 1848 and its irritating properties carefully studied during the nineteenth century (Prentiss, 1937[4]). Chloropicrin was used in World War I as a chemical warfare agent because of its potent activity as a lacrimator and as a lung-irritant. As such, most of the published irritation responses were the result of the military use of chloropicrin. Chloropicrin may cause eye and nasal irritation, vomiting, difficulty breathing, headache, dizziness, cyanosis, pulmonary edema, and possibly death. Clinical signs and pathological changes of the respiratory tract in animal laboratory studies are consistent with epidemiological and incident data. In acute toxicity testing with animals, chloropicrin is considered Acute Toxicity Category I (corrosive) for dermal irritation. Due to the corrosive nature of chloropicrin, the skin sensitization and eye irritation animal studies were held in reserve.

A. Animal Data

The database for chloropicrin has robust inhalation and/or port-of-entry toxicity studies. Acceptable inhalation studies in mice, rats, and rabbits are available in exposure durations ranging from 30 minutes to two years (108 weeks) and evaluate acute, subchronic, chronic/cancer, reproductive and developmental toxicity. Both acute rodent inhalation studies are acceptable/non-guideline. Executive summaries of these studies are provided in Appendix 1. The 30-minute mouse study (MRID no.45117901) is limited as it only provides a level at which 50% respiratory depression occurs and port-of-entry irritation symptoms are not available. In contrast, the four-hour inhalation rat study (MRID no.45117902) provides port-of-entry effects, at both lethal and sub-lethal concentrations.

Available rodent studies indicate that nasal lesions (rhinitis, epithelial hyalin inclusions, hyperplasia/dysplasia, and mucosal ulceration), lung lesions (hyperplasia, alveolar histiocytosis), and increased lung weights may occur at lower concentrations (0.5 ppm or 1.0 ppm) if exposure occurs over extended durations (see Table 1 below). A steep dose-response curve is also evident from the 4 hour chloropicrin rat study in that nasal and lung lesions were observed at 10.6 but caused death at 18 ppm and 25 ppm.

OPP has determined that the methods and dosimetry equations described in EPA's reference concentration (RfC) guidance (1994) are appropriate for converting NOAELs and LOAELs observed in laboratory animal experiments to human equivalent concentrations (HECs) for ambient exposure conditions. The dosimetric conversion to an HEC is necessary before the different adverse effects in the animal data array can be compared to available human data. The conversion of the animal exposure concentrations into HECs was based either on port-of-entry or systemic effects. The table below indicates that port-of-entry effects likely occur at lower concentrations than systemic effects.

[4] Prentiss A. 19.7. Chemicals in war. New York: McGraw Hill; pp. 140, 144-145, 161-163.

Table 1. Exposure Concentration and Duration Data from Rodent Inhalation Studies with Chloropicrin as Port-of-Entry (POE) and Systemic Human Equivalent Concentrations (HECs)*.

Duration	Animal Inhalation Studies	POE NOAEL (HEC) ppm	POE LOAEL (HEC) ppm	Systemic NOAEL (HEC) ppm	Systemic LOAEL (HEC) ppm
6 hrs/day 78 weeks	Mouse- LOAEL: ↑ lung weights, nasal and lung lesions, ↓ body weight and gains (0.5 ppm) NOAEL: (0.1 ppm)	0.004	0.02	0.018	0.9
6 hrs/day 13 weeks	Mouse & Rat – LOAEL: ↑ lung weights, lesions of the nasal cavity and lungs, ↓ body weight & food consumption (1.0 ppm) NOAEL (0.3 ppm)	0.008	0.027	0.054	0.18
4 hrs	Rat- LOAEL: deep lung necrosis, histological lesions of liver, adrenal wts (10.6 ppm); death at 18 & 25 ppm NOAEL: not identified	NA	0.26	NA	1.77

*The calculations used to generate the port-of-entry and systemic HECs differ such that the same NOAEL/LOAEL my result in different POE and systemic HECs.

B. Human Information

In humans, chloropicrin may cause eye and nasal irritation, vomiting, difficulty breathing, headache, dizziness, cyanosis, pulmonary edema, and possibly death. Currently, the Occupational Safety & Health Administration (OSHA) permissible exposure limits (PELs) and the American Conference of Governmental and Industrial Hygienists (ACGIH) threshold limit values (TLVs) are set at 0.1 ppm or 100 ppb as a Time Weighted Average (TWA). The OSHA website does not define the TWA, but is assumed to be over 8 hours. The odor threshold of chloropicrin is reported detectable at 0.9 ppm to 1.1 ppm (Clayton and Clayton, 1982[5], Krieger 1996[6]). The lacrimating effects of chloropicrin occur as low as 0.3 ppm (0.002 mg/L) (Prentiss, 1937) with immediate lacrimation and eye irritation reported from1.0 to 1.3 ppm (Clayton and Clayton, 1982). A higher concentration of 4.0 ppm (26.8 mg/m^3) for only a few seconds is reported to render a person unfit for military action, although no clinical details were provided (as cited in

[5] Clayton G, and Clayton F, editors. Patty's Industrial Hygiene and Toxicology. 3rd ed. Herbert E. Stokinger. Aliphatic nitro compounds, nitrates, nitrites. New York: John Sibley and Sons; 1982. Chapter 53 p. 4164-4166.

[6] Krieger, RI 1996. An assessment of implied worker exposure and risk associated with chloropicrin loading, application, and field tarping activities following application, and implied exposure and risk for off-field concentrations resulting from soil fumigation. Registration document submitted to CAL-EPA Department of Pesticide Regulation, October 1996.

Clayton and Clayton, 1982). A concentration of 298 ppm (2.0 mg/L) is reported lethal within 10 minutes of exposure (Prentiss, 1937).

A recent soil fumigant incident over a 2-day period occurred in which chloropicrin drifted offsite into a residential area of Kern County, California (2003)[7]. A published report indicated a total of 165 persons experienced symptoms consistent with chloropicrin exposure (MMWR Weekly, 2004). Of the 165 persons, 150 persons were community residents, 2 were day care workers, and 9 were firefighters responding to the scene. The remaining 4 persons were applicators or growers. The median age was 16 years with age ranging from 3 months to 63 years. Nearly the entire 165 persons (99%) had irritant symptoms (e.g., eye or upper respiratory). Symptoms in the eye included lacrimation, pain, and burning. Gastrointestinal symptoms were reported in 47% of persons that included vomiting, nausea, abdominal pain, and diarrhea. Respiratory symptoms (51%) included cough, dyspnea, upper respiratory irritation, chest pain, and asthma exacerbation. A total of 9 persons received medical evaluations and 7 persons had persistent respiratory symptoms when interviewed 11 days after the event. The concentrations of chloropicrin drifting off-site over the 2 days are not definitely known.

To answer questions surrounding the threshold for irritation and odor, a recently submitted human sensory irritation study examined the concentration and duration at which chloropicrin was irritating to the eyes, nose, and throat compared to a blank (air). The ability of healthy subjects to detect the odor of chloropicrin was also evaluated.

Summary of the chloropicrin human sensory irritation study:

To determine a subject's sensitivity for the detection and characterization of feel to the human eye, nose, and/or throat produced by chloropicrin vapors, as well as the odor threshold, healthy volunteers (18 to 35 years of age, average 23 years) were exposed to a range of vapor concentrations and exposure durations in a controlled laboratory setting (MRID 46443801). The investigation consisted of three phases:

- Phase 1: a brief exposure at 0, 356, 533, 800, and 1200 ppb
- Phase 2: a 20-30 minute exposure at 0, 50, 75, 100, and 150 ppb
- Phase 3: a 60 minute exposure for 4 consecutive days at 0, 100, and 150 ppb

Positive controls were not used in any phase; however, air was used as a blank. For more details on the conduct of this study, please refer to the data evaluation record (DER) of the chloropicrin human study (DP 312312).

Phase 1 Design: The objective of phase I was the identification of chloropicrin by odor (both nostrils, single sniff), eye feel (one eye, 25 seconds), or nasal feel (one nostril, 7 seconds) at 356 ppb, 533 ppb, 800 ppb and 1200 ppb (0.356, 0.533, 0.800, and 1.2 ppb) generated from a vapor delivery device. Phase I consisted of 62 subjects (32 male, 30 female) for odor and 63 subjects (32 male, 31 female) for eye feel. The same subjects participated for both odor and eye detection. Confidence of feel was

[7] MMWR Weekly 2004. Brief Report: Illness associated with drift of chloropicrin soil fumigant into a residential area—Kern County, California, 2003. August 20, 2004 53(32);740-742. www.cdc.gov/mmwr/preview/mmwrhtml/mm5332a4.htm

rated 1 to 5, with 1= very low, 3= moderate, and 5= very high confidence. Severity of feel was not rated in phase I.

Phase 1 Results (Table 2):
The examination of nasal feel was terminated prematurely by the study director during Phase I. Of the 20 subjects examined, only 10% detected nasal feel at 1200 ppb (highest concentration). Subject's responses to ocular detection and odor perception of chloropicrin varied greatly. Of the 62 participating subjects, 8 subjects (13%) failed to detect odor and 7 subjects (11%) failed to detect eye irritation. One of these subjects failed to detect chloropicrin as odor or in the eye.

The phase 1 data were analyzed in 2 ways; inclusion of all subjects and inclusion of only those subjects detecting. The analysis that included all subjects resulted in an odor median of 700 ppb for both sexes, or 590 ppb for males and 810 ppb for females. The median for detection in the eye is 900 ppb for both sexes, or 790 ppb for males and 1010 for females. Based on only those subjects responding, the EC10 for odor is 215 ppb and EC50 is 406 ppb. Likewise, the EC_{10} for eye detection is 38 ppb and EC_{50} is 242 ppb.

Table 2. Phase 1 results for odor and eye detection of chloropicrin

Odor Detection				
Exposure Concentrations	**Exposure Duration**	**# of subjects**	**All Subjects**	**Subjects Detecting Only**
0, 356, 533, 800 or 1200 ppb	"sniff"	62 (32 male, 30 female)	Odor Median = 700 ppb (590 ppb M and 810 F)	Median= 356 ppb EC10=215 ppb EC50=406 ppb
Eye Detection				
Exposure Concentrations	**Exposure Duration**	**# of subjects**	**All Subjects**	**Subjects Detecting Only**
0, 356, 533, 800 or 1200 ppb	25 seconds	63 (32 male, 31 female)	Eye Median = 900 ppb (790 ppb M and 1010 ppb F)	Median= 356 & 533 ppb EC10= 38 ppb EC50= 242 ppb
Examination of nasal feel was terminated by the study director in Phase I due to lack of sensitivity. data taken from MRID 46443801				

Phase 1 Discussion: Phase 1 of the study provides pertinent information on the odor and eye detection threshold for use as a warning agent. The duration of the 'sniff', however, was left to the judgment of the subject for an adequate inhalation for odor identification. The length of the sniff may have differed slightly among the subjects although the impact of the duration on the odor threshold is likely small. This phase provides odor and eye detection medians based either on a group level or on a more refined level (i.e., only those subjects detecting). In addition, the equal number of participating male and female subjects indicates no significant differences between the sexes for chloropicrin detection. The variability of the subject's ability to detect

chloropicrin over the range of concentrations examined also is evident. This variability in detection is based on subjective confidence scores with no severity scores or physiological parameters to further inform the response to chloropicrin.

Phase 2 Design: The second phase of the human study involved the positive detection of feel in the eyes, nose, and throat to 50, 75, 100, and 150 ppb chloropicrin vapor while in a walk-in chamber for 20 or 30 minutes (N=62, 32 males, 30 female). The number of subjects per day of testing ranged from one to four. On a day with more than one subject, they went through testing simultaneously. Subjects responded "yes" for a positive feel or "no" for no feel. A level of confidence to each event (eye, nose, throat) was also recorded with 1= not certain, 2= moderately certain, and 3= very certain. Odor was not a parameter in Phase II. The first exposure in a day consisted of a known blank (air). This exposure served to acclimate the subjects to the task in the chamber. The subjects were asked to perform ratings as they would for future blinded exposures. The testing periods and concentrations for phase 2 are listed in Table 3. The series of exposures outlined below were to occur over the course of one day and in the order presented.

Table 3. Listing of test periods and concentrations for Phase 2 of human sensory irritation testing to chloropicrin

Parameters:	N (Male)	N (Female)	Exposure Duration
Sensitivity to 20 or 30 min exposures with blanks in between chloropicrin exposure; "did you feel in the nose, eyes, or throat?"			
blank blinded	32	30	30 min
50 ppb chloropicrin	32	30	30 min
lunch break			45 min
75 ppb chloropicrin	32	30	20 min
blank blinded	32	29	30 min
100 ppb chloropicrin	32	30	20 min
blank blinded	32	30	30 min
150 ppb chloropicrin	32	30	20 min
Number of participating subjects and exposure duration taken from Appendix M of the original report (pgs 261 to 282)			

Phase 2 Results (Table 4)**:**
ANOVA results provided in the study report indicated level and duration of exposure had stronger effects on the eye than on the nose and throat, though significance was achieved for effects on all three parameters ($p<0.0001$). This indicates the time required for the positive detection of chloropicrin in the eye, nose, and throat was dependent upon the concentration. In general, the lower the concentration of exposure the longer the time required before high confidence of feel was reported. There were no significant differences between sexes in the confidence scores for the eyes, nose, or throat.

According to the individual subject scores in Appendix M of the study report, subjects left the chamber prior to scheduled times for the 75 ppb (1 female subject) and 150 ppb (4 subjects; 2 female and 2 male) test periods. The female subject that exited the chamber at 75 ppb also left the chamber at 150 ppb along with a male subject in the chamber. On another day of testing, one female and one male left the chamber at 150 ppb. No explanation was reported for the exit of the subjects from the chamber. No subject left the chamber at either 50 ppb or 100 ppb. As in phase 1 of the study, eye irritation was a more sensitive endpoint than nasal irritation with subject responses varying greatly.

Another analysis which focused on those subjects detecting chloropicrin with confidence indicates that 38% (16 of 42) of those subjects initially and consistently identified chloropicrin at 50 ppb. A simple tally method resulted in a median ocular detection level of 75 ppb. It should be noted that logistic regression methods were attempted for this data set; however, model fit was poor and estimates of the distribution of the log odds of detection were not made.

Table 4. Tabulation of eye irritation confidence of subjects in phase 2

Confidence of Eye Irritation					
Exposure Concentrations	**Exposure Duration**	**# of subjects**	**Exit from Chamber**	**Group Results**	**Detecting Subjects Only**
0, 50, 75, 100, 150 ppb	20-30 minutes	62 32 M, 30 F	- 75 ppb: 1 F after 16 minutes - 150 ppb: 4 subjects (2M,2F) after 15 minutes	ANOVA: P<0.0001, level and duration in eye	38% (16 of 42) initially & consistently detected at 50 ppb Ocular Median 75 ppb
data taken from MRID 46443801					

Phase 2 Discussion: This phase of the study involved a more realistic exposure scenario for informing an acute bystander scenario. The confidence of the feel of chloropicrin was employed, as in phase 1. However, the confidence scale was based on 1 to 3 whereas the confidence scale in phase 1 was based on 1 to 5. The confidence scores from phase 1 and 2 can not be directly compared. Severity of the feel of chloropicrin was also not included in this phase of the study. Although a high confidence of feel to chloropicrin may indicate a level of severity, this comparison can not be made from this phase. The design of the study did follow a low to high concentration exposure scenario. The duration of exposure for each period, however, was not consistent. The duration at 50 ppb was 30 minutes and the period for the blank was 30 minutes but the duration at 75, 100, and 150 ppb were only 20 minutes.

The statistics reported for this phase of the study were lacking. All statistics were based on a group level. The response to chloropicrin is important both on a group and individual scale. Analysis on an individual level provides the number of subjects able to detect chloropicrin with confidence compared to those subjects not detecting at any concentration.

Another uncertainty from this phase of the study is the possible residual effect from the previous exposure period. Since all testing was to be completed in one day, a

parameter or question to address any effects that may still be residual from the previous exposure period would have been helpful. Confidence scores of the first few minutes of each testing period, however, reveal low confidence scores of feel. These low confidence scores at the beginning of each testing period suggest that no residual effects were present from the previous period.
Another unknown is the lack of information on subjects leaving the chamber at 75 and 150 ppb. It is difficult to determine if the subjects left the chamber due to severity of feel or if social factors influenced the subject's decision to exit. Subjects were blinded to the exposure concentrations. If severity was the driving factor in the subject's decision to exit the chamber, then it would be expected that subjects would also exit the chamber at some point during the100 ppb period. A severity score and identification of any physical symptoms from the subjects leaving the chamber may have helped answer this issue.

Phase 3 Design (Table 5): The goal of Phase 3 was the detection of chloropicrin vapor as evidenced by irritation to the eyes, nose, and/or throat after 1 hour (60 minute) exposures repeated over 4 consecutive days. Concentrations tested included blank (air), 100 ppb, and 150 ppb. These concentrations, however, occurred in random order. This phase included a clinical exam of the eyes, nose, and throat, as well as pulmonary function testing with the outcome variable FEV_1 (Forced Expiratory Volume) and FVC (Forced Vital Capacity), rhinomanometry, and nasal cytology. In addition, an assessment was performed based on ocular cytology from cell samples taken from the conjunctival membrane inside the lower eyelid and from the concentration of exhaled nitric oxide sampled from the lung (eNO) and nose (nNO). Odor detection was not measured in phase 3.

Table 5. Listing of test measurements for Phase 3 of human sensory irritation testing for chloropicrin

Measurements:	N (M)	N (F)	Cytology	RQLQ	O2 Saturation	NO	NAR-Spirometry	Symptoms	Clinical Exam
Phase 3	Sensitivity to 60 minute (1 hr.) exposures over 4 days								
Fri: No exposure	15	17	♦	♦				♦	♦
Mon: Pre-exposure	15	17				♦	♦	♦	♦
During Exposure	15	17			♦			♦	
Post-Exposure	15	17			♦	♦	♦	♦	♦
Tues: Pre-Exposure	15	17			♦	♦	♦	♦	♦
During Exposure	15	17			♦			♦	
Post-Exposure	15	17			♦	♦	♦	♦	♦
Wed: Pre-Exposure	15	17				♦	♦	♦	♦
During Exposure	15	17			♦			♦	
Post-Exposure	15	17				♦	♦	♦	♦
Thurs: Pre-Exposure	15	17				♦	♦	♦	♦
During Exposure	15	17			♦			♦	

Table 5. Listing of test measurements for Phase 3 of human sensory irritation testing for chloropicrin									
Measurements:	**N (M)**	**N (F)**	**Cytology**	**RQLQ**	**O2 Saturation**	**NO**	**NAR-Spirometry**	**Symptoms**	**Clinical Exam**
Post-Exposure	15	17				♦	♦	♦	♦
Fri: No Exposure	15	17				♦	♦	♦	♦
Information about details of the timing of exposure measurements were taken from Figure 11 of the original study (pg 52).									

Subjects were asked to rate their symptoms in three settings:

1) On a scale of 0 (no symptom) to 3 (severe) for eye, nose, and/or throat irritation while in the chamber;

2) Before and after exposure in the chamber and at the beginning and end of each week of exposures; and

3) At the beginning and end of a cycle of exposures, via the Rhinconjunctivitis Quality of Life Questionnaire (RQLQ), a series of 28 questions in seven domains, where the subjects used a seven point scale from *Not Troubled to Very Troubled*.

The first two instruments referred to how the subject felt at the time of rating, the RQLQ referred to how the subject felt over the previous week.

When in the chamber, the subject rated symptoms after 30 seconds and then every 1 minute until the end of the exposure at 60 minutes. During this time, the subject remained under scrutiny for level of alertness and general condition.

Irritation severity scoring:
0: No symptom
1: Mild; symptom present, but minimal awareness, easily tolerated
2: Moderate; symptom definite and bothersome, but tolerated
3: Severe; symptom hard to tolerate and can interfere with activities of daily living or sleeping

Phase 3 Results (Table 6):

A. Chamber Results

As in Phase 2, subjects gave higher ratings to symptoms in the eye, than to those in the nose and throat. There was no indication of intensification of symptoms for any parameter among the four consecutive days of exposure. On a group level, a dose-response was evident on the time required for detection and the severity of the response. The average group ratings for nasal and throat irritation never went above background levels. None of the subjects left the chamber prior to scheduled times during any of the four consecutive days even though concentrations were similar to Phase 2.

Table 6. Average group responses (all subjects) for eye irritation to chloropicrin in Phase 3 of chamber exposures at 1 hour periods over 4 consecutive days

Exposure	Definition	Group Ocular Avg Rating	Time for Recognition
blank	No symptom	0.1	NA
100 ppb	Between no symptom and mild symptom	0.5	30 minutes
150 ppb	Mild; Symptom present, but minimal awareness, easily tolerated	1	20 minutes
Data taken from final study report pg 67 and Figure 20 (pg 69). NA = not available.			

Chloropicrin at 100 ppb and 150 ppb had both perceptual and physiological effects. The concentration of nasal nitric oxide (nNO) and air flow in the nose changed in association with exposure to chloropicrin from pre- to post-exposure in one day. This physiological parameter suggests the beginning of a response to inflammation in the nasal passage. In addition, the nNO increased despite the absence of nasal symptoms perceived by the subject and did not persist to the following day nor became progressively greater as the week of exposures wore on. Clinical examinations an hour after exposure indicated no chloropicrin-associated signs of the exposures, though at times some subjects rated residual ocular symptoms. The symptoms did not worsen during the four days of exposure, but dissipated between exposures and none existed the day after the final exposure of a cycle.

Phase 3 Discussion: This phase of the human study most closely resembles the acute bystander inhalation scenario for the human health risk assessment. Phase 3 provides both objective and subjective scores on the irritation of chloropicrin. Measurements reported every minute (repeated measurements) by the subjects provides the timing of recognition to chloropicrin and the maximal response period.

Eye irritation was the most sensitive endpoint compared to both the nose and throat, as was observed in phase 2. Even with fewer numbers of participating subjects, the variability of the severity of chloropicrin to the eye was observed. The physiological parameters examined also indicate that extended periods of exposure may cause inflammation and responses to the inflammation (e.g., increased nasal nitric oxide and changes in nasal air flow). Protection of the irritating effects of chloropicrin to the eyes, therefore, is important for protection against other physiological changes. Although this phase of the study had the smallest number of participating subjects, the equal number of male and female subjects suggests no differences between the sexes to chloropicrin.

None of the subjects left the chamber during the 60 minute exposures unlike some subjects in phase 2. Phase 3 of the study provides more supportable evidence for the severity of eye irritation and nasal/respiratory changes than for phase 2. According to the responses of the subjects in phase 3, the severity was not such that they felt the need to exit the chamber. Unfortunately, concentrations below 100 ppb were not investigated in order to compare with results from phase 2. The severity of eye irritation at 50 and 75 ppb for 60 minutes over 4 consecutive days may have provided insight where detection turns to severity of feel.

C. Point of Departure (PoD) and Uncertainty Factor(s)
Phase 3- Human Sensory Irritation Study- Eye

Phase 3 provides the most useful information for establishing a PoD for the acute inhalation bystander exposure scenario. The human sensory study provides not only eye irritation but also upper and lower respiratory parameters that demonstrate physiological changes occur simultaneously with eye irritation. Protection of eye irritation likely protect against changes in upper respiratory parameters. The human sensory irritation study appears to have been scientifically well conducted with current and sensitive methodologies. In the case of chloropicrin, therefore, it is appropriate to establish a PoD on eye irritation.

Based on the analyses provided by the TERA group, the $BMCL_{10}$ of 73 ppb is appropriate for a PoD for a 1-hour (acute) inhalation exposure scenario of the chloropicrin human health risk assessment. This lower bound estimate is based on an average ocular irritation score of 1.5 which is above the average background (air) irritation score of 0.87. In addition, this estimate is based on the maximal response data from phase 3 of the human study (30-55 minutes). The $BMCL_{10}$ of 73 ppb is also similar to the EC_{10} of 90 ppb, which was generated by combining the human and animal data for categorical regression analysis.

Because a human study is being used for the acute inhalation exposure scenario for chloropicrin, an interspecies extrapolation factor is not necessary. Due to the intra-individual variability of the responses to chloropicrin in every phase of the human study, a 10X is appropriate for intraspecies variability.

3. Conclusions

The general public may be exposed to soil fumigants, like chloropicrin, in air following application because of their volatility since these chemicals can off-gas into ambient air and can be transported off-site by wind to non-agricultural areas. The inhalation database for chloropicrin for acute exposures is sufficient. The Agency has selected the human sensory irritation study and $BMCL_{10}$ of 73 ppb for deriving a PoD for assessing 1-hour acute risk to chloropicrin.

Table 7. Summary of Human Study Results for Chloropicrin

ppb	Human Sensory Irritation Study
75 **73-90**	• 1/ 62 subjects exit after 16 minutes, no severity score (20 min exposure) • Range of BMCL & categorical regression analyses (avg. maximal response period)
100 (OSHA PEL)	• Sporadic severe* eye irritation scores in 8/32 subjects (25%) during 60 minutes (Phase 3); • Slight changes in upper respiratory parameters (nNO, nasal air flow)
150	• 4/62 subjects exit at 15 minutes of 20 minute exposure on 2 days of testing • Sporadic severe eye irritation scores in 7/32 (22%) during 60 minutes • Changes in upper respiratory parameters (nNO, nasal air flow)
356	• Median for odor detection, sniff, only those detecting
356 - 533	• Median for ocular feel, 25 seconds, only those detecting
700	• Median odor threshold; sniff; all subjects
900	• Median eye irritation, 25 seconds, all subjects
4000	• Military observations indicate person unfit for military activity

Appendix 1: Executive Summaries of Acute Inhalation Studies with Chloropicrin

CITATION: Hoffman, GM (1999) Chloropicrin: A Sensory irritation Study in the Mouse via Head-only exposure. Huntingdon Life Sciences, East Millstone, NJ. Study No. 99-5388 (11/11/99) Unpublished (MRID# 45117901).

EXECUTIVE SUMMARY: In an head only inhalation study, 4 Albino Swiss-Webster (Crl:CFW (SW) BR male mice per group were exposed to 0.99, 3.20, 4.20, 7.25, 10.00, 14.50 ppm (analytical concentration) or 0.00664, 0.0215, 0.0282, 0.0486, 0.0671, 0.0973 mg/L (calculated analytical concentration) of gaseous chloropicrin for 30 minutes (MRID# 45117901). Animals were held for 8 days after exposure to chloropicrin. Particle size and concentration was analyzed twice during the 30 minute exposure. Breaths per minute (BPM) were determined by a continuous recording plethysmograph and recorded with an osscilograph. BPM were determined for 30 minutes and the lowest recorded BPM during the 30 minute exposure was used as to calculate the respiratory depression (RD). The BPM were determined for 10 minutes pretest and used as the animals own control values. BPM was measured for 10 minutes after exposure as well. Test atmospheres were measure by gas chromatography. Particle sizes generated had a MMAD ranging from 1.2 µm to 6.8 µm.

No deaths at any dose level were seen during or immediately after exposure prior to sacrifice. All clinical observations were normal before and after exposure.

Body weights and body weight gains were determined from pretest to day 8. The body weight gain in the HDT may have been decreased at the HDT only (8% of initial body weight in control and 2% at the HDT).

The exposure level at 50% respiratory depression (RD50) was measure in these mice and found to be 2.34 ppm with 95% confidence limits of 1.84 to 2.98 ppm or RD50 of 0.016 mg/L and 95% confidence limits of 0.012 mg/L to 0.020 mg/L.

The study can also be used to determine an exposure level, which causes 0% depression in the respiration rate. This was done by plotting the % depression in respiration rate reported in the study versus log exposure level and extrapolating the graph to 0% depression. The RD0 respiratory depression occurs around 0.0017 to 0.0019 mg/L

The study is acceptable as a non-guideline (NG) study sensory irritation in the mouse from chloropicrin exposure.

CITATION: Hoffman, GM (1999) Chloropicrin: An Acute (4-hour) Inhalation Toxicity Study in the Rat via Whole Body Exposure. Huntingdon Life Sciences, East Millstone, NJ. Study No. 99-5387 (11/11/99) Unpublished (MRID# 45117902).

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EXECUTIVE SUMMARY: In a whole body inhalation study, 5 Sprague Dawley rats per sex per group were exposed to 0, 10.6, 18.0, or 28.5 ppm (analytical concentration) or 0, 0.071, 0.121, 0.158 mg/L (calculated from the analytical concentration) of aerosolized chloropicrin for 4-hours (MRID# 45117902). Animals were exposed on day 0 and held for 2 days after exposure to chloropicrin. Particle size and concentration was analyzed four times during the 4-hour exposure. Particle sizes generated had a MMAD ranging from 4.85 µm to 6.1 µm with a GDS of 1.4 to 1.6. Clinical observations and organs weights were taken and histology was conducted on the respiratory tract in addition to the kidneys and liver (all animals were sacrificed 48 hours after exposure). The dose at which 50% death occurred was 17 ppm for males and 19 ppm for females, for this limited study.

No deaths at the LDT were seen, however death occurred at the 2 top dose levels up to 2 days post exposure that the animals were held prior to sacrifice. Clinical observations were noted at all dose levels and included labored breathing, gasping, decreased activity, nasal discharge, salivation and moist rales. The 2 top dose level groups were observed to gasp for the last 2 hours of exposure.

Body weight loses (12 to 31%) were seen for males and females at sacrifice for all dose levels, while control gained weight (4 to 5%). The body weight gain in the HDT for males was unavailable because they all died.

Liver and adrenal weights were increased at the HDT as well as histological findings were seen at HDT. In the respiratory tract histological findings were seen at all dose levels and damage observed in the nasal lumen, nasoturbinal tissue (congestion, nasal epithelial atrophy), and lungs (congestion, bronchiole mucosal edema, necrosis and cellular infiltrates).

The LOAEL was 0.071 mg/L (LDT), based on decreased body weight and food consumption, and lesions of the nasal cavity and lungs. No NOAEL was demonstrated. The LC50 calculated for the study should not be considered to be a true LC50 for chloropicrin. Due to the sacrifice of all live animals at day 3 of the study instead of day 14, and too large of exposure particle sizes, the true LC50 could be lower.

The port-of-entry LOAEL is 10.6 ppm or 0.071 mg/L (LDT), based on lesions of the nasal cavity and lungs. No port-of-entry NOAEL was demonstrated.

The study is acceptable as a non-guideline (NG) study of 4-hour inhalation of chloropicrin in the rat, because it supplies useful information. **The study is unacceptable and not upgradeable as a guideline (870.1300) LC50 inhalation study in the rat.** The rats were held for only 2 days of the required 14 days post exposure and the MMAD of the chloropicrin particles in the exposure atmosphere were too large (5 to 6 µm), even for the new guidelines.