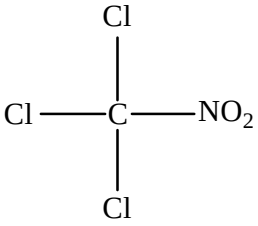
CHLOROPICRIN

RISK CHARACTERIZATION DOCUMENT



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CHLOROPICRIN

SUMMARY

Chloropicrin (trichloronitromethane) was first patented for use as an insecticide in 1908. Chloropicrin is a broad-spectrum fumigant with insecticidal, fungicidal, nematicidal and herbicidal properties. Chloropicrin also has a low odor threshold and causes sensory irritation at very low concentrations, so it has been added as a warning agent to other fumigants like methyl bromide, methyl iodide, 1,3-dichloropropene and sulfuryl fluoride which are odorless. The Department of Pesticide Regulation (DPR) placed chloropicrin into reevaluation in 2001 based on air monitoring data which found that air concentrations of chloropicrin at some distances from treated greenhouses were greater than established occupational exposure limits (Cortez, 2001). DPR conducted a risk assessment evaluating public airborne exposure to chloropicrin under the legislative mandate of the California Toxic Air Contaminant Act (AB 1807). As a result, DPR is preparing regulations to list chloropicrin as a toxic air contaminant and to require additional air monitoring and mitigation. DPR has also placed chloropicrin on the high-priority list for a comprehensive risk assessment based on possible adverse effects identified in genotoxicity and developmental toxicity studies submitted under the Birth Defect Prevention Act (SB 950). The purpose of this risk assessment is to evaluate the risks for potential human health effects from all exposure scenarios to chloropicrin for both workers and the general public.

Toxicity

The pharmacokinetic and toxicology studies were reviewed and presented in the Toxicology Profile section. Included in the Toxicology Profile are guideline studies submitted to DPR for registration purposes and studies from the open literature with the greatest weight generally given to studies that met the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) guidelines. From the treatment-related effects identified in the studies, the highest dose, which did not cause any toxicological effect, known as No-Observed-Effect Level (NOEL), was established for each study. For some studies where a NOEL was not observed, a benchmark concentration (BMC) estimate was determined instead. In the Hazard Identification section, the NOELs/BMCs and effects at the Lowest-Observed-Effect Levels (LOELs) from the available toxicity studies were evaluated to determine what would be the most appropriate NOEL/BMC, referred to as a critical NOEL, to evaluate particular exposure scenarios. The toxicity studies can be categorized as acute (< 7 days), subchronic (> 7 days to < 6 months), and chronic (1 or more years) in duration. To evaluate acute exposure, 1-hr, 8-hr and 24-hr NOELs/BMCs were selected.

The primary effects observed with short and long-term exposure to chloropicrin are sensory and respiratory irritation. The mechanism of action for chloropicrin is not well understood, but may involve an oxidative reaction with biological thiols, such as glutathione and hemoglobin. A sensory irritation study was conducted using human subjects with exposures up to one hour. A NOEL was not observed with the 1-hr exposure for eye irritation and increased nitric oxide (NO) in expired nasal air. Increased NO in expired nasal or pulmonary air is an indication of respiratory inflammation. A BMC estimate of 44 ppb was selected for evaluating 1-hr exposures to chloropicrin based on the increased NO in expired nasal air. Animal studies were used to evaluate longer-term exposures. The lowest acute NOEL in an animal study was

seen in an inhalation developmental toxicity study in rabbits based on mortalities, nasal discharge, reduced body weights and food consumption and red discoloration in lungs. This NOEL was selected for evaluating 8-hr and 24-hr exposures. The 8-hr and 24-hr NOELs estimated from this study were 300 and 100 ppb, respectively. The 8-hr human equivalent concentrations (HECs) were 270 and 580 ppb for children and adults, respectively. The 24-hr HECs were 92 and 190 ppb for children and adults, respectively. A BMC analysis was also performed to determine the most sensitive endpoint and species with seasonal and chronic inhalation exposure to chloropicrin. The lowest BMC estimate with subchronic inhalation exposure was rhinitis in female rats after adjusting for species differences in breathing rates. The BMC estimate for rhinitis, 120 ppb (HEC = 35 ppb for children and 73 ppb for adults), was selected for evaluating seasonal exposure to chloropicrin. The lowest BMC estimate with chronic inhalation exposure was bronchiectasis in male and female mice after adjusting for breathing rate. The BMC estimate for bronchiectasis, 49 ppb (HEC = 27 ppb for children and 56 ppb for adults) was selected for evaluating chronic exposure to chloropicrin.

There was evidence that chloropicrin was carcinogenic in two different species in two different laboratories. A slight increase in adenomas and carcinomas was seen in female mice that was significant by trend analysis and pair-wise comparison when survival was taken into consideration. There was also an increase in the multiplicity of these tumors and a slight shortening of the time-to-tumor at the high dose. A significant increase in fibroadenomas was also seen in female rats with oral exposure. Additional evidence suggesting that chloropicrin is carcinogenic includes that it is a strong electrophile due to the presence of the chlorine and nitro groups and DNA damage, gene mutation and clastogenicity were reported in a number of *in vitro* genotoxicity tests. Although the increases in the tumors in neither study were dramatic and all the *in vivo* genotoxicity studies were negative, DPR made a health protective assumption that chloropicrin was carcinogenic with a genotoxic mode of action based on its electrophilic structure and the positive *in vitro* genotoxicity tests. Therefore, a quantitative assessment of the carcinogenic risk was performed using a linear approach which assumes there is no threshold for carcinogenicity. The cancer potency was estimated to range from 1.3 $(mg/kg/day)^{-1}$ for the maximum likelihood estimate to 2.2 $(mg/kg/day)^{-1}$ for the 95th percent upper bound based on the incidence of lung tumors in female mice.

Several developmental and reproductive effects were seen in studies including reduced number of implantation sites, increased pre- and post-implantation losses, late-term abortions, and visceral and skeletal variations in fetuses. The NOELs for fetal or pup effects were equal to or higher than the maternal or parental NOELs, suggesting there is no increased pre- or post-natal sensitivity to chloropicrin. Direct exposure to neonates, however, was not evaluated. Theoretically, neonates could be more sensitive to chloropicrin due to higher breathing rates or the immaturity of their respiratory system, immune system and/or metabolic enzymes. Therefore, an additional uncertainty factor may be appropriate for infants and children.

Table 1 summarizes the critical endpoints used for evaluating the different exposure scenarios for chloropicrin along with their respective human equivalent concentrations and reference concentrations.

Table 1. DPR Critical Endpoints, Human Equivalent Concentrations and Reference Concentrations for Chloropicrin

Exposure Scenario	Critical Endpoints	HEC		RfC	
		Children	Adults	Children	Adults
Acute - 1 hr	↑ NO in nasal air of humans	44 ppb	44 ppb	4.4 ppb UF[a] = 10	4.4 ppb UF = 10
Acute - 8 hr & 24 hr	Mortalities (days 2-4), nasal discharge (onset day 0), ↓ body weights & food consumption (days 0-6), red discoloration in lungs of pregnant rabbits.	8-hr 270 ppb 24-hr 92 ppb	8-hr 580 ppb 24-hr 190 ppb	8-hr 2.7 ppb 24-hr 0.92 ppb UF = 100	8-hr 5.8 ppb 24-hr 1.9 ppb UF = 100
Seasonal	Rhinitis in female rats	35 ppb	73 ppb	0.35 ppb UF = 100	0.73 ppb UF = 100
Chronic	Bronchiectasis in male and female mice	27 ppb	56 ppb	0.27 ppb UF = 100	0.56 ppb UF = 100
Lifetime	Lung tumors in female mice	Potency = 2.2 $(mg/kg/day)^{-1}$		-------	0.24 ppt[b]

[a] UF = Uncertainty factor used to derive RfC.
[b] RfC for cancer is the air concentration corresponding to a negligible risk level (i.e., one in a million excess cancer cases)

Exposure

Occupational - Soil Fumigation

Occupational exposure for workers involved in soil fumigation were estimated from monitoring studies in which workers wore air samplers in their breathing zone while performing different tasks depending on the application method. Only shallow shank applications were monitored, but it was assumed that the worker exposures with deep shank applications would be equal or less than with shallow shank applications. Air concentrations were corrected for recoveries less than 90% and adjusted for a maximum application rate. For each scenario, different estimates were calculated assuming chloropicrin was an active ingredient (> 15% of formulation) or a warning agent (either at 10.5% or 2%). Short-term exposure estimates (i.e., 1-hr and 8-hr estimates) were set at the 95th percentile. One-hour estimates ranged from 5.19 to 2,310 ppb when chloropicrin was an active ingredient. Exposures were proportionately lower when used as a warning agent. Eight-hour estimates ranged from 1.22 ppb to 2,310 ppb when chloropicrin was an active ingredient. The highest short-term exposures were seen with tarp splitters and removers with broadcast, tarped applications. The lowest short-term exposures were with pipe layers with bedded, non-tarped applications. Seasonal exposure estimates ranged from 0.495 ppb to 51.2 ppb when chloropicrin was an active ingredient. Annual exposure estimates for soil fumigation workers were between 0.207 ppb and 21.3 ppb. Lifetime exposure estimates ranged from 0.110 ppb to 11.3 ppb. As with short-term exposure, some of the workers with the highest long-term exposures were the tarp splitters and removers involved in broadcast,

tarped application. However, drivers and co-pilots for broadcast, tarped applications also had high long-term exposures. Reentry workers with bedded applications had the lowest long-term exposures.

Occupational - Structural Fumigation

Two monitoring studies of structural fumigation where chloropicrin was used as a warning agent were considered in estimating occupational exposure to chloropicrin. In one study, workers wore personal air samplers which were used to estimate occupational exposure during tarp removal. Indoor air concentrations from this study and another study were used to estimate occupational exposure during fumigation introduction, tarp inspection and aeration. Exposures were adjusted for the maximum application rate with assumptions about the amount time spent for each activity. The 1-hr and 8-hr exposures ranged from 43.7 ppb for tarp removers during aeration to 4,760 ppb for applicators and fumigators. Seasonal exposures ranged from 15.8 ppb for tarp removers to 62.2 ppb for fumigators. Annual exposure was approximately half of seasonal exposure while lifetime exposure estimates were about one quarter of seasonal exposure when expressed in ppb. When expressed in μg/kg/day, the lifetime exposures ranged from 7.83 to 33.5 μg/kg/day.

Bystander - Soil Fumigation

The California Air Resources Board (ARB) monitored off-site air concentrations of chloropicrin in Monterey (1986 and 2001), Santa Cruz (2003), and Santa Barbara (2005) Counties in California following soil fumigation. In addition, off-site monitoring studies were conducted by registrants following soil fumigation in Washington, Florida, Arizona and California. The registrants also collected on-site flux data in their studies which DPR used to model off-site exposures since the off-site monitoring from the various studies may not have represented the worse-case scenario as far as weather and sampler location. The modeling estimated downwind centerline exposure estimates at 1.2 m above ground (breathing zone) and 3 m from the edge of a 40-acre square field treated at the maximum application rate which were considered reasonable worse-case estimates. From the modeling, 1-hr, 8-hr and 24-hr exposure estimates were generated for the different application methods used in these studies. Broadcast non-tarped application had the highest 1-hr, 8-hr and 24-hr estimates: 11,000 ppb, 4,600 ppb, and 800 ppb, respectively. Seasonal exposure was estimated from the 24-hr average flux over 2 weeks, adjusting for time using the peak-to-mean method. The bedded tarped application had the highest estimate, 34 ppb. Annual exposure was estimated by amortizing the seasonal exposure over a year assuming a 5-month use season. The highest annual exposure was 14 ppb for the bedded tarped application. Lifetime exposure for residential bystanders was the same as the annual exposure, except it was converted to mg/kg/day for ease of calculation of the cancer risk. The lifetime exposure estimate for residential bystanders for bedded tarped application was 26 μg/kg/day. The lifetime exposure for occupational bystanders assumed exposure was limited to 40 years of a 70-year lifespan. The estimated lifetime exposure for bedded tarped application was 15 μg/kg/day.

Ambient air monitoring studies were also conducted by ARB in Monterey (1986 and 2001), Santa Cruz (2001), Santa Barbara (2000) and Kern (2001) Counties. Exposure estimates were not calculated from these studies since the air concentrations were lower than at the application site as would be expected and it was assumed that any mitigation needed for

bystander exposure near application sites would mitigate any concerns regarding air concentrations in ambient air.

Bystander - Structural Fumigation

Off-site air concentrations were monitored by the registrants following structural fumigation with sulfuryl fluoride where chloropicrin was added as a warning agent in four houses in Ventura (Ojai), Riverside (Homeland) and Fresno (Reedley - 2 houses) Counties. Modeling was not possible with this use, so exposure estimates were based the actual air concentrations after correcting for recovery. The highest off-site air concentration of chloropicrin associated with structural fumigation was found in the Ojai house which had a fumigation volume of 32,000 ft^3. The corrected 1-hr, 8-hr and 24-hr air concentrations were 36.2, 10.1 and 7.39 ppb, respectively. These air concentrations were used to evaluate bystander exposure for structural fumigation. No seasonal and annual exposure estimates were calculated for bystanders following structural fumigation since multiple structural fumigations are not anticipated in the same area.

Residential - Structural Fumigation

Indoor air concentrations were also monitored in the registrant studies of structural fumigation with chloropicrin. The highest 1-hr, 8-hr and 24-hr indoor air concentrations after aeration was completed were found in the Homeland, Reedley and Reedley houses, respectively. After adjusting for recovery and application rate, the 1-hr, 8-hr and 24-hr indoor air concentrations were 456, 183 and 172 ppb in the first 24 hours after aeration was completed. As with bystander exposure, no seasonal or annual exposure for indoor air following structural fumigation was anticipated.

Risk Characterization

The risk for non-carcinogenic health effects is expressed as a margin of exposure (MOE) which is the ratio of the NOEL from the animal study to the human exposure dosage. Generally, an MOE of at least 100 is desirable when the NOEL is derived from an animal study assuming that humans are 10 times more sensitive than animals and that there is a 10-fold variation in the sensitivity between the lower distribution of the overall human population and the sensitive subgroup. When the NOEL is derived from a human study, a MOE of at least 10 is desirable, assuming a 10-fold variation in the sensitivity of the human population. It was assumed there was no threshold for the carcinogenicity based on the weight of evidence from genotoxicity and carcinogenicity studies. Therefore, the negligible risk level for cancer was assumed to be one in a million or 10^{-6}.

Occupational - Soil Fumigation

When chloropicrin was an active ingredient, all of the MOEs for workers involved in soil fumigation were less than 10. The lowest MOEs were seen in tarp splitters and tarp removers with broadcast, tarped fumigation. The MOEs were at least an order of magnitude higher when chloropicrin was used as only a warning agent. Only a few scenarios still had MOEs less than one with these lower concentration formulations. Similar patterns were seen in the 8-hr MOEs. When chloropicrin was used as an active ingredient, most of the 8-hr MOEs were less than 100

with lowest MOEs for tarp splitters and removers with broadcast, tarped application which had MOEs less than 1.0. When chloropicrin was used as a warning agent, most of the 8-hr MOEs were greater than 100, especially with the 2% formulation. All of the seasonal MOEs for soil fumigation are greater than one, but they were less than 100 for all scenarios except for tarp punchers with bedded, tarped applications when chloropicrin was an active ingredient. Most of the seasonal MOEs were greater than 100 when a 2% chloropicrin formulation was used. The annual MOEs were generally about twice as large as the seasonal MOEs. As with seasonal exposure, the annual MOEs were less than 100 for most scenarios when chloropicrin was an active ingredient. When chloropicrin was used as a warning agent, the annual MOEs were all greater than 100 with 2% of the formulation. The highest cancer risk estimates for workers involved in soil fumigation were for broadcast, tarped applications when chloropicrin was used as an active ingredient. With these application methods, the MLE risk ranged from 1.7×10^{-3} to 2.8×10^{-2} while the 95% UB risk ranged from 2.9×10^{-3} to 4.7×10^{-2}. When chloropicrin is used as a warning agent, the cancer risk estimates were all less than 9.4×10^{-4} for the 2% formulations.

Occupational - Structural Fumigation

The 1-hr MOEs for workers involved in structural fumigation were 1.0 or lower, with the lowest MOE seen in applicators. The 8-hr MOEs were larger, but still less than the target MOE of 100 with fumigators having the lowest MOE at 0.8. The seasonal and annual MOEs were all greater than 1.0, but less than 10. The cancer risk for workers involved in structural fumigation ranged from 1.0×10^{-2} to 7.4×10^{-2}. Fumigators had the highest cancer risk estimates.

Bystander - Soil Fumigation

The potential health risks from bystander exposure to chloropicrin following soil fumigation are of concern since all of the MOEs were less than 100 for both children and adults. The acute MOEs for soil fumigation are clearly of concern since they are all less than 1.0. With the 1-hr exposure, the MOEs are orders of magnitude lower than the target MOE of 10. The seasonal and chronic MOEs for soil fumigation were greater than or equal to 1.0, but still less than 100 which is the target MOE. In addition, the cancer risk estimates for bystanders of soil fumigation were several orders of magnitude greater than the negligible risk level, ranging between 2.5×10^{-3} and 3.3×10^{-2}.

Bystander - Structural Fumigation

The off-site air concentrations of chloropicrin following structural fumigation are lower than following soil fumigation, but the acute exposures are still of concern. The 1-hr MOEs are less than the target MOE of 10. The 8-hr and 24-hr MOEs are greater than 10, but less than the target MOE of 100 for these exposure durations.

Residential - Structural Fumigation

The residential exposure to indoor air concentrations following aeration with structural fumigation are of greater concern since the 1-hr MOEs are less than 0.1 and 8-hr and 24-hr MOEs are less than 10.

Conclusions

The potential health risks for workers involved in soil fumigation are of concern when chloropicrin is an active ingredient since the MOEs were less than their target for most scenarios. Broadcast, tarped applications had the lowest MOEs. There was less concern for occupational exposure with soil fumigation when chloropicrin was used only as a warning agent at 2% since the MOEs for most scenarios were above their target. There was concern about the potential health risks for workers involved in structural fumigation since all of the MOEs were less than their target MOEs. The potential health risks from bystander exposure to chloropicrin following soil fumigation are of concern, especially for acute exposure since they were well below the target MOEs. The potential health risks for bystanders from exposure to chloropicrin after structural fumigation are less, however, the MOEs were still less than the target MOEs and are of concern. Residential exposure to chloropicrin in indoor air following structural fumigation are of greater concern since the 1-hr MOEs were less than 1 and the 8-hr and 24-hr MOEs were less than 10.

Lifetime exposure for workers involved in soil fumigation are of concern since the cancer risk estimates were all greater than the negligible risk level, even when chloropicrin was used only as a warning agent at 2%. In addition, the lifetime exposures for structural fumigation workers were of concern since the cancer risk estimates were also all greater than the negligible risk level. The lifetime exposure for bystanders of soil fumigation were also a concern since their cancer risk estimates were orders of magnitude greater than the negligible risk level. However, it is possible the cancer risks for both occupational and bystander exposure may have been overestimated due to uncertainties related to the carcinogenicity potential.

Based on the low MOEs and high cancer risk estimates for most occupational and bystander exposure scenarios mitigation should be considered.

I. INTRODUCTION

I.A. HISTORICAL AND REGULATORY BACKGROUND

Chloropicrin (trichloronitromethane) was first patented for use as an insecticide in 1908 (Gehring *et al.*, 1991). In 1926, chloropicrin was first used as a fumigant in flour mills (Clemson Univ., 2006). Since then it has been used in soil or structural fumigation, either as an active ingredient or as a warning agent with other odorless fumigants. Chloropicrin is a broad-spectrum fumigant with insecticidal, fungicidal, nematicidal and herbicidal properties.

During World War I (WWI), chloropicrin was used as a chemical warfare agent because of its strong lacrimatory and respiratory irritant properties. It was primarily used in high explosive gas shells mixed with other gases due to its high boiling point and was rarely used alone (Underhill, 1920). Chloropicrin was not as poisonous as some of the other WWI warfare agents, but it penetrated gas masks more rapidly and produced nausea and vomiting. This forced the soldiers to remove their masks, exposing them to the more poisonous gases with which it had been mixed. Berghoff (1919) examined 2,000 cases of soldiers that survived gas attacks during World War I and only 38 cases involved chloropicrin exposure alone. Another 515 cases involved exposure to a mixture of gases, of which chloropicrin may have been one. Generally, the symptoms with chloropicrin were less severe than with other gases based on the percentage with coughs, other physical findings, and the average time in the hospital. Since chloropicrin was usually used in combination with other gases, it was difficult to distinguish the effects due to chloropicrin from other WWI warfare agents.

Lambert and Jackson (1920) identified some of the adverse effects for chloropicrin from accidents in gas manufacturing plants (Lambert and Jackson, 1920). In humans, inhalation of chloropicrin resulted in immediate cough, nausea and vomiting. With higher or prolonged exposure, dyspnea, cyanosis, and weakness developed. Death usually occurred within a few hours. Even if initial symptoms were not severe, some deaths occurred 3 or 4 days later due to respiratory infection. Fries and West (1921) reported that the eye was very sensitive to chloropicrin, causing essentially involuntary closing of the eye. Concentrations above 25 ppm caused the eye to close so rapidly after exposure that it was impossible to measure the time elapsed. Between 2 and 25 ppm, the eye closed within 3 to 30 seconds depending on the individuals sensitivity. Below 1 to 2 ppm, the eye did not close, but considerable blinking sometimes occurred. Vedder (1925) estimated the concentration of chloropicrin that incapacitated a man in a few seconds due to sensory or respiratory irritation was 0.026 mg/m^3 (4 ppm) and the concentration that resulted in respiratory lesions after 1-2 minutes was 0.1 mg/m^3 (15 ppm). Based on the information reported by Fries and West (1921) and Vedder (1925), the American Conference of Governmental Industrial Hygienists (ACGIH) initially set the time-weighted average threshold limit value (TWA-TLV) for chloropicrin in 1956 at 1.0 ppm (Stokinger, 1982). In 1959, the TLV was reduced to 0.1 ppm to provide greater protection for eye irritation and pulmonary changes (ACGIH, 2001). OHSA's Permissible Exposure Limit (PEL) and NIOSH's Recommended Exposure Limit (REL) were also set at 0.1 ppm. NIOSH's Immediately Dangerous to Life or Health (IDLH) value was initially set at 4 ppm for chloropicrin based on reports that exposure to chloropicrin for a few seconds at 4 ppm renders a man unfit for action (NIOSH, 1996). In 1996, it was reduced to 2 ppm taking into consideration more recent acute inhalation toxicity studies in animals.

The Department of Pesticide Regulation (DPR) placed chloropicrin into reevaluation in 2001 (Cortez, 2001). The basis for this decision was that air monitoring data submitted by the Chloropicrin Manufacturers Task Force (CMTF) indicated that air concentrations at some distances from treated greenhouses exceeded NIOSH's REL of 0.1 ppm. As a result, DPR requested that the chloropicrin registrants conduct and submit worker exposure and air monitoring studies associated with field and greenhouse applications of chloropicrin. Using the air monitoring studies submitted, DPR conducted a human health risk assessment which evaluated public airborne exposures to chloropicrin under the legislative mandate of the California Toxic Air Contaminant Act (AB 1807). Based on this risk assessment, DPR is preparing regulations to list it as a toxic air contaminant. DPR also placed chloropicrin on the high-priority list for a comprehensive risk assessment based on possible adverse effects identified in genotoxicity and developmental toxicity studies submitted under the Birth Defect Prevention Act (SB 950). This document represents the comprehensive risk assessment which evaluated the risks for potential human health effects from both occupational and public airborne exposures to chloropicrin.

I.B. CHEMICAL IDENTIFICATION

Chloropicrin is a broad-spectrum fumigant that rapidly diffuses through soil and kills common root destroying fungi, nematodes, soil insects and other plant pests (Wilhelm, 1996). Chloropicrin does not have the broader herbicidal properties of methyl bromide and metam sodium or the broader nematicidal properties of 1,3-dichloropropene, so it is usually used in combination with these other fumigants. Chloropicrin has a low odor threshold and causes sensory irritation at very low concentrations, so it has been added as a warning agent to other fumigants like methyl bromide, methyl iodide, 1,3-dichloropropene and sulfuryl fluoride which are odorless. Chloropicrin's mechanism of action is not well understood, but it may be related to its reaction with biological thiols like glutathione and hemoglobin (Sparks *et al.*, 1997). Chloropicrin also inhibits pyruvate and succinate dehydrogenase (Sparks *et al.*, 2000). The inhibition of these enzymes has been correlated to the lethality of various halonitromethanes, quinones, fungicides and other thiol-reactive chemicals. Today, its greatest use in California is on strawberries, usually in combination with methyl bromide. Due to the eventual phase out of methyl bromide because of its ozone-depleting properties, the amount of chloropicrin in these formulations has increased.

II. TOXICOLOGY PROFILE

All the available toxicity studies for chloropicrin are summarized in the Toxicology Profile including studies from the open literature and studies submitted to DPR for registration of pesticide products in California as required by the Birth Defects Prevention Act (SB-950). DPR reviews the studies submitted to fill data requirements for SB-950 and determines the acceptability of these toxicology studies based on study guidelines as required under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) (U.S. EPA, 2006). For SB-950, literature studies are generally considered supplemental because they do not follow FIFRA guideline protocols and/or do not provide sufficient detail in their reports to determine if they were conducted properly. In the risk assessment, greater weight is given to guideline studies, especially if they are found acceptable based on FIFRA guidelines. However, literature studies are useful in the selection of the critical NOEL in the Hazard Identification section to support effects seen in the guideline studies and can be used for the critical NOEL if they evaluate an endpoint not examined in the guideline studies and they appear to be scientifically valid studies. Except for the Pharmacokinetics and Acute Toxicity sections, the studies are generally organized within each section by route and species with the older studies discussed first. When mechanistic studies are available, they are discussed after the guideline studies under the appropriate route and species. The Pharmacokinetics section is organized by different phases in the disposition of xenobiotics in the body. The Acute Toxicity section is separated into data for the technical grade material and the various formulations.

II.A. PHARMACOKINETICS

There were no FIFRA guideline pharmacokinetics/metabolism studies for chloropicrin and very limited pharmacokinetic data available in the open literature. Sparks *et al.* (1997) administered ^{14}C-chloropicrin to male Swiss Webster mice intraperitoneally and orally at 1-3 mg/kg with triethylene glycol monomethyl ether as the vehicle. They monitored the radioactivity in the urine, feces and expired air for 48 hours. The urine was the major route of excretion with 43-47% excreted in the first 24 hours. Another 8-8.5% was excreted in the urine between 24 and 48 hours. The metabolites in urine were analyzed by TLC. None were identified, but they appeared to be polar and nonvolatile. The other major route of excretion was expired air with 6.5-15% excreted as CO_2 in 48 hours. Only 2.5-9% of the applied dose was excreted in the feces in the 48 hours following dosing. Tissue levels of radioactivity were measured at 1 hour (i.p.) and 48 hours (i.p. and oral) after dosing. At 1 hour and 48 hours, the liver had the highest level of radioactivity, followed by the kidney, lung, blood, fat and skin.

Sparks *et al.* (1997) also investigated the reaction of chloropicrin with biological thiols *in vitro*. Chloropicrin reacted quickly with various biological thiols including glutathione (GSH), cysteine, N-acetylcysteine, coenzyme A and reduced lipoic acid. These reactions resulted in the conversion of chloropicrin to dichloronitromethane and the formation of the corresponding disulfide of the thiol. The initial adduct with GSH and chloropicrin was unstable since attempts to isolate it were unsuccessful. Nitric oxide was an unlikely metabolite since S-nitroso-GSH was not found. Chloropicrin also oxidizes protein thiols *in vitro* including hemoglobin (Hb) and alcohol dehydrogenase. The change in the UV profile implied formation of internal and cross-linked disulfide bonds. The Hb adduct formation is more stable than GSH adduct, but it readily

dissociates in buffer. The proposed pathways for reaction of chloropicrin with GSH and Hb are shown in Figure 1.

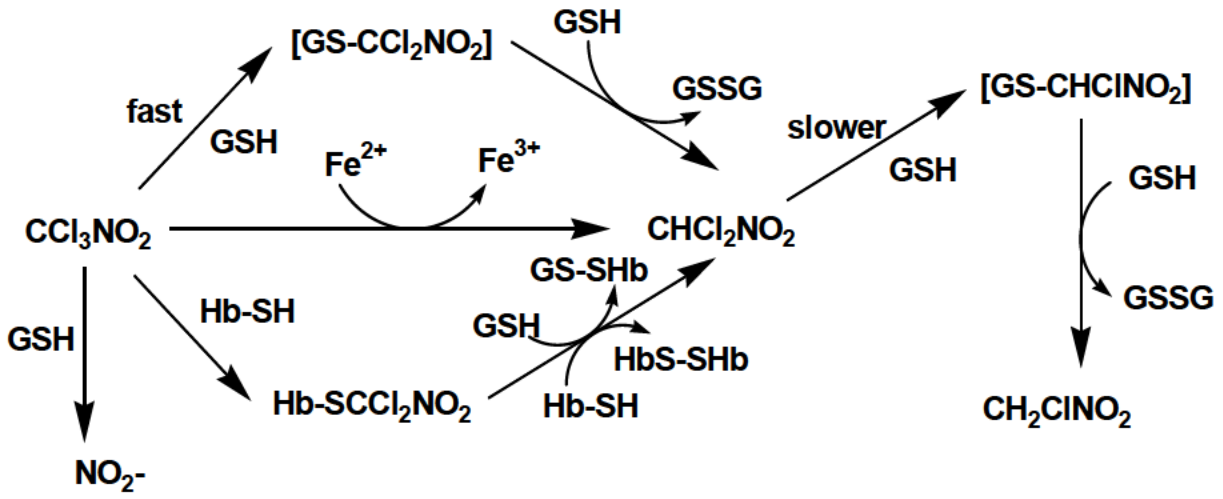

Figure 1. Proposed pathways for reaction of chloropicrin with glutathione and hemoglobin (Sparks *et al.*, 1997)

In a subsequent study, Sparks *et al.* (2000) administered chloropicrin intraperitoneally to male Swiss-Webster mice at 5 mg/kg with DMSO as the vehicle and kept them in metabolic chambers for 24 hours. They were able to identify raphanusamic acid (also known as 2-thioxothiazolidine-4-carboxylic acid, TTCA) in the urine that was equivalent to about 1% of the administered dose of chloropicrin. Based on this finding, these investigators proposed a metabolic pathway that involved the initial reaction of chloropicrin with glutathione to form the GS-CCl_2NO_2 metabolite which can either react further with glutathione to the form dichloro and monochloro metabolites or react with cysteine and then be cleaved by cysteine β-lyase to form raphanusamic acid via thiophosgene (Figure 2).

While chloropicrin can react with hemoglobin to form methemoglobin, Sparks *et al.* (2000) showed that methemoglobin is not important in the toxicity of chloropicrin. Instead oxyhemoglobin accumulates in the liver of mice when treated with chloropicrin. Although oxyhemoglobin is the normal form of hemoglobin when oxygen is bound to it, the investigators suggested that the elevated oxyhemoglobin levels were a marker for the toxicity of chloropicrin in mice. They proposed that the enzymes, pyruvate and succinate dehydrogenase (PDH and SDH), were possible targets for the lacrimatory effects of chloropicrin because of thiol groups in their active sites. Sparks *et al.* observed that chloropicrin was an inhibitor of these enzymes *in vitro* with moderate potency (IC_{50} values of 4 and 13 μM for PDH and SDH, respectively). They found that the dichloro and monochloro metabolites of chloropicrin were much less potent with IC_{50} values of 60-182 μM. They correlated the inhibition of PDH and SDH with the lethality of various halonitromethanes, quinones, fungicides and other thiol-reactive chemicals. The inhibition of PDH correlated most closely with the lethality of these chemicals. Sparks *et al.* (2000) concluded that the acute toxicity of chloropicrin is due to the parent compound or metabolites other than the dehalogenated metabolites and may be associated with the inhibition of PDH and elevated oxyhemoglobin.

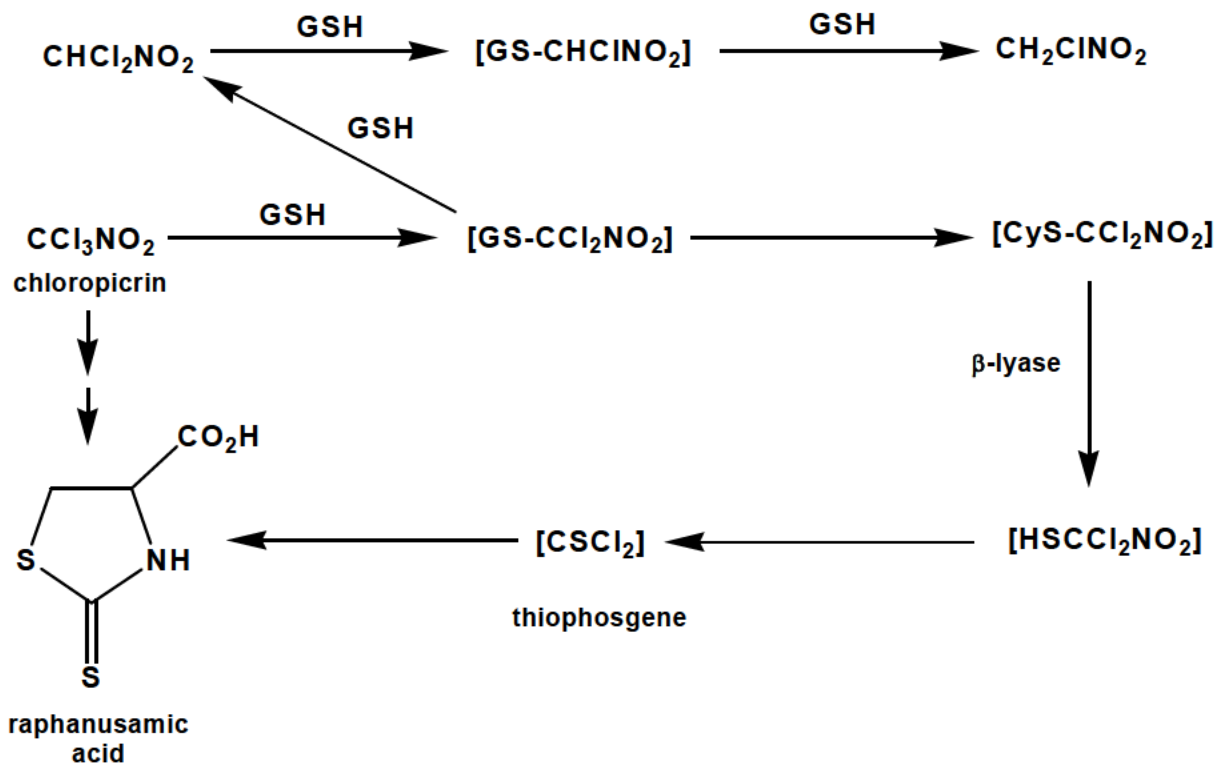

Figure 2. Proposed metabolism of chloropicrin in mice by dechlorination and conversion to raphanusamic acid via thiophosgene (Sparks *et al.*, 2000).

Although not isolated by Sparks *et al.*, nitromethane is considered a potential metabolite of halonitromethanes which are not stable in blood and undergo dehalogenation (Alwis *et al.*, 2008). Halonitromethanes are disinfection byproducts (DBPs) formed as the result of drinking water chlorination and nitromethane in the blood was proposed as a potential biomarker for exposure to them.

The toxicity of chloropicrin is probably not limited to its reaction with biological thiols. Chloropicrin is a strong electrophile due to the presence of the chlorine and nitro groups. Consequently, it is capable of covalently binding with various proteins, DNA and other nucleophiles within the body.

II.B. ACUTE TOXICITY

Summary: The acute toxicity of chloropicrin was first characterized around 1920 in studies with dogs. More recently, several LC_{50} studies were conducted with rats. The reported LC_{50} values ranged from 6.6 to 25.5 ppm (44 to 171 mg/m^3) depending on the duration of exposure and whether it was a whole body or nose only exposure. The LC_{50} values also varied depending on how long the observation period was after dosing. Deaths occurred in two phases, either within 24 hours or after 8 to 10 days. The later deaths were attributed to respiratory infection. The clinical signs were primarily respiratory, although eye irritation, lacrimation and eye closure were also noted. Numerous gross and histopathological lesions were observed

throughout the respiratory tract. In comparing chloropicrin to other lethal WWI warfare agents like chlorine gas and phosgene, early investigators described the respiratory effects to be intermediate in onset and primarily affecting small to medium bronchi. The ability of chloropicrin to cause respiratory depression in mice was also evaluated in two studies as an indication of sensory irritation in man. The RD_{50} (concentration that caused a 50% reduction in respiratory rate) values ranged from 2.34 ppm (15.7 mg/m^3; HEC_{1hr} - 3.57 ppm) for a 30 minute exposure to 7.98 ppm (53.7 mg/m^3; HEC_{1hr}- 4.06 ppm) for a 10 minute exposure. The RD_{50} was proposed as an intolerable concentration to man. More recently a human sensory irritation study was conducted which consisted of three phases. The first phase identified the median odor threshold for chloropicrin at 700 ppb. The median threshold for eye irritation was 900 ppb. The median threshold for nasal irritation was greater than 1200 ppb, the highest level tested. In phase 2, a NOEL for ocular irritation was established at 50 ppb with a 20-minute exposure in a walk-in chamber. No nasal or throat irritation was observed up to 150 ppb. In phase 3, the NOEL for ocular irritation appears to be less than 100 ppb after a 1-hour exposure in a walk-in chamber. No nasal or throat irritation was reported in this phase, but increased production of nitric oxide (NO) and decreased nasal airflow at 100 and 150 ppb suggests some subtle upper respiratory changes.

II.B.1. Animal Studies

Underhill (1920) exposed 219 dogs (both genders, various breeds, ages and states of nutrition) to chloropicrin for 30 minutes at air concentrations ranging from 0.36 to 1.25 mg/L (49 to 172 ppm). An LC_{50} value was not calculated, but 53% of dogs were killed when exposed to chloropicrin at 0.81 to 0.95 mg/L (111-131 ppm). Only one of 12 animals exposed to chloropicrin at the lowest concentration, 0.35 to 0.50 mg/L (49-69 ppm) died. The majority of the dogs died within 24 hours after exposure. However, several delayed deaths were seen. The clinical signs observed after exposure to chloropicrin were not reported, but the respiration, pulse, temperature, and composition of the urine and blood were examined in the dogs. There was an immediate lowering of the respiratory rate that returned to normal within 2-3 hours after exposure except in dogs that died. The respiratory passages became clogged with excessive mucus and the animals began mouth breathing with a gasping reflex. The pulse initially dropped to less than half the normal rate after being exposed to chloropicrin, followed by a return to normal or above normal in more severely affected dogs. A drop in body temperature was seen in most dogs after exposure to chloropicrin and continued to fall (up to 4°C) in animals that died. There was an increase in urinary total nitrogen, ammonia nitrogen, creatine nitrogen, phosphate and chloride levels after exposure. An increase in total blood solids, red blood cell count and hemoglobin concentration were seen in dogs after exposure. These values remained elevated in animals that died.

Lambert and Jackson (1920) examined 120 of the dogs that were exposed to chloropicrin gas in the studies conducted by Underhill. Dogs that died within in a few days of exposure had extreme edema and congestion of the lungs, necrosis of the bronchial epithelium and bronchiolar walls, dilation of the heart, and passive congestion of the abdominal viscera. The investigators concluded that the edema was not the cause of death because the severity was no greater in animals that died than those that survived. Instead, they proposed that the cause of death was due to the accumulation of fibrin in the pulmonary septa forming a barrier to blood flow through the lungs. There were a number of delayed deaths which were attributed to respiratory infection in most cases. The investigators compared the damage seen with chloropicrin to other lethal

WWI warfare agents, chlorine and phosgene. Chlorine acts very rapidly and affects primarily the upper respiratory tract (trachea, large and medium bronchi) where it first comes in contact. Phosgene, on the other hand, has a delayed action and primarily affects the lower respiratory tract (smaller bronchi, bronchioles and alveoli) presumably due to its metabolism to hydrogen chloride. Chloropicrin is intermediate in its onset and primarily affects the medium and small bronchi. The information in these early investigations was too limited and the dose levels too high to be useful for estimating an acute NOEL.

The U.S. Department of Transportation reported a one-hour LC_{50} (whole body) of 25.5 ppm (analytical; 171 mg/m^3; HEC_{1hr}[1] - 41.5 ppm) for chloropicrin in rats (both sexes, Sherman strain) (Harton and Rawl, 1976) (Table 2). The animals exhibited gagging response and irritation to the eyes and mucous membranes during exposure (dose response not indicated). This study had major deficiencies in that there were no data reported on clinical signs or necropsy findings.

Table 2. The Acute Toxicity of Technical Grade Chloropicrin

Species	Sex	Results	References[a]
		Acute Inhalation LC_{50}	
Rat	M/F	25.5 ppm (1 hr, whole body) (I)	1
Rat	M	11.9 ppm (4-hr, whole body) (I)	2
Rat	M	14.4 ppm (4-hr, whole body) (I)	3
Rat	M	6.6 ppm (4-hr, nose only) (I)	
Rat	M	16.7 ppm (4-hr, whole body) (I)	4
	F	20.1 ppm (4-hr, whole body) (I)	
		Acute RD_{50}	
Mice	M/F	7.98ppm (10 min, head only)	5
	M	2.34 ppm (30 min., head only)	6
		Acute Intraperitoneal LD_{50}	
Mice	M/F	8 mg/kg	7
		Acute Oral LD_{50}	
Rat	M/F	37.5 mg/kg (I)	1
		Acute Dermal LD_{50}	
Rabbit	M/F	100 mg/kg (I)	1
		Primary Dermal Irritation	
Rabbit	M/F	Corrosive (I)	1

a References: 1. Harton and Rawl, 1976; 2. Yoshida *et al.*, 1987a; 3. Yoshida *et al.*, 1991; 4. Hoffman, 1999a; 5. Kane *et al.*, 1979; 6. Hoffman, 1999b; 7. Sparks *et al.*, 1997.

Yoshida *et al.* (1987a) conducted a 4-hr LC_{50} study in which male Fisher 344 rats were exposed (whole body) to chloropicrin vapors at 0, 8.8, 11.0, 11.4, 12.1, 13.6 or 16.0 ppm (analytical; 0, 59, 74, 77, 81, 91 or 108 mg/m^3; HEC_{8hr}[2] - 0, 7.16, 8.95, 9.27, 9.84, 11.1 or 13.0

1 HEC (Human Equivalent Concentration) = ppm x RR_a/RR_h x E_a/E_h. RR_a = respiratory rate in animals which was assumed to be 0.96 m^3/kg/day for the rat (Zielhuis and van der Kreek, 1979). RR_h = respiratory rate in humans which was assumed to be 0.59 m^3/kg/day for a child (DPR, 2000). E_a = exposure duration for animals which was 1 hour/day. E_h = exposure duration for humans which was set at 1 hour/day.

2 HEC = ppm x RR_a/RR_h x E_a/E_h. RR_a = 0.96 m^3/kg/day for the rat (Zielhuis and van der Kreek, 1979). RR_h = 0.59 m^3/kg/day for a child (DPR, 2000). E_a = 4 hours/day. E_h = 8 hours/day.

ppm). The 4-hr LC_{50} was estimated to be 11.9 ppm (analytical; 80 mg/m^3; HEC_{8hr} - 9.68 ppm). During exposure, eyelid closure, reduced activity, labored breathing, salivation, lacrimation, and rhinorrhea were seen. All but the labored breathing and lacrimation disappeared within a few hours after removal from the exposure chambers. Deaths were biphasic, occurring either within 24 hours or after 8 to 10 days. Animals that died exhibited gasping and cyanosis before dying. At necropsy, they had reduced body weights, increased absolute and relative (to body or brain) lung weights, diffuse pulmonary edema and emphysema, hydrothorax, scattered dark red patches in the lungs, and gastric gaseous distension. Survivors had similar gross pathological lesions at the study termination (day 14), except no hydrothorax. These investigators also exposed rats to chloropicrin for 30 minutes at 21.7 and 45.5 ppm (analytical; 146 and 306 mg/m^3; HEC_{1hr} - 17.7 and 37.0 ppm). They were unable to establish an exact LC_{50} for this exposure duration, but it appears to be between these two dose levels. A no-observed-effect level (NOEL) could not be established for either the 4-hour or the 30-minute exposure period.

An acute LC_{50} study in rats was also submitted to DPR by the Chloropicrin Manufacturers Task Force (Hoffman, 1999a). Five Crl:CD®(SD)IGS BR rats/sex/dose were exposed (whole body) to chloropicrin (purity > 99%) at 0, 10.5, 18.0 or 23.5 ppm (analytical; 0, 71, 121 or 158 mg/m^3; HEC_{8hr}[3] - 0, 8.54, 14.6 or 19.1 ppm) for 4 hours. Deaths occurred at 18.0 ppm (3 males, 1 female) and 23.5 ppm (5 males and 4 females) during the 2-day observation period. The clinical signs observed during exposure included labored breathing and/or gasping, decreased activity and closed eyes. After exposure, lacrimation, nasal discharge, salivation, dried brown material on face, labored breathing and/or gasping, and moist rales were observed. Significant decreases in the terminal body weights were seen at 10.5 and 18.0 ppm. Gross pathological findings included red lungs and fluid in the trachea and lungs. Numerous histopathological changes were seen in the respiratory tract at all treatment levels with little or no dose-related differences in the incidence or severity. Lumenal fibrin admixed with inflammatory cells, epithelial and/or mucosal necrosis, erosions, edema and inflammation were seen throughout the respiratory tract. Congestion of respiratory mucosa was observed in the nasoturbinates. Thin mucosal epithelium was seen in the nasopharynx and trachea. Vascular congestion was observed in the larynx and lungs. The lungs had bronchiolar and peribronchiolar chronic active inflammation and focal hemorrhages. No NOEL was established for clinical signs or pathological lesions. The estimated LC_{50} was 16.7 ppm (112 mg/m^3; HEC_{8hr} - 13.6 ppm) and 20.1 ppm (135 mg/m^3; HEC_{8hr} - 16.4 ppm) in males and females, respectively, suggesting that the males are slightly more sensitive than females to chloropicrin. This study did not meet FIFRA guidelines due to the short observation period. The LC_{50} values from this study are slightly higher than those reported by Yoshida, probably due to the delayed deaths that were seen in the Yoshida study 8 to 10 days after exposure.

Yoshida *et al.* (1991) compared the acute toxicity of chloropicrin vapors with whole body, nose only and dermal exposure in male Fisher 344 rats for 4 hours. The LC_{50} values with whole body and nose only were 14.4 and 6.6 ppm (actual; 96.8 and 44.4 mg/m^3; HEC_{8hr}[4] - 11.7 and 5.37 ppm), respectively. Interestingly, the nose only exposure resulted in a lower LC_{50} value. This might be due to more rapid breathing of the rats in nose-only chambers due to stress.

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3 HEC = ppm x RR_a/RR_h x E_a/E_h. RR_a = 0.96 m^3/kg/day for the rat (Zielhuis and van der Kreek, 1979). RR_h = 0.59 m^3/kg/day for a child (DPR, 2000). E_a = 4 hours/day. E_h = 8 hours/day.

4 HEC = ppm x RR_a/RR_h x E_a/E_h. RR_a = 0.96 m^3/kg/day for the rat (Zielhuis and van der Kreek, 1979). RR_h = 0.59 m^3/kg/day for a child (DPR, 2000). E_a = 4 hours/day. E_h = 8 hours/day.

No deaths or toxic signs were observed at the one dose level, 25 ppm (actual: 168 mg/m^3; HEC_{8hr} - 20.3 ppm), tested with dermal exposure. Most of the deaths occurred within 24 hours. Clinical signs and pathological lesions similar to those in their previous study were seen in this study. Insufficient information was provided to establish a NOEL from this study, except with dermal exposure.

Sensory irritation is caused by the stimulation of unspecialized free nerve endings of the afferent trigeminal nerve located in the corneal, nasal and oral mucosa (Kane *et al*., 1979). Stimulation of the trigeminal nerve results in a burning or pungent sensation and numerous physiological reflex responses, including a reduction in respiratory rate. Based on earlier research by these investigators, they were able to show that a reduction in respiratory rate of mice was a good predictor of sensory irritation in man which shows a concentration-response relationship. The concentration which caused a 50% reduction in the respiratory rate (RD_{50}) of mice is used to compare the relative potency of various irritants. They proposed that the RD_{50} would be an intolerable concentration in man. Kane *et al*. (1979) determined the RD_{50} of chloropicrin was 7.98 ppm (53.7 mg/m^3; HEC_{1hr}[5] - 4.06 ppm) with a 10-minute exposure. The Chloropicrin Manufacturers Task Force also submitted a sensory irritation study in mice (Hoffman, 1999b). Four male Swiss-Webster mice/dose were exposed (head only) to chloropicrin (purity > 99%) at 0.99, 3.20, 4.20, 7.25, 10.0 or 14.5 ppm (analytical: 6.7, 21.5, 28.2, 48.7, 67.2 or 97.5 mg/m^3; HEC_{1hr}[6] - 1.51, 4.88, 6.41, 11.1, 15.3 or 22.1 ppm) for 30 minutes. No mortalities or clinical signs were seen. The respiratory rate was decreased from pre-exposure level by 30, 55, 65, 72, 73, and 77% at the respective dose levels. The estimated RD_{50} was 2.34 ppm (15.7 mg/m^3; HEC_{1hr} - 3.57 ppm). Buckley *et al.* (1984) reported that mice exposed to chloropicrin at 7.98 ppm (10-min RD_{50}) for 6 hrs/day for 5 days (HEC_{8hr}[7] = 18.3 ppm) exhibited body weight reductions, nasal discharge, and gaseous distention of the abdomen. When examined histopathologically, the mice had inflammation, exfoliation, erosion, ulceration and necrosis of the upper respiratory epithelium and ulceration and necrosis of the olfactory epithelium. Lesions were also seen in the lower respiratory tract including severe fibrosing peribronchitis and peribronchiolitis. It is unclear from the data presented if any deaths occurred at 7.98 ppm. None of these studies were FIFRA guideline-type studies, but the study by Hoffman (1999b) was conducted in accordance with Good Laboratory Practice regulations.

The Department of Transportation also reported oral and dermal LD_{50} values for chloropicrin (Harton and Rawl, 1976). The oral LD_{50} in rats was 37.5 mg/kg. No other details were reported on clinical signs or necropsy findings. The dermal LD_{50} in rabbits was 100 mg/kg. Moderate edema was seen during the first 48 hours after exposure. Discoloration and necrosis were also reported. No details were reported on other clinical signs or necropsy findings. In a standard dermal irritation test in rabbits, they determined that chloropicrin was corrosive based on necrosis at 72 hours. Sparks *et al.* (1997) determined the LD_{50} for chloropicrin in mice to be 8 mg/kg after intraperitoneal injection. They also estimated the LD_{50} for the metabolites, $CHCl_2NO_2$, CH_2ClNO2 and CH_3NO_2. Their respective LD_{50} values were 70, 56 and > 200

5 HEC = ppm x RR_a/RR_h x E_a/E_h. RR_a =1.8 m^3/kg/day for the mouse (Zielhuis and van der Kreek, 1979). RR_h = 0.59 m^3/kg/day for a child (DPR, 2000). E_a = 10 minutes/day. E_h = 60 minutes/day.

6 HEC = ppm x RR_a/RR_h x E_a/E_h. RR_a =1.8 m^3/kg/day for the mouse (Zielhuis and van der Kreek, 1979). RR_h = 0.59 m^3/kg/day for a child (DPR, 2000). E_a = 30 minutes/day. E_h = 60 minutes/day.

7 HEC = ppm x RR_a/RR_h x E_a/E_h. RR_a =1.8 m^3/kg/day for the mouse (Zielhuis and van der Kreek, 1979). RR_h = 0.59 m^3/kg/day for a child (DPR, 2000). E_a = 6 hours/day. E_h = 8 hours/day.

mg/kg. The signs of toxicity were similar to chloropicrin in that they were primarily neurological with tremors and seizures before death. No other details of clinical signs, body weights, food consumption or necropsy findings were reported.

II.B.2. Human Studies

II.B.2.a. Case Reports

There are several case reports of effects in humans after accidental exposure to chloropicrin. In one case, the owner of a house released chloropicrin in the basement to get rid of bats 3 to 4 weeks before the new owners moved in (TeSlaa *et al*., 1986). In the week following the arrival at their new house, the family members (2 adults and 2 children) experienced runny noses, lacrimation and coughing. The father who was a smoker developed the most severe symptoms including a dry cough and red, edematous nasal and pharyngeal mucosa. He was diagnosed with bronchitis and sinusitis. A month later he developed a heart murmur and showed some thickening of the aortic valve with slight left ventricular dilatation. However, the cardiologist and consulting toxicologist concluded it was not related to chloropicrin exposure. The family dog, which was kept in the basement at night, developed lacrimation, dyspnea, and repeated coughing. It was diagnosed with bronchitis and pneumonia. Chloropicrin residues measured at 6, 18 and 38 weeks after application were 30, 2 and 2 ppb, respectively.

In October of 1984, the fumigation of a strawberry field (pre-plant) near Ceres, California, with methyl bromide and chloropicrin resulted in 32 people being seen at an emergency room with symptoms such as eye irritation, sore throat, headache, shortness of breath and cough (Goldman *et al.*, 1987). No air samples were taken at the time of the incident, but air samples taken the next day were negative (minimum detection limit was 1 ppb). Several days later, a community survey was conducted to determine the extent of the exposure and nature of symptoms experienced. Among 94 people reporting new illnesses after the incident, 32 adults and 4 children had symptoms consistent with exposure to either methyl bromide or chloropicrin. The vast majority (31 adults and 4 children) had symptoms that were attributed to chloropicrin poisoning. The most common symptoms attributed to chloropicrin exposure were eye irritation (65%), headache (48%), throat irritation (45%) and unusual odors (39%). The reporting of symptoms was related to the distance from the field with 30% of the people living or working within 1 kilometer of the field.

In an unusual incident in Japan, an 18-year-old woman and 21-year-old man were sprayed with chloropicrin by an assailant while parked in a car on a farm road (Gonmori *et al.*, 1987). The woman was transferred to a hospital 75 minutes after the incident, but died 3 hours later. Dark purple discoloration of the skin and pulmonary edema were the main findings at autopsy. Chemical analysis of lung tissue and wiped samples from the car confirmed the presence of chloropicrin. The male survivor of the incident recovered after spending 30 days in the hospital. No details were reported of his symptoms.

In an incident in Belgium, a farmer accidentally fumigated a greenhouse with a mixture of chloropicrin and metam-sodium due to a mislabeling of a bottle containing pure chloropicrin as metam-sodium (Selala *et al.*, 1989). The fumes escaped through the vents of the greenhouse and dissipated into neighboring areas. A number of animals (2,500 turkeys, numerous

ducklings, 4 sheep, and a goat) adjacent to the greenhouse died as a result of exposure to the fumes. No human fatalities were reported, but residents within a 200 to 600 meter radius of the greenhouse reported various complaints including eye irritation, lacrimation, coughing, runny nose, nausea, sore throat, headache, dyspnea, and skin irritations. Thirty-five people including some rescue workers were admitted to an emergency room. Seven of these 35 people had elevated methemoglobin levels. Based on the complaints, the investigators estimated that the air concentration of chloropicrin was between 0.05 and 0.1 mg/L (7.5 and 15 ppm, approximately).

Three workers from a freight transportation company were briefly exposed to chloropicrin while unloading palettes of canisters containing methyl bromide or chloropicrin from a trailer truck (Prudhomme *et al*., 1999). Apparently several of the chloropicrin canisters were overfilled at the factory and residue had evaporated from the outside of the canister. One worker was initially exposed for approximately a minute before severe eye irritation and burning chest pain forced him to leave the truck. A co-worker was exposed for about 30 seconds before eye irritation caused him to leave. The third person, a supervisor, held his breath during the 15 seconds while he was inside. The first worker had the most severe symptoms including unusual taste or odor, eye, nose and throat irritation, runny nose, headache, nausea, dizziness, lethargy, burning in chest, shortness of breath, stomach/abdominal and generalized muscle cramping, rash, pleuritic chest pain, dysphagia, dysuria, anxiety, fatigue, and peripheral numbness. Laboratory results showed a marked elevation in his serum creatine phosphokinase activity. After his discharge from the hospital 4 days later, he continued to experience headaches and diffuse muscular pain in his upper extremities, chest and abdomen. He remained off work for several months due to lethargy, musculoskeletal pain and poor tolerance to exertion. The second worker experienced less severe symptoms (eye irritation, nausea, shortness of breath, abdominal and stomach cramping, fatigue) and slightly elevated serum creatine phosphokinase activity. He was released from the hospital after 2 days and returned to light-duty work 11 days after the incident. The supervisor had the mildest symptoms (headache, nausea, lethargy, chest pain, and stomach cramping). He was discharged after being seen in the emergency room.

From 1992 to 2008, there were a total of 1,059 cases with health effects definitely, probably, or possibly related to chloropicrin exposure reported to the California Pesticide Illness Surveillance Program (Beauvais, 2011; Oriel *et al.*, 2009). Of these, 571 cases were associated with six incidents where chloropicrin was the sole active ingredient. Two major incidents were responsible for most of these illness reports. One incident in Kern County in 2003 was associated with 165 cases following the application of 100% chloropicrin over a 2-day period to fallow land with a buffer zone of 18 m. The chloropicrin was injected in the soil and applicators attempted to confine the fumigant by dragging a weighted board behind the tractor, but they did not compact the soil. Complaints of eye and throat irritation were reported each evening after the applications, but the source of the irritation was not located until the second evening. In 2005, another 324 cases were associated with an application of 94% chloropicrin in Monterey County. The fumigant was applied to a tarped bedded field through a drip irrigation system which apparently was not flushed with an adequate amount of water. Complaints occurred up to 3 miles from the application site and mostly involved odor and eye irritation. Another 218 cases were associated with 58 incidents where chloropicrin was used as an active ingredient in combination with other fumigants, all involving soil fumigation. In 260 cases, chloropicrin was used as a warning agent with other fumigants which involved 172 incidents. Most of these cases (206 cases) were related to its use as a warning agent in structural fumigation.

Systemic effects as well as local effects to the eye, respiratory tract and skin were reported. Eye irritation was seen in 96% of the cases where chloropicrin was used alone, but was seen in only 73% of the cases where it was used as an active ingredient in combination with another fumigant and in only 47% of the cases where it was used as a warning agent in combination with another fumigant. Systemic effects showed the opposite trend with the highest percentage of cases (64%) with systemic effects associated with the use of chloropicrin as a warning agent and the lowest percentage of cases (32%) associated with its use as an active ingredient alone. The incidence of skin effects also tended to be greater with the warning agent use (22%) and in combination with other fumigants (7%) compared to chloropicrin alone (1%). No clear trend was seen with respiratory effects.

II.B.2.b. Controlled Study

The sensory irritation potential of chloropicrin vapors was evaluated in human subjects by Cain (2004). Young adults were used for this study because it has been observed that olfactory and trigeminal nerve sensitivity declines with age (Cain *et al.*, 1995; Hummel *et al.*, 2003; Kjaergaard *et al.*, 1992; Shusterman *et al.* 2003; Wysocki *et al.*, 2003). Subjects underwent a physical examination to ensure that subjects were healthy, nonsmokers free from exposure to chloropicrin, mood-altering drugs and medications that could interfere with the conduct of the study and the female subjects were not pregnant. Potential subjects underwent a brief odor identification test to ensure their sense of smell was normal. The study was divided into three phases. Some subjects participated in more than one phase of the study. In phase 1, the odor, nasal and ocular sensitivity was evaluated in subjects who were asked if they could detect the presence of chloropicrin by odor, ocular “feel” or nasal “feel” after brief exposures (5 seconds for odor and nasal localization and 25 seconds for ocular) to increasing concentrations at 356, 533, 800 and 1200 ppb. Each subject was exposed to the 4 different levels in 30 rounds. The subjects were blinded to their exposure by randomly exposing them through one of 3 cones at a station, which varied from trial to trial. With ocular detection, the subjects wore nose clips. For nasal localization, tubes from separate cones were directed to the left and right nostrils. For odor detection, 62 subjects (32 males, 30 females) were tested. The median level of detection for odor was 700 ppb (males - 590 ppb; females - 810 ppb). The ocular detection was tested in 63 subjects (32 males, 31 females). The median level of detection by eye irritation was 900 ppb (males - 790 ppb males; females - 1010 ppb). Nasal localization was only tested in 20 subjects. Due to their inability to localize nasal irritation, no additional subjects were tested.

In phase 2, 30 male and 30 female subjects were exposed to chloropicrin in a walk-in chamber in the following order at 0 ppm for 30 minutes, 50 ppb for 30 minutes, 75 ppb for 20 minutes, 100 ppb for 20 minutes and 150 ppb for 20 minutes with 30 minute blank exposures or a break in between exposures to chloropicrin. The subjects were asked to report the “feel” in the eyes, nose and throat during exposures and the certainty of their detection (on a scale of 1-6). The detection of the chloropicrin in the eyes was greater than in the nose and throat and increased with concentration and duration of exposure (Figure 3). The detection in the nose and throat diverged only slightly from the blank and the average ratings of confidence were approximately 2 or lower. For ocular detection, the average ratings at 50, 75, 100 and 150 ppb diverged from the blank after the first 20, 5, 3 and 2 minutes, respectively. However, only exposures at 100 and 150 ppb reached a point where the average rating crossed over into the yes zone (i.e., the average confidence score was greater than 3.5). The average rating of confidence at 75 ppb clearly diverged from the blank, but the highest average rating was just over 2.5. At 50

ppb, the average rating of confidence was similar to the controls until after 20 minutes and even at 30 minutes was only slightly over 2. The clear divergence of the average rating of confidence in the ocular detection of chloropicrin from the blank at 75 ppb suggests some detected it even if they were not certain. There was no significant difference between sexes in the eye irritation scores. Therefore, the NOEL appears to be 50 ppb with a 20 minute exposure in phase 2.

In phase 3, subjects (15 males and 17 females) were exposed to chloropicrin at 0, 100 or 150 ppb in a walk-in chamber for 1 hour/day for 4 consecutive days. The 4-day exposure represented one cycle. Subjects were exposed to all concentrations in three different cycles with one week separating each cycle. Subjects were asked to rate their symptoms with a scale of 0 to 3 for severity. Clinical examination of the eyes, nose and throat was also performed on the subjects before and after each exposure. There was no residual effect from one day to the next in either ocular irritation (Figure 4) or upper respiratory effects. There were no significant gender-related differences in ocular irritation or upper respiratory effects during in this phase so the sexes were combined. The mean rating for ocular symptoms was approximately 1 (mild with minimal awareness; easily tolerated) at 150 ppb which reached a plateau after 15 minutes (Table 3, Figure 5). The mean rating for ocular symptoms at 100 ppb was approximately 0.5 with a maximal rating after 30 minutes. Interestingly, a few subjects reported no eye irritation even at the highest dose level (15, 6 and 5 at 0, 100 and 150 ppb). Average scores are shown for the entire exposure and for just the plateau (minutes 31-55 of exposure). The mean ratings for nasal and throat symptoms were similar between the treated and blank exposures. Nasal air flow and pulmonary function was evaluated based on the forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1) before and after each exposure. There was no treatment-related effect on FVC or FEV_1; however, the post-exposure nasal flow rates were significantly lower (~10%) at 150 ppb than the pre-exposure flow rates. The amount of nitric oxide (NO) in the exhaled air of subjects was measured for the lungs and nose before and after each exposure as an indicator of respiratory inflammation. The NO in expired nasal air was significantly elevated at both 100 and 150 ppb, although the dose response was relatively flat (Table 3). The investigators suggested that the reduced air flow at 150 ppb was due to some engorgement which may have impeded the diffusion of NO from the tissue resulting in the flat dose response. The NOEL in phase 3 appears to be less than 100 ppb based on ocular irritation and upper respiratory changes in NO production and airflow. See the Risk Assessment section (Section III.A.1) and the Risk Appraisal section (Section IV.A) of this document for a discussion of the benchmark dose analysis of this study. Although there currently are no FIFRA guidelines for conducting human studies, this study was conducted in accordance with Good Laboratory Practice regulations and was approved by the Internal Review Board of the University of California, San Diego, which reviewed the protocol and informed consent forms signed by subjects. In addition, the study protocol was reviewed prior to the study start by a biostatistician, Dr. Robert Sielken, to ensure there was sufficient statistical power. The study was also reviewed by U.S. EPA's Human Studies Review Board and found the be ethically conducted and scientifically valid.

II.B.3. Formulations

All of the currently registered formulations containing chloropicrin are labeled as Category I pesticides and as such, are not required to submit acute toxicity data to DPR to register them in California. Consequently, DPR has no acute toxicity data on file for the formulations containing methyl bromide or 1,3-dichloropropene, except for one 1,3-dichloropropene/chloropicrin formulation which is not currently registered.

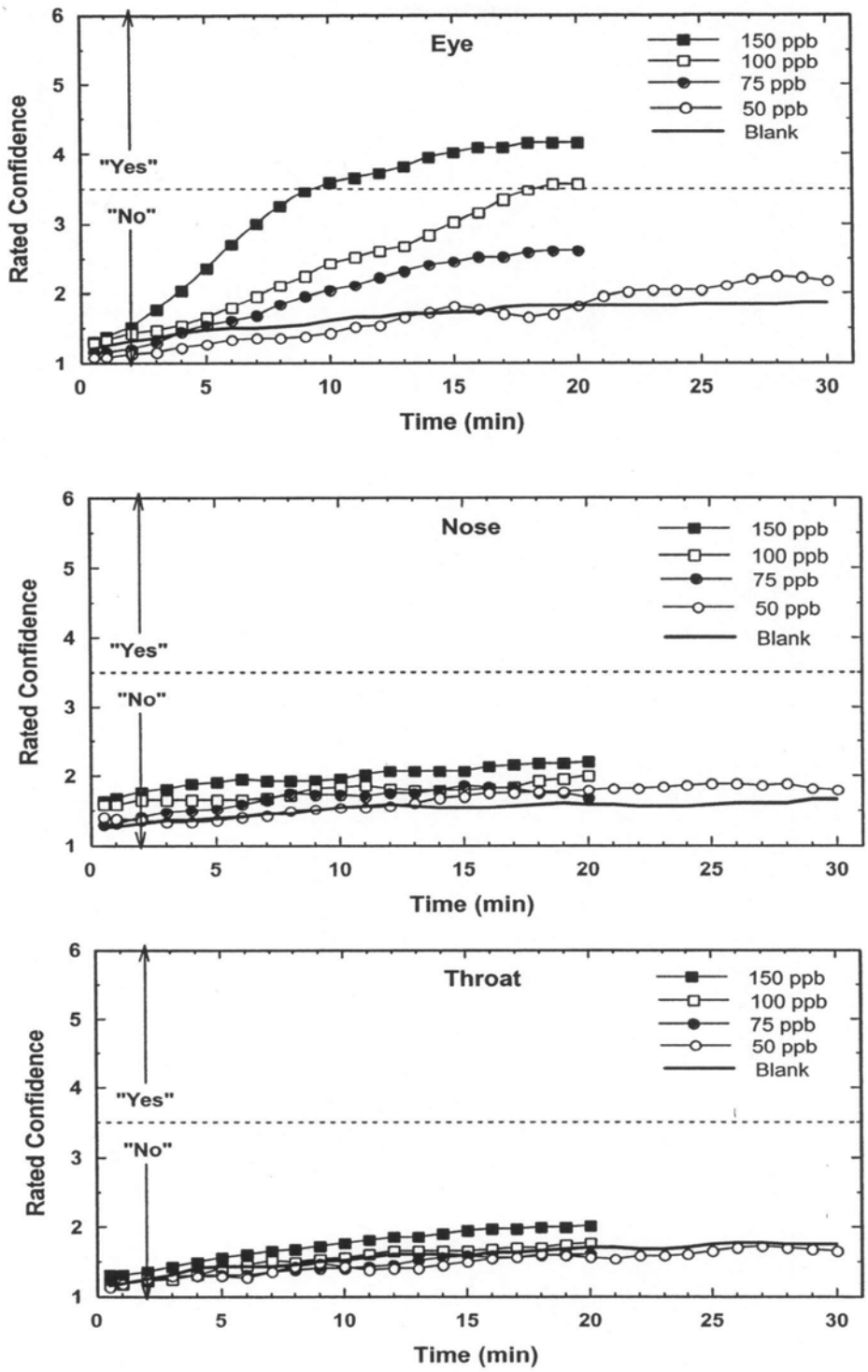

Figure 3 (from Cain, 2004). Average ratings of confidence for detection on transformed scale of 1-6 in phase 2 of the human sensory irritation study for chloropicrin (n = 60, males and females combined). Omitted for clarity, the SEM equaled approximately 0.3. Numbers below the midpoint of the y-axis (3.5) represent judgments of "no" with one or another level of confidence whereas ratings above it reflect "yes" judgements.

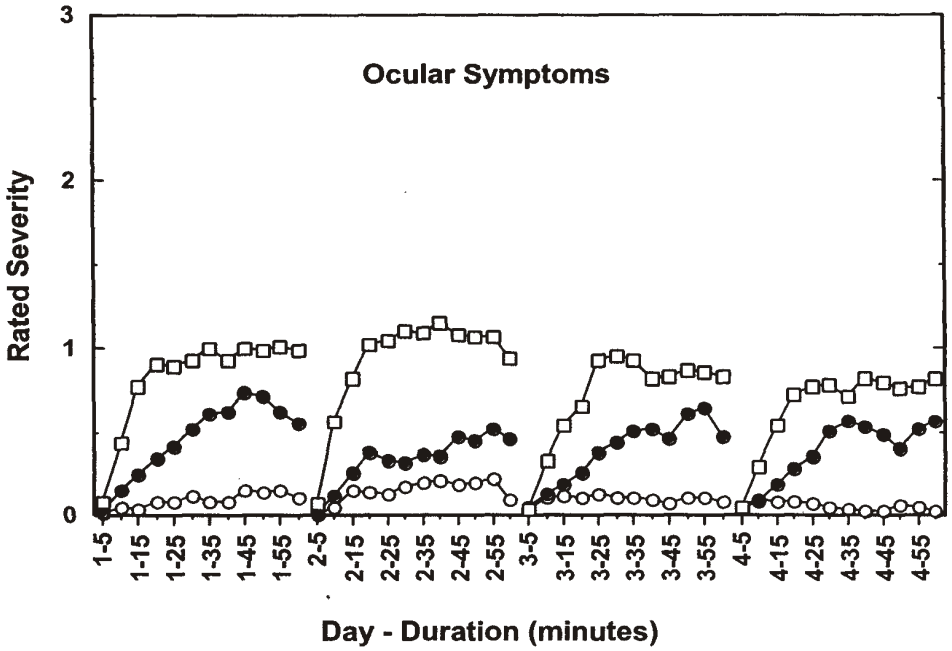

Figure 4 (from Cain, 2004). Ratings of ocular symptoms in the chamber by day of exposure in phase 3. Each point represents the average of five minutes of exposure (n = 32, males and females combined). Blank air shown by unfilled circles, 100 ppb by filled circles and 150 ppb by unfilled squares.

Table 3. Ocular and Nasal Irritation in Human Subjects after 1-Hour Exposures for 4 Consecutive Days to Chloropicrin[a]

	Dose Level (ppm)		
	0	100	150
Ocular Irritation Average score, overall[b]	0.10±0.19[c]	0.39±0.39	0.77±0.70
Average score, plateau[e]	0.12±0.22	0.54±0.51	0.94±0.85
Nasal Irritation Average difference in NO in expired nasal air[d]	1.6±15.6	12.0±11.9	12.7±16.6

a Cain, 2004.
b. The average score for ocular irritation overall is the average of the reported severity score for every minute of the 1 hour exposure for all four days of exposure. The severity score had a four point scale from 0 (no symptom) to 3 (severe; symptom hard to tolerate and can interfere with activities of daily living or sleeping).
c mean±standard deviation. n = 32, males and females combined since no significant gender-related differences.
d The average difference in the nitric oxide (NO) concentration (ppb) in expired nasal air is the average of the difference in the pre- and post-exposure levels in expired nasal air for an each individual for all four days of exposure. Increased NO production is an indication of inflammation. Individual increases of greater than 25% are considered clinically significant.

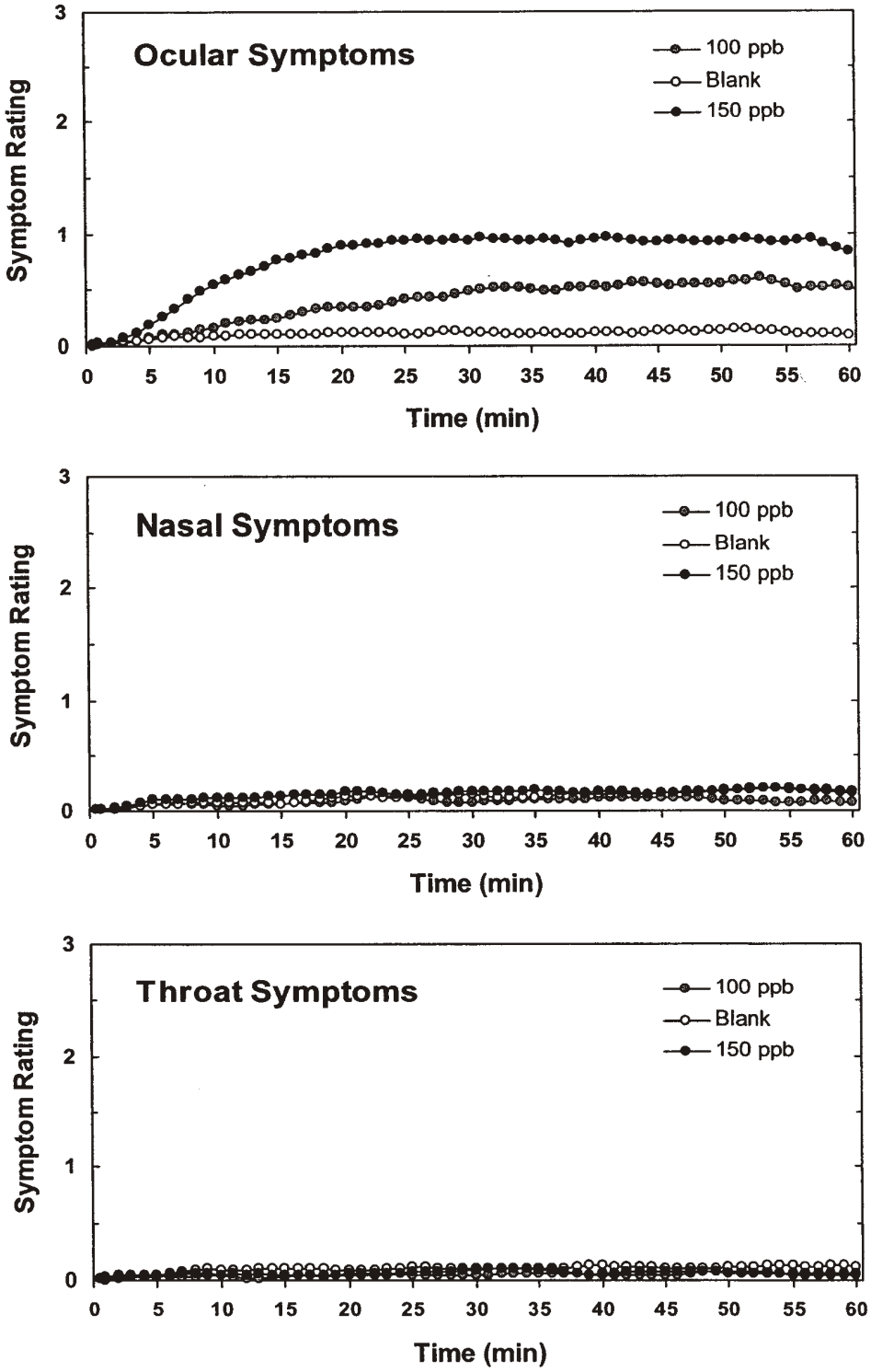

Figure 5 (from Cain, 2004). Average rated severity of symptoms during 1-hour exposures in the chamber during phase 3 in the human sensory irritation study for chloropicrin (n = 32, males and females combined). Omitted for clarity, the SEM equaled approximately 0.03, 0.06 and 0.09 for ocular symptoms at 0, 100 and 150 ppb, respectively, during the plateau.

II.C. SUBCHRONIC TOXICITY

Summary: Four subacute/subchronic toxicity studies in rats were available for chloropicrin, two inhalation toxicity studies and two oral toxicity studies (one 10-day and one 90-day study). In addition, one subchronic inhalation toxicity study in mice was conducted. Three of the studies are published reports and two others were conducted by registrants in accordance with FIFRA guidelines. It is uncertain if the published studies were conducted according to FIFRA guidelines. The effects seen in the inhalation studies included eye closure, reddened eyes, labored respiration, reduced activity, reduced body weights and food consumption, changes in hematological and clinical chemistry values, increased lung weights and various histopathological lesions in the nasal cavity and lungs. A NOEL of 0.3 ppm (2.20 mg/m^3) was established in both rats (HEC - 0.088 ppm) and mice (HEC - 0.16 ppm). The effects seen with oral administration in rats included reduced body weights, changes in thymus, liver and spleen weights, changes in hematological and clinical chemistry values, and histopathological lesions in the forestomach (nonglandular stomach). The NOEL in the 90-day oral gavage study appears to be 8 mg/kg/day based on body weight reduction, hematological changes and histological changes in the forestomach.

II.C.1. Inhalation-Mouse

CD-1® mice (10 mice/sex/dose) were exposed (whole body) to chloropicrin vapors (99.6% purity) at 0, 0.3, 1.03 or 2.89 ppm (actual; 0, 2.02, 6.93 or 19.4 mg/m^3; HEC[8] - 0, 0.16, 0.56 or 1.57 ppm) for 6 hours/day, 5 days/week for 13 weeks (Chun and Kintigh, 1993). One male at 1.03 ppm was found dead and one control female was sacrificed in extremis, but these deaths were not considered treatment-related. The only clinical sign observed during exposure were blepharospasm (tonic spasm of the orbicularis oculi muscle, producing more or less complete closure of the eye) at 2.89 ppm. After exposure, dehydration was observed in mice at 2.89 ppm during the first 2 weeks of exposure. Male mice had significantly reduced body weights (1.03 ppm – 7%; 2.89 ppm - 17%) and body weight gains (1.03 ppm – 44%; 2.89 ppm – 95%). Female mice at 2.89 ppm also had significantly reduced body weights (8%) and body weight gain (58%). The food consumption was significantly reduced in both sexes at 1.03 ppm (M: 9-12%; F: 13-25%) and 2.89 ppm (M: 17-38%; F: 17-44%). Male mice had significant increases in red blood cell (RBC) and eosinophil counts and significant decreases of the mean cell volume (MCV) and mean corpuscular hemoglobin (MCH). Female mice only had a significant decrease in monocytes at 1.03 ppm. Total serum protein, albumin and calcium were significantly elevated in male mice at 2.89 ppm. Blood urea nitrogen (BUN) was significantly reduced at 0.3 and 2.89 ppm, but did not show a clear dose response relationship. Only globulin levels were significantly elevated in females at 2.89 ppm. The toxicological significance of the hematological and clinical chemistry changes is uncertain. Significant reductions in organ weights were seen in both sexes at 2.89 ppm including liver (absolute: M&F), kidneys (absolute: M; relative to brain: M) and spleen (absolute: M&F; relative to body: M; relative to brain: M&F). A significant reduction was seen in spleen weights of males at 0.3 ppm (absolute, relative body and relative to brain) and in liver weights of females at 1.03 ppm (absolute and relative to brain). Lung weights were significantly elevated at 1.03 and 2.89 ppm in both sexes (absolute, relative body and relative brain) (Tables 4 and 5). Significant increases in

8 HEC = ppm x RR_a/RR_h x E_a/E_h. RR_a =1.8 m^3/kg/day for the mouse (Zielhuis and van der Kreek, 1979). RR_h = 0.59 m^3/kg/day for a child (DPR, 2000). E_a = 6 hours/day, 5 days/week. E_h = 24 hours/day, 7 days/week.

Table 4. Respiratory Effects Observed in Male Mice Exposed to Chloropicrin Vapors for 90 Days[a]

Effects Observed	Dose Level (ppm)			
	0	**0.3**	**1.03**	**2.89**
Body Weight (g) - wk 13	39.5±2.01	37.1±2.86	36.8±3.13*	32.4±3.42**
Lung Weight – Absolute (g)	0.23±0.02[b]	0.22±0.02	0.25±0.02*	0.32±0.04**
Relative to Body Weight (%)	0.57±0.04	0.59±0.04	0.67±0.06**	0.96±0.12**
Relative to Brain Weight (%)	45.6±3.1	45.6±3.7	50.5±3.9**	66.1±8.0**
Nasal Cavity				
Epithelial Hyalin Inclusions	0/10 (0%)	0/10 (0%)	3/9 (33%)	10/10** (100%)
Respiratory Epithelial Hyperplasia/Dysplasia	0/10 (0%)	0/10 (0%)	1/9 (11%)	7/10** (70%)
Rhinitis	0/10 (0%)	1/10 (10%)	1/9 (11%)	10/10** (100%)
Mucosal Ulceration	0/10 (0%)	0/10 (0%)	1/9 (11%)	7/10** (70%)
Lung				
Alveolar Histiocytosis	2/10 (20%)	1/10 (10%)	5/9 (56%)	9/10** (90%)
Bronchitis/Bronchiolitis	0/10 (0%)	0/10 (0%)	1/9 (11%)	5/10* (50%)
Perivascular Infiltrates	0/10 (0%)	0/10 (0%)	3/9 (33%)	4/10 (40%)
Interstitial Pneumonitis	1/10 (10%)	0/10 (0%)	0/9 (0%)	4/10 (40%)
Peribronchial/Peribronichiolar Fibrosis	0/10 (0%)	0/10 (0%)	1/9 (11%)	6/10* (60%)
Bronchial/Bronchiolar Epithelial Hyperplasia	0/10 (0%)	0/10 (0%)	1/9 (11%)	8/10** (80%)
Peribronchial/Peribronichiolar Muscle Hyperplasia	0/10 (0%)	0/10 (0%)	3/9 (33%)	6/10* (60%)

a Chun and Kintigh, 1993.
b Mean ± standard deviation
*,** Significantly different from controls based on pair-wise comparisons using a pooled t-test for continuous data and Fisher's exact test for quantal data.

histopathological lesions were seen in the nasal cavity of both sexes at 2.89 ppm including epithelial hyalin inclusions, respiratory epithelial hyperplasia/dysplasia, rhinitis and mucosal ulceration (Tables 4 and 5). Females at 1.03 ppm also had a significant increase in epithelial hyalin inclusions in the nasal cavity. Numerous histopathological lesions were found in the lungs of both sexes at 2.89 ppm including alveolar histiocytosis, bronchitis/bronchiolitis, perivascular infiltrates, interstitial pneumonitis, peribronchial/peribronchiolar fibrosis, bronchial/bronchiolar epithelial hyperplasia and peribronchial/peribronchiolar muscle hyperplasia (Tables 4 and 5). Alveolar histiocytosis and bronchial/bronchiolar epithelial hyperplasia were also significantly elevated at 1.03 ppm in females. The increases in lung weights were probably related to the histopathological lesions found in the lung. The toxicological significance of the reduction in the other organ weights is uncertain, but may be

Table 5. Respiratory Effects Observed in Female Mice Exposed to Chloropicrin Vapors for 90 Days[a]

Effects Observed	Dose Level (ppm)			
	0	**0.3**	**1.03**	**2.89**
Body Weight (g) - wk 13	27.7±1.58	27.9±1.93	27.4±1.28	25.6±2.31*
Lung Weight – Absolute (g)	0.20±0.01[b]	0.20±0.02	0.23±0.02**	0.28±0.03**
Relative to Body Weight (%)	0.70±0.05	0.72±0.03	0.85±0.09**	1.11±0.13**
Relative to Brain Weight (%)	41.2±4.7	42.9±2.7	48.6±4.7**	61.5±5.8**
Nasal Cavity				
Epithelial Hyalin Inclusions	0/9 (0%)	2/10 (20%)	6/10* (60%)	10/10** (100%)
Respiratory Epithelial Hyperplasia/Dysplasia	0/9 (0%)	0/10 (0%)	0/10 (0%)	8/10** (80%)
Rhinitis	1/9 (11%)	0/10 (0%)	4/10 (40%)	9/10** (90%)
Mucosal Ulceration	0/9 (0%)	0/10 (0%)	0/10 (0%)	2/10 (20%)
Lung				
Alveolar Histiocytosis	1/9 (11%)	2/10 (20%)	8/10** (80%)	10/10** (100%)
Bronchitis/Bronchiolitis	0/9 (0%)	0/10 (0%)	2/10 (11%)	4/10 (40%)
Perivascular Infiltrates	0/9 (0%)	1/10 (10%)	2/10 (20%)	3/10 (30%)
Interstitial Pneumonitis	0/9 (0%)	0/10 (0%)	0/10 (0%)	4/10 (40%)
Peribronchial/Peribronichiolar Fibrosis	0/9 (0%)	0/10 (0%)	1/10 (10%)	8/10** (80%)
Bronchial/Bronchiolar Epithelial Hyperplasia	0/9 (0%)	0/10 (0%)	1/10 (10%)	8/10** (80%)
Peribronchial/Peribronichiolar Muscle Hyperplasia	0/9 (0%)	0/10 (0%)	0/10 (0%)	9/10** (90%)

a Chun and Kintigh, 1993.
b Mean ± standard deviation
*,** Significantly different from controls based on pair-wise comparisons using a pooled t-test for continuous data and Fisher's exact test for quantal data.

related to the reduced body weights. The NOEL appears to be 0.3 ppm (2.02 mg/m^3; HEC - 0.16 ppm) based on reduced body weights in males, reduced food consumption in both sexes, increased lung weights in both sexes and lesions in the nasal cavity and lungs of females at 1.03 ppm. This study was found acceptable to DPR toxicologists based on the FIFRA guidelines.

II.C.2. Inhalation-Rat

Five male Fischer 344 rats/dose were exposed (whole body) to chloropicrin vapor (99.7% purity) at 0, 0.37, 0.67, 1.58 or 2.93 ppm (actual; 0, 2.5, 4.5, 10.6 or 19.7 mg/m^3; HEC[9] - 0, 0.11,

9 HEC = ppm x RR_a/RR_h x E_a/E_h. RR_a = 0.96 m^3/kg/day for the rat (Zielhuis and van der Kreek, 1979). RR_h = 0.59 m^3/kg/day for a child (DPR, 2000). E_a = 6 hours/day, 5 days/week. E_h = 24 hours/day, 7 days/week.

0.19, 0.46 or 0.85 ppm) for 6 hours/day, 5 days/week for 13 weeks (Yoshida *et al.*, 1987b). No mortalities were seen at any dose level. During exposure, eyelid closure and decreased motor activity was observed at all dose levels. The mean body weights were significantly lower than controls at 1.58 ppm (8-11%) and 2.93 ppm (16-30%) throughout the study. Food consumption and food efficiency were also significantly reduced at 2.93 ppm during the week 1 and 2. There was a significant increase in red blood cell count values at 1.58 ppm (2.9%) and 2.93 ppm (4.4%). Hemoglobin values were significantly elevated at 0.67 ppm (3.2%) and 2.93 ppm (4.5%). Hematocrit values were only significantly higher at 2.93 ppm (3.3%). Several significant changes in clinical chemistry values were seen at 2.93 ppm including a decrease in total cholesterol (16%), an increase in BUN (9.5%) and an increase in alkaline phosphatase (ALP) (7.3%). There was no treatment-related effect on ophthalmology or gross pathology.

The absolute and relative lung weights were significantly higher at 2.93 ppm. Rats at 1.58 ppm had only a significant increase in relative lung weights. Significant increases in the relative brain, adrenal and testes weight were also seen at 2.93 ppm, but the investigators suggested these increases were due partly to the severe growth depression at this dose level. Histopathological lesions were seen in the respiratory tract at 1.58 and 2.93 ppm. These lesions included catarrhal inflammation of the nasal mucosa, thickening of the epithelial layer in the larynx, epithelial hypertrophy in the trachea, bronchus and bronchiole, epithelial degeneration/ necrosis/desquamation in the bronchus and bronchiole, epithelial hypertrophy of bronchial gland in the bronchus, and thickening of the bronchial wall in the bronchus and bronchiole. The NOEL for this study appears to be less than 0.37 ppm (2.5 mg/m^3; HEC - 0.60 ppm) based on the eye closure and reduced activity during exposure. It was reported that this study was conducted in accordance with U.S. EPA guidelines; however, there was insufficient documentation to verify this.

In a second study, groups of 10 CD® rats/sex/dose were exposed (whole body) to chloropicrin vapors (99.6% purity) at 0 (filtered air), 0.3, 1.03 or 2.89 ppm (actual; 0, 2.02, 6.93 or 19.4 mg/m^3; HEC[10] - 0, 0.088, 0.30 or 0.84 ppm) for 6 hours/day, 5 days/week for 13 weeks (Chun and Kintigh, 1993). Three male rats at 2.89 ppm were sacrificed *in extremis* with signs of emaciation, dehydration, urogenital stains and wetness, hunched posture, labored respiration and reddened eyes. The only clinical sign observed during exposure was blepharospasm at 2.89 ppm. After exposure, discoloration of fur was observed on the face, neck and front limbs of rats during most of the study. There was a significant reduction in terminal body weights (M: 17%) and overall body weight gains (M: 41%; F: 15%) in rats at 2.89 ppm. Male rats at 2.89 ppm also have significantly reduced food consumption (9-29%) during most weeks throughout the study. A significant increase in the hemoglobin level was seen in male rats at 2.89 ppm, although the toxicological significance of this change is uncertain. There were significant reductions in several organ weights at 2.89 ppm including liver (absolute: M&F; relative to brain: M&F), kidneys (absolute: M&F; relative to brain: F) and spleen (absolute: M; relative to brain: M). There were also significant increases in lung weights at 1.03 ppm (absolute: M&F; relative to body: M) and 2.89 ppm (absolute: M&F; relative to body: M&F) (Tables 6 and 7). There were significant increases in several histopathological lesions in the nasal cavity of males and/or females at 2.89 ppm, including the following lesions: rhinitis, respiratory epithelial hyperplasia/dysplasia, and goblet cell hyperplasia (females only) (Tables 6 and 7). Females also

10 HEC = ppm x RR_a/RR_h x E_a/E_h. RR_a = 0.96 m^3/kg/day for the rat (Zielhuis and van der Kreek, 1979). RR_h = 0.59 m^3/kg/day for a child (DPR, 2000). E_a = 6 hours/day, 5 days/week. E_h = 24 hours/day, 7 days/week.

Table 6. Respiratory Effects Observed in Male Rats Exposed to Chloropicrin Vapors for 90 Days[a]

Effects Observed	Dose Level (ppm)			
	0	**0.3**	**1.03**	**2.89**
Body Weight (g) - wk 13	488±33.9	489±39.4	499±62.6	403.4±34.5**
Lung Weight – Absolute (g)	1.54±0.13[b]	1.63±0.11	1.78±0.10**	1.94±0.29**
Relative to Body Weight (%)	0.31±0.03	0.33±0.02	0.36±0.04*	0.49±0.10**
Nasal Cavity				
Rhinitis	2/10 (20%)	2/10 (20%)	4/10 (40%)	10/10** (100%)
Respiratory Epithelial Hyperplasia/Dysplasia	1/10 (10%)	0/10 (0%)	2/10 (20%)	10/10** (100%)
Goblet Cell Hyperplasia	7/10 (70%)	7/10 (70%)	8/10 (80%)	9/10 (90%)
Lung				
Peribronchial/Peribronichiolar Muscle Hyperplasia	0/10 (0%)	0/10 (0%)	3/10 (30%)	8/10** (80%)
Bronchitis/Bronchiolitis	0/10 (0%)	0/10 (0%)	0/10 (0%)	7/10** (70%)
Peribronchial/Peribronichiolar Fibrosis	0/10 (0%)	0/10 (0%)	2/10 (20%)	9/10** (90%)
Bronchial/Bronchiolar Epithelial Hyperplasia	0/10 (0%)	0/10 (0%)	4/10 (40%)	9/10** (90%)

a Chun and Kintigh, 1993.
b Mean ± standard deviation
*,** Significantly different from controls based on pair-wise comparisons using a pooled t-test for continuous data and Fisher's exact test for quantal data.

had a significant increase in goblet cell hyperplasia at 0.3 and 1.03 ppm, although the investigator suggested that this was a sign of irritation, but was not toxicologically significant. The following histopathological lesions were significantly increased in the lungs of both sexes at 2.89 ppm: peribronchial/peribronchiolar muscle hyperplasia, bronchitis/ bronchiolitis (males only), peribronchial/peribronchiolar fibrosis, and bronchial/bronchiolar epithelial hyperplasia (Tables 6 and 7). There was also a significant increase in peribronchial/peribronchiolar muscle hyperplasia and bronchial/bronchiolar epithelial hyperplasia in females at 1.03 ppm. DPR considered the increases in lung weights related to the lung lesions observed. The NOEL appears to be 0.3 ppm (2.02 mg/m^3; HEC - 0.088 ppm) based on the increase in weights and histopathological lesions in the lung at 1.03 ppm. DPR toxicologists found this study to be acceptable based on FIFRA guidelines.

II.C.3. Oral-Rat

Chloropicrin (98.3% pure) was administered by oral gavage to 10 Sprague-Dawley rats/sex/dose at 0 (corn oil), 10, 20, 40 and 80 mg/kg/day for 10 consecutive days (Condie *et al.*, 1994). Two males at 80 mg/kg/day and 6 females at 20, 40 and 80 mg/kg/day died and were considered treatment-related by the investigators. No clinical signs were reported. The mean terminal body weight was significantly reduced at 40 (M: 9%) and 80 mg/kg/day (M: 25%; F: 8%). Significant reductions in the absolute and relative (to body) mean organ weights were seen

Table 7. Respiratory Effects Observed in Female Rats Exposed to Chloropicrin Vapors for 90 Days[a]

Effects Observed	Dose Level (ppm)			
	0	**0.3**	**1.03**	**2.89**
Body Weight (g) - wk 13	325±24.9	330±30.4	316±19.9	306±21.1
Lung Weight – Absolute (g)	1.31±0.08[b]	1.33±0.08	1.39±0.10	1.57±0.12**
Relative to Body Weight (%)	0.40±0.03	0.40±0.02	0.44±0.04*	0.51±0.05**
Nasal Cavity				
Rhinitis	1/10 (10%)	1/10 (10%)	7/10* (70%)	8/10** (80%)
Respiratory Epithelial Hyperplasia/Dysplasia	0/10 (0%)	0/10 (0%)	0/10 (0%)	9/10** (90%)
Goblet Cell Hyperplasia	0/10 (0%)	6/10* (60%)	7/10** (70%)	5/10* (50%)
Lung				
Peribronchial/Peribronichiolar Muscle Hyperplasia	0/10 (0%)	0/10 (0%)	6/10* (60%)	7/10** (70%)
Bronchitis/Bronchiolitis	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)
Peribronchial/Peribronichiolar Fibrosis	0/10 (0%)	0/10 (0%)	0/10 (0%)	8/10** (80%)
Bronchial/Bronchiolar Epithelial Hyperplasia	0/10 (0%)	0/10 (0%)	5/10* (50%)	7/10** (70%)

a Chun and Kintigh, 1993.
b Mean ± standard deviation
*,** Significantly different from controls based on pair-wise comparisons using a pooled t-test for continuous data and Fisher's exact test for quantal data.

at 40 and 80 mg/kg including a reduction in thymus weight (males and females) and an increase in liver and spleen weights (females only). Hematological changes were also noted at 40 and/or 80 mg/kg/day including an increase in white blood cell (WBC) counts and reticulocytes and a reduction in red blood cell (RBC) counts, hemoglobin levels and hematocrits. Changes in several clinical chemistry values were noted including a reduction in the aspartate aminotransaminase (AST) values in both sexes at 40 and 80 mg/kg and an increase in phosphate levels at 20, 40 and 80 mg/kg/day in both sexes. Histopathological changes in the forestomach (nonglandular stomach) were reported at all dose levels including inflammation, necrosis, acantholysis, hyperkeratosis, epithelial hyperplasia, and ulceration. The severity was dose-related with the changes generally minimal at the lowest dose level and marked at the highest dose level. The NOEL appears to be less than 10 mg/kg/day based on the histological lesions in the forestomach. This subacute study was a non-guideline type study.

Condie *et al.* (1994) also administered chloropicrin by oral gavage to 10 Sprague-Dawley rats/sex/dose at 0 (corn oil), 2, 8, or 32 mg/kg/day for 90 days. Sixty percent of males and 80% of females at 32 mg/kg/day died. Most of the deaths were due to pulmonary complications that the investigators suggested were probably due to aspiration of chloropicrin. Wheezing and dyspnea were the main clinical signs observed. Significant body weight reductions were observed at the study termination in males at 32 mg/kg/day (21%). The reduction in the terminal body weights for females at 32 mg/kg/day was not statistically significant, but was greater than

10% (18%). Slight changes in hematological values were noted at 32 mg/kg/day including a reduction in hemoglobin and hematocrit values in males and an increase in red blood cell counts in females. A significant decrease in WBC counts was seen in females at 8 mg/kg/day. The only organ weight change was a significant reduction in the absolute thymus weight at 8 (M: 25%) and 32 mg/kg/day (F: 12%). The investigators suggested that the reduced thymus weight and WBC counts suggests an adverse effect on the immune system. However, the reduction in the WBC count in females at 8 mg/kg/day does not correlate with a reduction in thymus weight nor does the reduction in thymus weights in males at 8 mg/kg/day correlate with a reduction in WBC counts. Histopathological changes in the forestomach were observed at 32 mg/kg/day including chronic inflammation, acantholysis and hyperkeratosis. In animals that died, chronic pulmonary inflammation and congestion were seen. The NOEL for this study appears to be 8 mg/kg/day based on body weight reduction, hematological changes and histological changes in the forestomach. There was insufficient information in this published report to determine if this study met FIFRA guidelines.

II.D. CHRONIC TOXICITY/CARCINOGENICITY

Summary: Six chronic toxicity/carcinogenicity studies were available for chloropicrin. Two studies were mouse carcinogenicity studies (one oral, one inhalation). Three studies were rat chronic toxicity/carcinogenicity studies (two oral, one inhalation). One oral chronic toxicity study was conducted in dogs. Four of these studies met FIFRA guidelines. The effects observed with oral exposure included reduced survival, ptyalism, emesis, diarrhea, hunched posture, squinted or reddened eyes, reddened ears, urogenital stains, reduced body weights, hematological and clinical chemistry changes, nonneoplastic lesions in the forestomach/-nonglandular stomach and liver, and neoplastic lesions in the mammary gland and stomach. The lowest NOEL with oral exposure was 0.1 mg/kg/day based on reduced body weights and periportal hepatocyte vacuolation in rats. The effects seen with inhalation exposure included reduced survival, reduced body weights and food consumption, increased lung weights, and nonneoplastic and neoplastic lesions in the respiratory tract. The lowest NOEL with inhalation exposure was 0.1 ppm (0.67 mg/m^3) in both rats (HEC = 0.029 ppm) and mice (HEC = 0.054 ppm).

II.D.1. Inhalation-Mouse

Fifty CD-1 mice/sex/dose were exposed (whole body) to chloropicrin (99.6% pure) vapors at 0, 0.1, 0.5 or 1.0 ppm (analytical; 0, 0.67, 3.36 or 6.72 mg/m^3; HEC[11] - 0.054, 0.27 or 0.54 ppm) for 6 hours/day, 5 days/week for at least 78 weeks (Burleigh-Flayer *et al.*, 1995). Surviving animals were sacrificed at week 82. There was no treatment-related effect on mortality or clinical signs. Significant decreases in the mean body weights (M: 3 and 7%; F: 4 and 10% at week 53) and the mean body weight gains (M: 8 and 24%; F: 15 and 35% at week 53) were seen at 0.5 and 1.0 ppm, respectively, throughout the study. Decreases in the mean food consumption corresponded with the body weight changes in males at 1.0 ppm and in females at 0.5 and 1.0 ppm. No treatment-related changes in hematological values were seen. Significant increases in absolute and/or relative lung weights (to body or brain) were seen in

11 HEC = ppm x RR_a/RR_h x E_a/E_h. RR_a =1.8 m^3/kg/day for the mouse (Zielhuis and van der Kreek, 1979). RR_h = 0.59 m^3/kg/day for a child (DPR, 2000). E_a = 6 hours/day, 5 days/week. E_h = 24 hours/day, 7 days/week.

both sexes at 0.5 ppm (absolute – M: 14%) and 1.0 ppm (absolute – M: 16%; F: 36%). There was also a significant decrease in the absolute brain weight in females at 1.0 ppm (4%), but there were no microscopic findings in this tissue so the toxicological significance of this finding is uncertain. Macroscopic pathological changes were seen in the lung (color change, hyperinflation, nodules and/or masses) and kidney (cysts, size decrease and color change), primarily at 1.0 ppm. Significant increases in numerous microscopic lesions in the respiratory tract were seen in both sexes at 0.5 and 1.0 ppm (Tables 8 and 9). These microscopic lesions involved both the nasal cavity (serous exudate, epithelial hyalin inclusions, rhinitis, olfactory epithelial atrophy) and the lungs (alveolar protein deposits – females only, alveolar histiocytosis, peribronchial lymphocytic infiltrates, bronchiectasis, bronchial submucosal fibrosis, bronchioalveolar cell hyperplasia – females only, peribronchial smooth muscle hyperplasia – females only). The slight increase in adenomas and carcinomas in the lungs was significant by trend analysis but was not significant by Fisher's exact test even when combined although the p value was 0.053.

There was no treatment-related effect on survival in this study, however, Peto *et al.* (1980) recommends that tumor rates be routinely adjusted for survival when presenting experimental data whether or not there is a difference in survival rates among treatment groups. Consequently, the combined incidence of adenomas and carcinomas in females was further analyzed using the continuity-corrected Poly-3 trend test with the Bieler-Williams modification that takes survival into consideration (Bieler and Williams, 1993). The Poly-3 trend test is the default trend test of the National Toxicology Program (NTP), even when survival is not affected as in the case of α-methylstyrene (NTP, 2007). Although the Poly-3 trend test has not been validated in CD-1 mice, it seems unlikely that the distribution curve of pulmonary adenomas and carcinomas in CD-1 mice would be significantly different from those of the B6C3F1 mice with which this test was validated by NTP. The historical control range for pulmonary adenomas in female CD-1 mice (0-27%; Giknis and Clifford, 2000) is similar to that of female B6C3F1 female mice (0-24%; Haseman et al, 1999). With the Poly-3 trend test, the combined incidence not only had a significant trend ($p = 0.009$), but the incidence at the high dose was significant ($p = 0.03$) based on the pair-wise comparison which is part of this test. Also noteworthy was an increase in the number of animals with multiple lung adenomas and/or carcinomas in males (4/49, 0/49, 6/45 and 10/50) and females (3/48, 3/48, 6/47 and 9/49) which were significant by trend analysis in both sexes ($p = 0.003$ in males and $p = 0.02$ in females), but not significant in either sex by Fisher's exact. The average time to tumor did not show a dose-related decrease in males (562, 540, 546 and 549 days at 0, 100, 500 and 1,000 ppb, respectively), but was slightly shorter in the high dose females (554, 562, 564 and 543 days at 0, 100, 500 and 1,000 ppb, respectively). The shorter time to tumor in the high dose females may be primarily due to two deaths that occurred within the first year that were unrelated to the tumors (both had adenomas, not carcinomas; trauma in one case and undetermined cause of death in another). No historical control data were available for this laboratory, but historical control data published by Charles River for this strain for studies conducted between 1987 and 1996 had an average incidence of 14% (0-28%) and 8.7% (0-27%) for adenomas in males (46 studies) and females (48 studies), respectively (Giknis and Clifford, 2000). The incidence of adenomas in the male control group was outside the historical control range which may be one reason why a significant increase in these tumors was not seen in males.

Other possible treatment-related increases in microscopic lesions included auditory sebaceous gland adenitis (7/50, -, -, 17/50*) in males at 1.0 ppm, liver Ito cell hyperplasia

Table 8. Microscopic Lesions in the Respiratory Tract of Male Mice Exposed to Chloropicrin Vapors for 78 Weeks[a]

Lesion	Treatment Level (ppm)			
	0	**0.1**	**0.5**	**1.0**
Nasal Cavity				
Serous Exudate	4/50+++ (8%)	7/50 (14%)	18/50** (36%)	38/50** (76%)
Epithelial Hyalin Inclusion	3/50+++ (6%)	6/50 (12%)	7/50 (14%)	16/50** (32%)
Rhinitis	6/50+++ (12%)	7/50 (14%)	17/50** (34%)	35/50** (70%)
Olfactory Epithelial Atrophy	5/50+++ (10%)	6/50 (12%)	8/50 (16%)	40/50** (80%)
Lungs				
Alveolar Histiocytosis	18/50++ (36%)	17/50 (34%)	22/50 (44%)	29/50* (58%)
Peribronchial Lymphocytic Infiltrates	1/50++ (2%)	6/50 (12%)	10/50** (20%)	12/50** (24%)
Bronchiectasis	0/50+++ (0%)	3/50 (6%)	28/50** (56%)	41/50** (82%)
Bronchial Submucosal Fibrosis	0/50+++ (0%)	0/50 (0%)	16/50** (32%)	19/50** (38%)
Adenoma[c]	16/49 (33%)	14/49 (29%)	18/45 (40%)	18/50 (36%)
Carcinoma	1/49 (2%)	0/49 (0%)	5/45 (11%)	2/50 (4%)
Combined Adenoma and Carcinoma	17/49[b] (35%)	14/49 (29%)	22/45 (49%)	20/50 (40%)

a Burleigh-Flayer *et al.*, 1995.
b The denominator is the number of animals at risk which are animals that survived up to the day the first tumor was observed, 253 days.
c Historical control data published by Charles River for this strain for studies conducted between 1987 and 1996 had an average incidence of 14% (0-28%) and 8.7% (0-27%) for adenomas in males (46 studies) and females (48 studies), respectively (Giknis and Clifford, 2000)
++,+++ Significant trend based on the Armitage-Cochran trend test at $p < 0.01$ and 0.001, respectively (Gart *et al.*, 1986).
*,** Significantly different from the control group based on the Fisher's exact test at $p < 0.05$ and 0.01, respectively.

(29/50, 23/50, 31/50, 43/50**) and endocervical metaplasia (0/50, 0/50, 2/50, 5/50*) in females at 1.0 ppm, and kidney cysts (5/50, 10/50, 14/50*, 13/50) in females at 0.5 ppm. In addition, at week 82 there was a significant increase in corneal mineralization (2/34, 2/34, 2/31, 9/32*) and vascularization (0/34, 2/34, 3/31, 4/32*) in the eyes of females at 1.0 ppm. No other treatment-related increases in tumors were observed. The NOEL for this study was 0.1 ppm (0.67 mg/m^3; HEC - 0.054 ppm) based on the reduction in body weights and food consumption, increased lung weights and microscopic lesions in the nasal cavity and lungs. DPR found this study acceptable based on FIFRA guidelines.

Table 9. Microscopic Lesions in the Respiratory Tract of Female Mice Exposed to Chloropicrin Vapors for 78 Weeks[a]

Lesion	Treatment Level (ppm)			
	0	0.1	0.5	1.0
Nasal Cavity				
Serous Exudate	4/50[+++] (8%)	3/50 (6%)	36/50** (72%)	46/50** (92%)
Epithelial Hyalin Inclusion	10/50[+++] (20%)	11/50 (22%)	24/50** (48%)	37/50** (74%)
Rhinitis	3/50[+++] (6%)	6/50 (12%)	18/50** (36%)	32/50** (64%)
Olfactory Epithelial Atrophy	13/50[+++] (26%)	14/50 (28%)	39/50** (78%)	36/50** (72%)
Lungs				
Alveolar Protein Deposits	0/50[+++] (0%)	1/50 (2%)	1/50 (2%)	9/50** (18%)
Alveolar Histiocytosis	14/50[+++] (28%)	14/50 (28%)	19/50 (38%)	35/50** (70%)
Peribronchial Lymphocytic Infiltrates	5/50[+++] (10%)	10/50 (20%)	17/50** (34%)	28/50** (56%)
Bronchiectasis	0/50[+++] (0%)	5/50 (10%)	28/50** (56%)	44/50** (88%)
Bronchial Submucosal Fibrosis	0/50[+++] (0%)	0/50 (0%)	13/50** (26%)	22/50** (44%)
Peribronchial Smooth Muscle Hyperplasia	0/50[+++] (0%)	0/50 (0%)	0/50 (0%)	5/50* (10%)
Adenoma	13/48[+b] (27%)	9/48 (19%)	17/47 (36%)	19/49 (39%)
Carcinoma	0/48[b] (0%)	4/48 (8%)	3/47 (6%)	4/49 (8%)
Combined Adenoma and Carcinoma	13/48[++b] (27%)	12/48 (25%)	20/47 (43%)	22/49 (45%)
Combined Adenoma and Carcinoma - Adjusted	13/42[++d] (31%)	12/41 (29%)	20/43 (46%)	22/42* (54%)

a Burleigh-Flayer *et al.*, 1995.
b The denominator is the number of animals at risk which are animals that survived up to the day the first tumor was observed, 253 days.
c Historical control data published by Charles River for this strain for studies conducted between 1987 and 1996 had an average incidence of 14% (0-28%) and 8.7% (0-27%) for adenomas in males (46 studies) and females (48 studies), respectively (Giknis and Clifford, 2000).
d The animals at risk was determined in the Poly-3 trend test by weighting the animals without tumors based on their time of death. The Poly-3 trend test is utilized by the National Toxicology Program (Portier and Bailer, 1989).
+,++,+++ Significant trend based on the Armitage-Cochran trend test at $p < 0.05$, 0.01 and 0.001, respectively (Gart *et al.*, 1986).
*,** Significantly different from the control group based on the Fisher's exact test at $p < 0.05$ and 0.01, respectively.

II.D.2. Oral-Mouse

Groups of 50 B653F1 mice/sex/dose were administered chloropicrin (98% purity) by oral gavage in corn oil at 25 and 50 mg/kg/day during weeks 1 through 13 and 35 and 70 mg/kg/day, respectively, during weeks 14 to 78 weeks followed by an observation period of 13 weeks (NCI,

1978). The respective time-weighted average dosages were 33 and 66 mg/kg/day. Twenty mice/sex were assigned to untreated and vehicle (corn oil) control groups. A significant reduction in survival was seen in both sexes at 66 mg/kg/day. There was a progressive depression of body weights in female mice at both 33 and 66 mg/kg/day. No consistent difference in male body weight gains was seen. After the first 6 months of the study, there was a higher frequency of hunched or bloated appearance in treated animals compared to controls. An increased incidence of acanthosis and hyperkeratosis in the stomach was seen in both sexes at 33 and 66 mg/kg/day, especially the females. Two squamous cell carcinomas were seen the stomach of males at 66 mg/kg/day and one papilloma in the stomach of a female at 33 mg/kg/day. However, the incidence of neither of these lesions was statistically significant. The NOEL appears to be less than 33 mg/kg/day based on the acanthosis and hyperkeratosis in the forestomach in both sexes and the body weight depression in females. The study had major deficiencies including an inadequate number of dose groups and control animals. The report also lacks data on the analysis of dosing solution, individual body weights, food consumption and clinical data.

II.D.3. Inhalation-Rat

In a rat inhalation carcinogenicity study, groups of 50 CD® rats/sex/dose were exposed (whole body) to chloropicrin (99.6% purity) vapors at 0 (air), 0.1, 0.5 and 1.0 ppm (analytical; 0, 0.67, 3.36 or 6.72 mg/m^3; HEC[12] - 0, 0.029, 0.15 or 0.29 ppm) for 6 hours/day, 5 days/week for at least 107 weeks (Burleigh-Flayer and Benson, 1995). A significant reduction in the survival rate of males at 0.5 and 1.0 ppm were observed (Table 10). The incidence of a few clinical signs were elevated at 1.0 ppm, including hypoactivity, prostration, cold extremities, urogenital wetness, bleopharospasm, and periocular encrustation. There was no significant difference in absolute body weights, but the body weight gains were significantly reduced during the first few weeks of exposure at 0.5 and 1.0 ppm (M: 8-28%; F: 9-25%) in both sexes. Female rats at 0.1 ppm also had significant reductions in body weight gains (6-10%) during this time; however, these minor reductions in body weight gain were of uncertain toxicological significance. There was no treatment-related effect on food consumption, palpable masses or hematology. A few significant differences in the absolute liver and kidney weights were seen in females at 0.1 and 0.5 ppm which the investigators suggested was due to the lower terminal body weights in these groups and not treatment-related. The increases in the absolute and relative (to body and brain) lung weights at 1.0 ppm were considered treatment-related by the investigators, although not statistically significant. There appeared to be a treatment-related increase in spleen weight and/or in the incidence of increased spleen size especially in males, but the differences were not statistically significant in either sex. Males also appeared to have an increased incidence of hyperinflated lung that was observed macroscopically, but the increase was not statistically significant. No other treatment- related macroscopic pathological lesions were observed. The only significant increase in microscopic lesions was rhinitis in the anterior nasal cavities in male rats at 1.0 ppm. The rhinitis was characterized by sporadic lymphocytic or neutrophilic mucosal/submucosal infiltrates and occasionally by purulent exudate. There was no treatment-related increase in tumor incidence, except for the incidence in fibroadenomas in females. However, this incidence was not statistically significant and within the reported historical control range for this strain from this laboratory (11-47%). The NOEL for this study was 0.1 ppm (0.67

12. HEC = ppm x RR_a/RR_h x E_a/E_h. RR_a = 0.96 m^3/kg/day for the rat (Zielhuis and van der Kreek, 1979). RR_h = 0.59 m^3/kg/day for a child (DPR, 2000). E_a = 6 hours/day, 5 days/week. E_h = 24 hours/day, 7 days/week.

Table 10. Possible Treatment-Related Effects in Rats Exposed to Chloropicrin Vapors for 107 Weeks[a]

Lesion	Treatment Level (ppm)			
	0	0.1	0.5	1.0
MALES				
Mean survival, days	696±97[b]	669±118	672±99*	647±110**
Mortality rate	42%	58%	66%	70%
Body weight gains, wk 0-1	31.2.±4.2	30.1±4.0	28.6±2.9**	22.6±4.6**
Liver weights, grams	14.4±2.6	14.3±3.2	12.4±2.5*	14.7±2.7
Kidney weights, grams	4.90±1.52	4.54±0.71	4.98±1.02	5.35±1.18
Spleen weights, grams	1.03±0.26	1.16±0.30	1.40±0.96	1.23±0.46
Lung weights, grams	2.09±0.65	2.09±0.22	2.20±0.32	2.45±0.78
Lung weights, relative (% brain)	95.9±31.0	94.4±11.1	100.6±14.8	112.5±35.0
Hyperinflated lung	2/50[c] (4%)	6/50 (12%)	5/50 (10%)	6/50 (12%)
Nasal cavity Rhinitis	20/50[++] (40%)	24/50 (48%)	21/50 (42%)	35/50** (70%)
Mammary gland Fibroadenoma	1/16 (6%)	0/10 (0%)	0/15 (0%)	1/15 (7%)
FEMALES				
Mean survival, days	690±97	673±99	666±102	661±128
Mortality rate	48%	64%	56%	56%
Body weight gains, wk 0-1	15.8±3.6	14.3±3.7	13.4±3.6**	11.9±3.4**
Liver weights, grams	14.4±2.6	14.3±3.2	12.4±2.5*	14.8±2.7
Kidney weights, grams	3.25±0.57	2.93±0.30*	2.90±0.36*	3.00±0.52
Spleen weights, grams	0.79±0.27	0.89±0.54	0.69±0.16	0.90±0.46
Lung weights, grams	1.57±0.29	1.46±0.14	1.46±0.12	1.63±0.35
Lung weights, relative (% brain)	79.9±16.1	75.0±7.37	74.2±6.50	89.1±37.7
Hyperinflated lung	3/50 (6%)	4/50 (8%)	3/50 (6%)	2/50 (4%)
Nasal cavity Rhinitis	18/50 (36%)	17/50 (34%)	26/50 (52%)	23/50 (46%)
Mammary gland Fibroadenoma	10/49 (20%)	16/50 (32%)	14/50 (28%)	16/47 (34%)

a Burleigh-Flayer and Benson, 1995.
b Mean ± standard deviation
c Denominator represents the number examined except for mammary gland fibroadenomas in females in which case the denominator is the number of animals at risk (i.e., animals that survived > 365 days).
++ Significant trend based on the Armitage-Cochran trend test at $p < 0.01$ (Gart *et al.*, 1986).
*,** Significantly different from the control group based on product-limit survival analysis for survival, Dunnett's test for weights and the Fisher's exact for lesions at $p < 0.05$ and 0.01, respectively.

mg/m^3; HEC - 0.029 ppm) based on the reduced survival rate in males and reduced body weight gain in both sexes. DPR found this study acceptable based on FIFRA guidelines.

II.D.4. Oral-Rat

In an NCI study, 50 Osborne-Mendel rats that were administered chloropicrin (95% pure) by oral gavage 5 days per week at two dose levels (NCI, 1978). Rats of both sexes initially

received 23 and 46 mg/kg/day at the low and high-dose level during the first 4 weeks. Starting at week 5, the dose levels for males were increased to 28 and 56 mg/kg/day for the low and high dose-groups while the dose levels for females remained the same. After week 17, the dosing was stopped for the high dose animals for 13 weeks, but was continued for low dose animals. At week 31, high-dose animals resumed dosing at the same dose level as the low dose animals. Beginning with week 34, a cyclic pattern of dosing was started with all the treated animals beginning with one week of no dosing, followed by 4 weeks of dosing. This continued through week 78 of the study followed by a 32-week observation period before the study was terminated. This dosing regimen resulted in a time-weighted average of 25 and 26 for the low- and high-dose males, respectively, and 20 and 22 mg/kg/day for the low- and high-dose females, respectively, during the 78-week dosing period. The vehicle control group consisted of 20 rats/sex which were administered corn oil by gavage during weeks 1 through 78. The untreated control group consisted of 20 rats/sex that were not gavaged. There was a high incidence of mortality in the treated rats. Fifty percent of the male rats were dead after 54 and 48 weeks at the low- and high-dose levels, respectively. The same percent of female rats were dead after 59 and 70 weeks at the low- and high-dose levels, respectively. By contrast, over 50% of the control animals survived past week 89 for males and week 108 for females. No dose-related increases in tumors were seen; however, it is unlikely that treated rats survived long enough to develop late-appearing tumors. The only other effects reported were reduced body weights and clinical signs. The clinical signs included hunched or thin appearance, squinted or reddened eyes, reddened ears, and urogenital stains. The NOEL appears to be less than 20 mg/kg/day based on the increased mortalities, reduced body weights and clinical signs. This study had major deficiencies including an inadequate number of control animals, inadequate number of dose levels, frequent dose-level changes, no hematology data, and no individual data.

Chloropicrin (99% pure) was administered at 0 (corn oil), 0.1, 1 and 10 mg/kg/day by oral gavage to 30 Sprague-Dawley derived rats (Crl:CD®BR, VAF/Plus)/sex/dose for 2 years (Slauter, 1995). There was no treatment-related effect on survival. Increased salivation was observed at 10 mg/kg/day in both sexes throughout the study after dosing for about 15 to 30 minutes. At study termination, male body weights were reduced 11.6% from controls at both 1.0 and 10 mg/kg/day. No treatment-related differences in food consumption, ophthalmology, and hematology were observed. Increases in serum calcium and phosphorus levels were seen in females at 10 mg/kg/day, but were of uncertain toxicological significance since they were not associated with any histopathological changes. Subcutis skin masses were observed in females that exhibited an apparent dose-response relationship. Microscopic examination of these masses confirmed the presence of mammary fibroadenomas (Table 11) which were statistically significant by trend analysis ($p < 0.05$) and by pair-wise comparison with controls at 10 mg/kg/day ($p < 0.05$). The toxicological significance of this dose-related increase is uncertain since the incidence was within the historical control range for this strain from this laboratory (up to 55%) and from other facilities (up to 49%). Other dose-related increases in microscopic lesions were seen including periportal hepatocyte vacuolation in the liver and hyperkeratosis and epithelial hyperplasia of the nonglandular stomach. The historical control range for hepatocyte vacuolation from this laboratory was reported to be 12-41% and 6-35% in males and females, respectively. The distribution of the vacuolation within the lobule was generally not specified, but in one other study, the incidence of periportal hepatocyte vacuolation was 7 and 13% in males and females, respectively. The historical control range for hyperkeratosis of the nonglandular stomach was reported to be 0-28% and 0-24% in males and females, respectively. The historical control range for hyperplasia/acanthosis was 0-30% in males and 0-9% in females.

Table 11. Microscopic Lesions in Rats Administered Chloropicrin by Oral Gavage for 2 Years[a]

Lesion	Treatment Level (mg/kg/day)			
	0	0.1	1.0	10.0
MALES				
Liver				
Periportal hepatocyte vacuolation	2/30 (7%)	8/30 (27%)	3/30 (10%)	6/30 (20%)
Nonglandular Stomach				
Hyperkeratosis	7/30+++ (23%)	9/30 (30%)	11/30 (37%)	20/30** (67%)
Epithelial Hyperplasia	3/30+++ (10%)	5/30 (17%)	4/30 (13%)	18/30** (60%)
FEMALES				
Liver				
Periportal hepatocyte vacuolation	2/30++ (7%)	6/30 (20%)	10/30* (33%)	13/30** (43%)
Nonglandular Stomach				
Hyperkeratosis	6/30+++ (20%)	5/30 (17%)	11/30 (37%)	24/30** (80%)
Epithelial Hyperplasia	6/30++ (20%)	5/30 (17%)	6/30 (20%)	14/30* (47%)
Mammary Gland				
Fibroadenoma	6/30+ (20%)	9/30 (30%)	12/30 (40%)	14/30* (47%)

a Slauter, 1995.
+,++,+++ Significant trend based on the Armitage-Cochran trend test at $p < 0.05$, 0.01 and 0.001, respectively (Gart *et al.*, 1986).
*,** Significantly different from the control group based on the Fisher's exact test at $p < 0.05$ and 0.01, respectively.

A papilloma in the nonglandular stomach was observed microscopically in one male rat at 10 mg/kg/day that could have been treatment-related based on the increase in hyperplasia and hyperkeratosis in this tissue. However, the incidence was not statistically significant and was reported to be within the historical control range for this laboratory (data not provided). The NOEL for this study was 0.1 mg/kg/day based on the reduction in male body weights and periportal hepatocyte vacuolation in females at 1.0 mg/kg/day. This study was considered acceptable by DPR based on the FIFRA guidelines.

II.D.5. Oral-Dog

Four beagle dogs/sex/dose were administered chloropicrin (99% pure) in capsules at 0 (corn oil), 0.1, 1.0 and 5.0 mg/kg for 1 year (Wisler, 1994). There was no treatment-related effect on mortality, food consumption, ophthalmology, urology, gross pathology or histopathology. There was an increase in ptyalism, food-like or frothy emesis, and soft stool/diarrhea in dogs at 5.0 mg/kg/day. Discolored feces were observed in half the animals of both sexes during the last 13 weeks of the study. Food-like emesis was also observed with increased frequency at 1.0 mg/kg/day. The mean body weights of males at 5.0 mg/kg/day were reduced (~10%) throughout the study compared to controls. There was a significant decrease in the mean corpuscular volume and mean corpuscular hemoglobin in both sexes at 5.0 mg/kg/day throughout the study. A decrease in aspartate aminotransferase, total protein and albumin were

also seen in both sexes at 5.0 mg/kg/day throughout the study. In addition, the calcium levels were reduced during the last 6 months of the study. The investigators suggested that the diarrhea/soft stools, and reduced body weights in conjunction with the clinical pathological changes at 5.0 mg/kg /day were indicative of an enterogenous malabsorption condition. The NOEL was 1.0 mg/kg/day based on the clinical signs, reduced body weights (males) and clinical pathology changes. This study was considered acceptable to DPR based on FIFRA guidelines.

II. E. GENOTOXICITY

Summary: Chloropicrin tested positive in eight reverse mutation assays with *Salmonella typhimurium* strains with and without activation; however, only one of these studies met FIFRA guidelines. One study found that the addition of GSH alone also converted chloropicrin to a mutagenic metabolite either through reductive dechlorination or through the formation of a reactive intermediate GSH conjugate, such as $GSCCl_2NO_2$ or $GSCHClNO_2$. In addition, chloropicrin tested positive in a reverse mutation assay with *Escherichia coli* WP2 *hcr*. Chloropicrin was negative in a mouse lymphoma assay which met FIFRA guidelines. Results from the *Drosophila* sex-linked recessive lethal assay were mixed. One study reported it was weakly mutagenic, but another reported it was negative. It is unclear if either of these published studies met FIFRA guidelines. A published *Drosophila* wing-spot test was also negative, although this was a non-guideline study. Results from chromosomal aberrations assays were mixed. One study, which met FIFRA guidelines, reported that chloropicrin induced chromosomal aberrations in Chinese hamster ovary cells without S-9. In a published report, no increase in chromosomal aberrations was seen in human lymphocytes with or without S-9; however, an increase in sister chromatid exchanges was observed with and without S-9. No increase in micronuclei was seen *in vitro* with TK6 cells and human lymphocytes and *in vivo* with newt larvae or mice. Only the *in vivo* assay with mice met FIFRA guidelines. There was no increase in unscheduled DNA synthesis either *in vitro* with rat primary hepatocytes or *in vivo* with rats. Both of these studies met FIFRA guidelines. Increased DNA damage was seen in three published, non-guideline studies, a SOS chromotest with *E. coli*, a Comet assay with TK6 cells and a single-cell gel electrophoresis assay with CHO cells. Repair kinetics in the Comet assay indicated this damage was readily repaired.

II.E.1. Gene Mutation

Chloropicrin (99.5%) was tested in a reverse mutation assay with *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 with and without S-9 up to 1,000 µg/plate in the initial assay and up to 500 µg/plate in the confirmatory assay (San and Wagner, 1990). An increase in revertant colonies with seen in strain TA98 with S-9. TA 1537 and TA1538 were also positive without S-9. DPR found this study acceptable based on FIFRA guidelines. Moriya *et al* (1983) reported that chloropicrin (purity not stated) was mutagenic using the reverse mutation assay with *S. typhimurium* TA98 (weakly positive) and TA 100 (with S-9) and *E. coli* WP2 *hcr* (weakly positive). No increase in mutation frequency was seen with TA 1535, TA1537 and TA1538 strains. Doses were reported to be tested up to 5,000 µg/plate, unless toxic to bacteria. Insufficient information was provided in this published report to determine if this study was conducted in accordance with FIFRA guidelines. There were other published reports of positive responses in the reverse mutation assay with *S. typhimurium*. Shirasu *et al.* (1982) reported an increase in mutation frequency with TA100, but only with S-9. Haworth *et al.*

(1983) also reported an increase in mutation frequency with TA100 with S-9, but not with TA98, TA1535 and TA1537 strains. Kawai *et al.* (1987) observed an increase in mutation frequency with *S. typhimurium* TA100 and TA98 strains (+ S9 only) and *E. coli* WP2uvrA/pKM101 strain (+/- S9). In a modified Ames assay with *S. typhimurium* strains TA98 and TA1538, Sariaslani and Stahl (1990) found an increase in mutation frequency with TA98 after activation with *Streptomyces griseus* cells. In an another adaptation of the reverse mutation assay with *S. typhimurium* TA100 in liquid medium, Giller *et al.* (1995) observed a significant increase in wells containing prototrophic revertants with S-9. Schneider *et al.* (1999) reported that chloropicrin was toxic to *S. typhimurium* TA100 at 500 nmol/plate, but not mutagenic. Chloropicrin became mutagenic, but not toxic at this concentration with the addition of S-9 or 1-2 molar equivalents of glutathione (GSH). The dechlorination products, $CHCl_2NO_2$ and CH_2ClNO_2, were also mutagenic with and without GSH. The investigators suggested that the mutagenicity of chloropicrin may be due to its reductive dechlorination or from a reactive intermediate GSH conjugate, such as $GSCCl_2NO_2$ or $GSCHClNO_2$.

A forward mutation assay was conducted in which L5178Y TK +/− mouse lymphoma cells were incubated with chloropicrin (99.5% pure) up to 0.5 nl/ml without S-9 and up to 21 nl/ml with S-9 in the initial trial (San and Sigler, 1990). In the confirmatory assay, chloropicrin was tested up to 0.75 nl/ml without S-9 and up to16 nl/ml with S-9. No increase in forward mutation frequency was reported. This study was acceptable to DPR based on FIFRA guidelines.

A sex-linked recessive lethal assay was conducted in which *Drosophila melanogaster* Canton-S wild-type males were fed chloropicrin (91% pure) at 0 and 150 ppm for 4 hours or injected at 0 and 100 ppm (Valencia *et al.*, 1985). Males were then mated with 3 harems of *Basc* virgin females to produce 3 broods of 3, 2, and 2, days. To reduce the chances of recovering several lethals from the same male, no more than 40 F_1 females were mated individually from each brood of each male. Therefore, no more than 120 chromosomes were tested from each P_1 male. F_2 cultures were scored as lethal if the number of wild-type males recovered was less than 5% of the number of *Basc* males (or *Basc*/+ females). Chloropicrin was negative when administered by injection, but gave equivocal results when administered in the feed. Insufficient information was provided in this published report to determine if this study was conducted in accordance with FIFRA guidelines.

Auerbach (1950) evaluated both mustard gas and chloropicrin for their ability to induce sex-linked recessive lethality in *Drosophila melanogaster* to confirm that the mutagenicity of mustard gas in not related to its ability to react with –SH groups. Chloropicrin is also an effective blocker of –SH groups. A series of three tests were conducted. In the first test, young males were exposed to chloropicrin vapor (purity and dose level not reported) for as long as they could tolerate (2-3 minutes). Survivors were then tested for sex-linked lethals. Only 1 lethal was found out of 1318 X chromosomes. Since exposure may have been too short to ensure penetration to the germ cells, chloropicrin was mixed with liquid paraffin in the second test. The tolerance threshold was shifted by altering the proportion of the two fluids. Only 2 lethals out of 463 X chromosomes were found after exposure for 6 to 9 minutes in the second test. The males were exposed 5 to 7 minutes to a mixture of chloropicrin and liquid paraffin in a third test and then mated with a succession of virgin females every 3-4 days. Only 7 out of 4454 X chromosomes were lethals. The incidence of lethals was no greater than usually found in

untreated controls. Therefore, it was concluded that the blockage of –SH groups is not associated with its mutagenic activity.

In another non-guideline study, genotoxicity of chloropicrin was evaluated using the *Drosophila* wing-spot test (García-Quispes *et al.*, 2009). This *in vivo* test is based on the loss of heterozygosity in normal genes and the corresponding expression of two recessive markers, multiple wing hairs (mwh) and flare-3 (flr^3), in the wing blade. An increase in the frequency of mutant spots (mwh or flr^3) indicates a genotoxic effect indicating a mitotic recombination and a diverse set of mutational events such as point mutations, deletions and certain types of chromosome aberrations. No increase in mutant spots was seen in this study.

II.E.2. Chromosome Aberrations

A chromosome aberration assay was conducted in which Chinese hamster ovary (CHO) cells were exposed to chloropicrin (99.5% pure) at concentrations up to 0.003 µl/ml without S-9 and up to 0.006 µl/ml with S-9 in the initial assay (Putman and Morris, 1990). In the first confirmatory assay, concentrations up to 0.002 µl/ml without S-9 and 0.006 µl/ml with S-9 were tested. A second confirmatory assay was conducted to confirm the positive findings without activation at concentrations up to 0.001µl/ml. A significant increase in chromosomal aberrations was seen in both confirmatory assays without S-9 in the presence of some cytotoxicity as determined by a decrease in the mitotic index. A significant increase in chromosomal aberrations was also seen in the initial assay with S-9, but the increase was not dose-responsive or reproducible. This study was found acceptable to DPR based on the FIFRA guidelines. Garry *et al.* (1990) reported no increase in chromosome aberrations in cultured human lymphocytes with or without S-9 using an unusual protocol where the cells were exposed to chloropicrin ½ hour before stimulation with PHA rather than after stimulation. However, they did report an increase in sister chromatid exchanges with or without S-9. There was insufficient information available in this published report to determine if the study met FIFRA guidelines.

No increase in micronuclei were seen in an *in vitro* assay with TK6 cells or human lymphocytes (Liviac *et el.*, 2009). Insufficient information was available for this study to determine if it met FIFRA guidelines. Giller *et al.* (1995) conducted an *in vivo* micronucleus assay using *Pleurodeles waltl* newt larvae. After a 12-day exposure peripheral blood erythrocytes were evaluated for clastogenic or spindle poison activity. No increase in micronuclei was observed with this assay. This was a non-guideline type study. In another *in vivo* micronucleus assay, no increase in polychromatic erythrocytes with micronuclei were seen in mice administered chloropicrin by oral gavage at 0 (vehicle: corn oil), 62.5, 125 or 250 mg/kg (Mehmood, 2003a). Mortalities and clinical signs were seen at the highest dose level. This study was found acceptable to DPR toxicologists based on FIFRA guidelines.

II.E.3. Other Genotoxic Effects

Chloropicrin was positive for DNA damage in three non-guideline studies. Giller *et al.* (1995) conducted a SOS chromotest which is an *in vitro* assay which detects primary DNA damage in *Escherichia coli*. Chloropicrin tested positive with S-9 in this assay. Plewa *et al.* (2004) reported that chloropicrin caused DNA damage in CHO cells using a single-cell gel electrophoresis (SCGE) assay which measures the tail moment (integrated migrated DNA density multiplied by the migration distance) of the nuclei as an index of DNA damage. In this

assay, chloropicrin produced DNA damage at lower concentrations than the dehalogenated metabolites, dichloronitromethane and chloronitromethane. In another study, chloropicrin induced high levels of DNA breaks using the Comet assay with TK6 cells (Liviac *et al.*, 2009). This assay determines not only the proportion of oxidative DNA damage, but also repair kinetics. Although the level of DNA damage caused by chloropicrin was higher than that seen with the positive controls in this study, this damage was readily repaired.

Chloropicrin was negative in two unscheduled DNA synthesis (UDS) assays. No increase in UDS was observed in either the initial assay or the confirmatory assay when chloropicrin (99.5% pure) was tested *in vitro* with rat primary hepatocytes at concentrations up to 0.009 µl/ml (Curren, 1990). DPR found this study acceptable based on FIFRA guidelines. There was also no increase in UDS in another *in vivo* UDS assay conducted by Mehmood (2003b) where rats were administered chloropicrin by oral gavage at 0, 85 and 250 mg/kg. Clinical signs were observed at 250 mg/kg. This study was found acceptable to DPR toxicologists based on FIFRA guidelines.

II.F. REPRODUCTIVE TOXICITY

Summary: One range-finding and one main study were conducted to evaluate the reproductive toxicity of chloropicrin. In the range-finding study, only one generation was exposed to chloropicrin vapors while the main study exposed 2 generations to chloropicrin vapors. The main study met FIFRA guidelines. The only reproductive effect seen was in the range finding study in which there was a reduced number of implantation sites at 2 ppm. No adverse effects were seen in pups in either study. The only other adverse effects reported were reductions in body weights and food consumption, and macroscopic and microscopic lesions in the lungs of adults. The reproductive NOEL was equal to or greater than 1.5 ppm (10.09 mg/m^3; HEC - 0.61 ppm), the highest dose tested in the main study. The parental NOEL was 0.5 ppm (3.36 mg/m^3; HEC - 0.20 ppm) based on body weight reductions and pathological lesions in the lungs in the main study.

II.F.1. Inhalation-Rat

Groups of 10 CRL:CD® VAF/Plus® rats/sex/dose were exposed (whole body) to chloropicrin (purity >99%) vapors at 0, 0.4, 1.0 or 2.0 ppm (0, 2.69, 6.72 or 13.45 mg/m^3; HEC[13] - 0, 0.16, 0.41 or 0.81 ppm) for 6 hrs/day beginning 2 weeks prior to mating and continuing through gestation day 20 (Denny, 1996). There were no deaths or clinical signs. Significant reductions in body weights and food consumption were seen at 2.0 ppm. All the reproductive parameters were normal, except the average litter size was reduced at 2.0 ppm. This appears to be due to a reduced number of implantation sites. The parental NOEL was 1.0 ppm (6.72 mg/m^3; HEC - 0.41 ppm) based on the reduced body weights and food consumption. The reproductive NOEL was also 1.0 ppm based on the reduced number of implantation sites at 2.0 ppm. This range-finding study was considered supplemental by DPR toxicologists.

13 HEC = ppm x RR_a/RR_h x E_a/E_h. RR_a = 0.96 m^3/kg/day for the rat (Zielhuis and van der Kreek, 1979). RR_h = 0.59 m^3/kg/day for a child (DPR, 2000). E_a = 6 hours/day, 7 days/week. E_h = 24 hours/day, 7 days/week.

Twenty-six Charles River Crl:CD® VAF/Plus® rats/sex/dose were exposed (whole body) to chloropicrin (99% pure) vapors at 0, 0.5, 1.0 and 1.5 ppm (0, 3.36, 6.72 or 10.09 mg/m^3; HEC[14] - 0, 0.20, 0.41 or 0.61 ppm) for 6 hours/day, 7 days/week for 2 generations (Schardein, 1994). Dams were not exposed from gestation day 21 to lactation day 4. On lactation days 4-21, only the dams were exposed. The F_1 parental generation was exposed from 28 days of age to a minimum of 83 days prior to mating. In the F_0 generation, one control female, one female at 0.5 ppm, two animals (1 M & 1 F) at 1.0 ppm and 4 animals (2 M & 2 F) at 1.5 ppm died prior to scheduled sacrifices, but none of the deaths were considered treatment-related by the study investigator. There were no deaths in the F_1 animals. There was no treatment-related effect on clinical signs in either generation. Transient significant reductions in mean body weights were seen in both sexes of both generations at 1.0 and/or 1.5 ppm. F_1 females at 1.5 ppm had significantly lower food consumption during gestation. There was no treatment-related effect on reproductive parameters including fertility indices, gestation length, and spermatogenesis. No treatment-related effect on pup survival, growth and gross pathological findings. A slight increase in macroscopic pathological lesions was found in the lungs of females (primarily F_0) at 1.0 and 1.5 ppm, including red discoloration, tan foci, white foci, nodule and adhesions (Table 12). The increase in these lesions was insufficient to reach statistical significance by either trend analysis or pair-wise comparison with controls. There was also a slight dose-related increase in the incidence and severity of acute/subacute inflammation in the lungs of F_0 females; however, this increase also was not statistically significant. Despite the lack of statistical significance, these lesions were considered treatment-related by DPR. Consequently, the parental NOEL for the study was set at 0.5 ppm (3.36 mg/m^3; HEC - 0.20 ppm) based on the body weight changes in both sexes and pathological lesions in the lungs of females. The reproductive NOEL for the study was equal to or greater than 1.5 ppm (10.09 mg/m^3; HEC - 0.61 ppm) based on the lack of any reproductive effects in the adults or developmental effects in the pups at any dose level tested. This study was considered acceptable to DPR based on the FIFRA guidelines.

II.G. DEVELOPMENTAL TOXICITY

Summary: Two developmental toxicity studies were available for chloropicrin, one in rats and one in rabbits. Both exposed animals by the inhalation route. Maternal toxicity was observed in both studies including mortalities, clinical signs, reduced body weights and food consumption, and red discoloration and edema of lungs. The lowest maternal NOEL was 0.4 ppm (2.7 mg/m^3; HEC_{8hr} - 0.27 ppm) based on mortalities, nasal discharge, reduced body weights and food consumption, and red discoloration of the lungs in rabbits. Developmental effects were seen including miscellaneous visceral and skeletal variations, increased pre-implantation losses, late-term abortions and reduced fetal weights. The lowest developmental NOEL was also 0.4 ppm based on skeletal variations in both rats and rabbits.

II.G.1. Inhalation-Rat

Schardein (1993) exposed (whole-body) 30 pregnant female Crl:CD® VAF/Plus rats/dose to chloropicrin (99% pure) vapors at 0, 0.4, 1.2 or 3.5 ppm (analytical; 0, 2.7, 8.1 or

14 HEC = ppm x RR_a/RR_h x E_a/E_h. RR_a = 0.96 m^3/kg/day for the rat (Zielhuis and van der Kreek, 1979). RR_h = 0.59 m^3/kg/day for a child (DPR, 2000). E_a = 6 hours/day, 7 days/week. E_h = 24 hours/day, 7 days/week.

Table 12. Possible Treatment-Related Pathological Lesions in the Lungs of Female Rats Exposed to Chloropicrin Vapors for Two Generations[a]

Lesion	Treatment Level (ppm)			
	0	**0.5**	**1.0**	**1.5**
Macroscopic (F_0)				
Red discoloration	1/26 (4%)	1/26 (4%)	1/26 (4%)	2/26 (8%)
Tan foci	0/26 (0%)	1/26 (4%)	1/26 (4%)	1/26 (4%)
White foci	0/26 (0%)	0/26 (0%)	1/26 (4%)	0/26 (0%)
Nodule	0/26 (0%)	0/26 (0%)	1/26 (4%)	1/26 (4%)
Adhesions	0/26 (0%)	0/26 (0%)	1/26 (4%)	0/26 (0%)
Microscopic (F_0)				
Acute/subacute inflammation	7/16 (44%)	10/21 (48%)	12/24 (50%)	11/18 (61%)
Macroscopic (F_1)				
Yellow foci	1/26 (4%)	0/26 (0%)	2/26 (8%)	3/26 (12%)
Adhesions	0/26 (0%)	0/26 (0%)	0/26 (0%)	1/26 (4%)

a Schardein, 1994

23.5mg/m^3; HEC[15] - 0, 0.16, 0.49 or 1.42 ppm) for 6 hrs/day from gestation days 6-15. Four deaths were observed at 3.5 ppm between gestation days 14 and 18. At necropsy, these four animals had red discolored lungs. No exposure-related necropsy findings were seen in the survivors. In addition, labored breathing, emaciation, coldness to touch, reduced activity, and red nasal stains were seen at 3.5 ppm primarily after gestation day 12. Emaciation, however, was observed as early as gestation day 8. In addition, animals at 1.2 and 3.5 ppm had significantly reduced mean body weights (−3% and −9%, respectively), body weight changes (-7% and -27%, respectively) and mean food consumption (−16% and −47%, respectively) during gestation days 6-9. Fetal body weights were also reduced (-6%) at 3.5 ppm. There was an increase in several skeletal variations (reduced ossification of skull bone, less than 13 rib pairs, 14th rudimentary ribs, bent ribs, unossified 5th and 6th sternebrae) in fetuses at 1.2 and 3.5 ppm. However, the difference was only statistically significant at 3.5 ppm when the total number of fetuses with developmental variations was combined. The developmental NOEL was 0.4 ppm (2.7 mg/m^3; HEC_{8hr} - 0.49 ppm) based on the skeletal variations in fetuses. The maternal NOEL was also 0.4 ppm based on clinical signs, reduced body weight, body weight gains, and food consumption. DPR found this study acceptable based on FIFRA guidelines.

15 HEC = ppm x RR_a/RR_h x E_a/E_h. RR_a = 0.96 m^3/kg/day for the rat (Zielhuis and van der Kreek, 1979). RR_h = 0.59 m^3/kg/day for a child (DPR, 2000). E_a = 6 hours/day, 7 days/week. E_h = 24 hours/day, 7 days/week.

II.G.2. Inhalation-Rabbit

Twenty pregnant female New Zealand White rabbits/dose were exposed (whole body) to chloropicrin (99% pure) vapors at 0, 0.4, 1.2, or 2.0 ppm (analytical; 0, 2.7, 8.1 or 13.4 mg/m^3; HEC[16] - 0, 0.092, 0.27 or 0.46 ppm) for 6 hrs/day during gestation days 7 to 20 (York, 1993). Deaths occurred at 1.2 ppm (2 deaths on gestation days 9 and 19) and 2.0 ppm (10 deaths on gestation days 9, 10, 11, and 19) (Table 13). All of the animals that died had red discoloration of the lungs at necropsy. In addition, 1 animal at 1.2 ppm (died gestation day 19) and 7 animals at 2.0 ppm (died gestation days 9-11, and 19) had edema of the lungs. Various clinical signs indicative of sensory or respiratory irritation were seen at 1.2 and/or 2.0 ppm, including gasping, labored breathing, increased salivation, clear nasal discharge, red area around eyes/eyelids, and excessive lacrimation. Some of these signs occurred within the first few days of exposure, so they could be considered acute effects. The nasal discharge appears to be one of the more sensitive acute endpoints with an onset between gestation days 7 and 11 in 7 of 18 animals at 1.2 ppm. Reductions in body weight and food consumption also appear to be an acute effect due to the early onset. Animals at 1.2 and 2.0 ppm had reduced body weight gains (-243% and -401%, respectively) and food consumption (−49% and −79%) from gestation days 7 to 13. One rabbit at 1.2 ppm and 2 rabbits at 2.0 ppm had late-term abortions between gestation days 25-29. Due to the late onset, this was not considered an acute effect. The fetal effects included a slight increase in percentage of pre- (44.4% vs. 40.8% in controls) and post-implantation losses (13.3% vs. 3.7% in controls) and a slight reduction in fetal body weights (8.4%) at 2.0 ppm that were not statistically significant. The post-implantation losses were also within the historical control and, therefore, were not considered treatment related by the study investigators. There was a slight increase in several developmental variations in the fetuses including visceral (left carotid artery arising from the innominate artery) and skeletal variations (unossified hyoid body and unossified tail) which were considered toxicologically significant at 2.0 ppm, although they were not statistically significant. The developmental NOEL was 1.2 ppm (2.7 mg/m^3; HEC_{8hr} - 0.27 ppm) based on the increased developmental variations, increased pre- and post-implantation losses, late-term abortions and reduced fetal body weights. The maternal NOEL was 0.4 ppm based on mortalities, nasal discharge, reductions in body weights and food consumption, late-term abortions and red discoloration and edema in the lung. This study was acceptable to DPR based on FIFRA guidelines.

16 HEC = ppm x RR_a/RR_h x E_a/E_h. RR_a = 0.54 m^3/kg/day for the rabbit (Zielhuis and van der Kreek, 1979). RR_h = 0.59 m^3/kg/day for a child (DPR, 2000). E_a = 6 hours/day, 7 days/week. E_h = 24 hours/day, 7 days/week..

Table 13. Acute Effects in Pregnant Rabbits Exposed to Chloropicrin Vapors During Gestation Days 7-20[a]

Endpoint	Dose Level (ppm)			
	0	0.4	1.2	2.0
Death	0[b](0[c])	0 (0)	1 (1)	8 (2)
Death without signs	0 (0)	0 (0)	1 (0)	5 (0)
Gasping[d]	0 (0)	0 (0)	0 (0)	1 (1)
Labored breathing[d]	0 (0)	0 (0)	0 (1)	1 (2)
Increased salivation[d]	0 (0)	0 (0)	0 (0)	2 (0)
Excessive lacrimation	0 (0)	0 (0)	0 (1)	1 (2)
Nasal discharge	0 (1)	0 (3)	7 (10)	1 (10)
Red around eyes/eyelids	0 (0)	0 (0)	0 (0)	1 (4)
Red discolored lungs	0 (0)	0 (0)	1 (2)	8 (2)
Edema lungs	0 (0)	0 (0)	0 (1)	5 (2)
Body weight gain (g), GDs[e] 7-13	-20±89	15±65	-243±165**	-407±194**
Food consumption (g) GDs 7-13	145±24	145±25	74±29**	32±28**
Pre-implantation loss (%)	40.8±24.9	41.6±21.0	43.1±25.9	44.4±30.2
Post-implantation loss (%)	3.7±7.7	13.5±24.1	7.2±10.4	13.3±16.9
Fetal body weights[f] (g)	43.0±7.9	45.2±6.4	43.8±8.7	39.4±8.9

a York, 1993
b Incidence between gestation days 7 and 11
c Incidence between gestation days 12 and 29.
d These signs were only observed in animals that eventually died
e GDs = Gestation Days
f Males and females combined

III. RISK ASSESSMENT

III.A. HAZARD IDENTIFICATION

III.A.1. Calculation of Human Equivalent Concentrations

For ease of comparison with other studies and with the exposure dosages, the air concentrations in the Risk Assessment and Risk Appraisal sections are expressed in ppb. Due to differences in exposure duration and breathing rates for different species, the dose levels in the various animal studies were also expressed as human equivalent concentrations (HECs) for ease of comparison. DPR converted the dose levels from the animal studies to human equivalent concentrations (HECs) as follows:

$$HEC(ppb) = Dose\ (ppb)\ X\ \frac{RR_a\ (m^3/kg/day)}{RR_h\ (m^3/kg/day)}\ X\ \frac{E_a\ (hrs/day)}{E_h\ (hrs/day)}$$

$$HEC(\mu g/m^3) = HEC(ppb)\ X\ \frac{M.Wt.(164.38g)}{M.Vol.(24.45L@25^oC)}$$

where RR_a is the respiratory rate in animals, RR_h is the respiratory rate in humans, E_a is the exposure duration in animals, and E_h is the exposure duration in humans, assuming a default respiratory rate of 0.28, 0.59, 0.54, 0.96 and 1.8 m^3/kg/day for adults, children, rabbits, rats, and mice, respectively. Note that DPR's HEC calculation is different from U.S. EPA's HEC calculation which is discussed in more detail in the Risk Appraisal section (Section IV.A.).

III.A.2. Acute Toxicity

III.A.2.a. Animal Studies

The available acute toxicity studies which were potentially useful for identifying NOELs for acute effects are summarized in Table 14. Several LC_{50} studies were conducted in rats of which two had sufficient information to establish a LOEL, but a NOEL was not observed in either study (Yoshida *et al*., 1987a; Hoffman, 1999a). The effects at the LOEL were severe in both studies, but no deaths occurred. The effects at the LOEL in both studies included reductions in body weights, clinical signs and pathological lesions in the respiratory tract. The clinical signs were primarily respiratory, although eye irritation, lacrimation and eye closure were also noted. Numerous gross and histopathological lesions were observed throughout the respiratory tract.

Chloropicrin produces sensory irritation of the eyes, nose and throat. Sensory irritation is caused by the stimulation of unspecialized free nerve endings of the afferent trigeminal nerve located in the corneal, nasal and oral mucosa (Kane *et al*., 1979). Stimulation of the trigeminal nerve results in a burning or pungent sensation and numerous physiological reflex responses, including a reduction in respiratory rate. Based on earlier research by these investigators they were able to show that a reduction in the respiratory rate of mice was a good predictor of sensory irritation in man and shows a concentration-response relationship. The RD_{50} (concentration that caused a 50% reduction in respiratory rate) is used to compare the relative potency of various irritants. They proposed that the RD_{50} would be an intolerable concentration in man. The RD_{50} of chloropicrin was estimated in two studies with mice. The RD_{50} values ranged from 2,340 ppb

for a 30 minute exposure (Hoffman, 1999b) to 7,980 ppb for a 10 minute exposure (Kane *et al.*, 1979). The RD_{50} values for these two studies expressed as 1-hr HECs[17] were 3,570 ppb for the Hoffman study and 4,060 ppb for the Kane *et al.* study. A NOEL was not identified in either of these studies due to insufficient information and/or high exposure levels; however, LOELs based on the respiratory depression were included in Table 14. A 30% depression in respiratory rate was observed at the lowest dose level tested, 990 ppb by Hoffman (1999b) which was equivalent to an 1-hr HEC of 1,510 ppb. Buckley *et al.* (1984) evaluated the respiratory tract lesions in mice caused by chloropicrin when exposed at 7,980 ppb (10-min. RD_{50}) for 6 hrs/day for 5 days (HEC_{8hr} - 18,300 ppb). In addition to numerous histopathological lesions in the respiratory and olfactory epithelium, the mice had reduced body weights, nasal discharge and gaseous distension of the abdomen. Since only one concentration was tested in this study, a NOEL was not observed, but the LOEL for this study is included in Table 14.

Two developmental toxicity studies submitted to DPR by registrants were useful for identifying acute NOELs for chloropicrin (Table 14). Maternal effects seen within the first few days of exposure and all fetal effects were considered signs of acute toxicity. Death, labored breathing, emaciation, coldness to the touch, reduced activity, red nasal stains, reduced body weights and food consumption were seen in the dams, but most of these effects were not considered acute since they occurred after 6 days of exposure (Schardein, 1993). Maternal effects seen within the first few days of exposure in rats included emaciation (onset day 2), reduced body weight, body weight gains, and food consumption (days 0-3) with an acute NOEL of 400 ppb (HEC_{8hr}[18] - 490 ppb). Fetal effects in rats included reduced fetal weights and various skeletal variations (reduced ossification of skull bone, less than 13 rib pairs, 14th rudimentary ribs, bent ribs, unossified 5th and 6th sternebrae). The NOEL for fetal effects in the rat study was also 400 ppb based on skeletal variations. Maternal effects in rabbits included death, red discoloration and edema in lungs of rabbits that died, clinical signs of sensory or respiratory irritation (gasping, labored breathing, increased salivation, clear nasal discharge, red area around eyes/eyelids, excessive lacrimation), reduced body weights and food consumption (York, 1993). The acute NOEL for maternal effects in rabbits was 400 ppb (HEC_{8hr}[19] - 270 ppb) based on mortalities, nasal discharge, reductions in body weights and food consumption, and red discoloration and edema in the lung. Developmental effects in rabbits included increased pre- and post-implantation losses, late-term abortions, reduced fetal body weights, visceral (left carotid arising from the innominate) and skeletal variations (unossified hyoid body and unossified tail). The acute NOEL in rabbit fetuses was 1,200 ppb based on the increased developmental variations. Both of the developmental toxicity studies met FIFRA guidelines.

III.A.2.b. Human Study

A sensory irritation study was conducted recently with human volunteers which consisted of three phases (Cain, 2004). The first phase identified the median odor threshold for chloropicrin after a 5 second exposure at 700 ppb. The median threshold for detection by eye

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17 HEC = ppb x RR_a/RR_h x E_a/E_h. RR_a = 1.8 m^3/kg/day for the mouse (Zielhuis and van der Kreek, 1979). RR_h = 0.59 m^3/kg/day for a child (DPR, 2000). E_a = 30 minutes/day. E_h = 60 minutes/day.

18 HEC = ppb x RR_a/RR_h x E_a/E_h. RR_a = 0.96 m^3/kg/day for the rat (Zielhuis and van der Kreek, 1979). RR_h = 0.59 m^3/kg/day for a child (DPR, 2000). E_a = 6 hours/day. E_h = 8 hours/day.

19 HEC = ppb x RR_a/RR_h x E_a/E_h. RR_a = 0.54 m^3/kg/day for the rabbit (Zielhuis and van der Kreek, 1979). RR_h = 0.59 m^3/kg/day for a child (DPR, 2000). E_a = 6 hours/day. E_h = 8 hours/day.

Table 14. Acute Effects of Chloropicrin and Their Respective NOELs and LOELs

Species	Exposure	Effect	NOEL	LOEL	Ref.[b]
			ppb (HEC[a])		
Inhalation					
Rat[e]	Single, 4-hr, WB[f]	↓ Body weight, clinical signs, histopathological lesions in respiratory tract, gastric gaseous distention	-----	8,800 (7,160-8 hr) (2,390-24 hr)	1
Rat[e]	Single, 4-hr, WB	↓ Body weight, clinical signs, histopathological lesions in respiratory tract		10,500 (17,100-8 hr) (5,690-24 hr)	2
Mouse[c]	Single, 10 min, HO[d]	50% depression in respiratory rate	-----	7,980 (4,060-1 hr)	3
Mouse[c]	Single, 30 min, HO	30% depression in respiratory rate	-----	990 (1,510-1 hr)	4
Mouse	6 hrs/day, 5 days, WB	↓Body weight, nasal discharge, gaseous distention of stomach, histopathological lesions in olfactory and respiratory epithelium	-----	7,980 (18,300-8 hr) (6,090-24 hr)	5
Rat[g]	6 hrs/day, 10 days, WB	Maternal: Emaciation (onset day 2), ↓ body weight and food consumption (days 0-3) Fetal: Skeletal variations	400 (490-8 hr) (160-24 hr)	1,200 (1,460-8 hr) (490-24 hr)	6*
Rabbit[g]	**6 hrs/day, 14 days, WB**	**Maternal: Mortalities (days 2-4), nasal discharge (onset day 0), ↓ body weights & food consumption (days 0-6), red discoloration & edema in lungs**	**400 (270-8 hr) (92-24 hr)**	**1,200 (820-8 hr) (270-24 hr)**	**7***
Human	Single, 20 min, WB	Ocular irritation	50	75	**8**
	Single, 1 hr, WB	Ocular irritation **↑ NO in expired nasal air** ↓ Nasal air flow	26[h] **44[i]** 100	100 150	

a HEC (Human Equivalent Concentration) = ppb x RR_a/RR_h x E_a/E_h. RR_a = respiratory rate in animals which was assumed to be 1.8, 0.96 and 0.54 m^3/kg/day for the mouse, rat and rabbit, respectively (Zielhuis and van der Kreek, 1979). RR_h = respiratory rate in humans which was assumed to be 0.59 m^3/kg/day for a child (DPR, 2000). E_a = exposure duration for animals. E_h = exposure duration for humans as indicated.

b References: 1. Yoshida *et al.*, 1987a; 2. Hoffman, 1999a; 3. Kane *et al.*, 1979; 4. Hoffman, 1999b; 5. Buckley *et al.*, 1984; 6. Schardein, 1993; 7. York, 1993; 8. Cain, 2004.

c RD_{50} study designed to determine the concentration at which the respiratory rate is depressed by 50% as an indication of sensory irritation.

d HO = head only exposure

e LC_{50} study

f WB = whole body exposure

g Developmental toxicity study: All fetal effects were considered acute effects; however, only maternal effects observed within the first few days of exposure were considered acute exposure.

h The NOEL was set at the $BMCL_{10}$ using the hybrid approach developed by Crump (1995). The multiplier, k, of the standard deviation was set to 0.61 which corresponded to the P_0 and π (BMR) set to 0.05 and 0.1, respectively. See the Risk Appraisal section (Section IV.A) of this document for additional discussion of BMC analysis of this study.

i A $BMCL_{05}$ was calculated for this endpoint due to greater concern about this endpoint. The multiplier, k, for this response level was 0.36.

* Acceptable study based on FIFRA guidelines

irritation after a 25 second exposure was 900 ppb. The median threshold for detection by nasal irritation after 5 second exposure was greater than 1200 ppb, the highest level tested. In phase 2, a NOEL for ocular irritation was established at 50 ppb with a 20-minute exposure in a walk-in chamber. No nasal or throat irritation was observed up to 150 ppb. In phase 3, the NOEL for ocular irritation appears to be less than 100 ppb after a 1-hour exposure in a walk-in chamber based on mild irritation observed at the lowest dose level tested. No nasal or throat irritation was reported in this phase nor was there any affect on pulmonary function (based forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1)), but increased concentration of nitric oxide (NO) in expired nasal air (an indication of inflammation) at 100 and 150 ppb and decreased nasal airflow at 150 ppb suggests some subtle upper respiratory irritation. There are no FIFRA guidelines for human studies. This study, however, was conducted in accordance with Good Laboratory Practice regulations and was approved by the Internal Review Board at the University of California, San Diego, which reviewed the protocol and informed consent forms signed by the subjects. In addition, the study protocol was reviewed prior to the study start by a biostatistician, Dr. Robert Sielken, to ensure there was sufficient statistical power.

A benchmark concentration (BMC) analysis was performed to identify a NOEL for phase 3. Only the average scores for ocular irritation during the plateau period (minutes 31-55) were used since this reflected the most severe response during the exposure. U.S. EPA's Bench Mark Dose Software (BMDS, version 1.3.2) was used to calculate the lower limit on the BMC (BMCL). A 10% response level was selected for eye irritation instead of the default 5% response level because it was a mild and reversible endpoint. Therefore, the level of protection needed was not considered to be as great. A hybrid approach was used in which the benchmark response (BMR) was defined as a change of the mean response at a specified multiplier of the standard deviation (Crump, 1995). The multiplier, k, was set to 0.61 which corresponded to a background risk, P_0, of 0.05 and a risk above the background, π, of 0.10 (i.e., BMR = 10%). Four models for continuous data were available with the BMDS software. The Hill model could not be run with these data because it required more treatment groups. The Akaike's Information Criterion (AIC) scores were provided for each model which is an indication of fit. In general, the lower the AIC value, the better the model fits the data. However, sometimes models with higher AIC scores have better fits visually, especially around the BMC and BMCL. The two models with the lowest AICs and best fit visually with this data set were the polynomial and power models with identical AIC values. Therefore, the NOEL was set at the average of the BMCLs for these two models, 26 ppb (170 $\mu g/m^3$). The same approach was used for estimating BMCLs for the increase in NO in expired nasal air except that the default 5% response level was used since there was greater concern about this endpoint. The multiplier, k, used for this response level was 0.36. The difference in the NO in expired nasal air was averaged for the 4 days of exposure. The model with the lowest AIC was the linear model with a corresponding $BMCL_{05}$ of 44 ppb (299 $\mu g/m^3$).

The BMC analysis of these two endpoints suggests that the ocular irritation is the more sensitive endpoint. However, the reference concentration (RfC) for eye irritation would end up higher than for the increased NO in nasal air because the uncertainty factor applied to the eye irritation is smaller. The default intraspecies uncertainty factor used to derive a RfC from a human study is 10. The intraspecies uncertainty factors may be further divided into toxicokinetic and toxicodynamic components of 3.16 ($10^{0.5}$) each (Renwick and Lazarus, 1998). No toxicokinetic variation is anticipated for eye irritation which involves the direct interaction of

the compound with the free trigeminal nerve endings in the respiratory mucosa. Therefore, the RfC for eye irritation was estimated to be 8.7 ppb by dividing the $BMCL_{10}$ by 3 whereas the RfC for the increased NO in nasal air was estimated to 4.4 ppb by dividing the $BMCL_{05}$ by 10. Consequently, the $BMCL_{05}$ for increased NO in nasal air was selected as the NOEL to evaluate the 1-hour inhalation exposures since it resulted in a lower RfC and, therefore, should be more health protective. The differences in breathing rate between adults and children were considered unimportant with this upper respiratory effect, so the same NOEL was used for children and adults.

There is evidence from this study and in the open literature that Haber's Law (c x t = k) may not apply to sensory irritation. The plateau in the sensory irritation with the 1 hour exposure in the human study for chloropicrin suggests that concentration is more important than time in the severity of the effects observed with exposure. This appears to be true with other sensory irritants and Shusterman *et al.* (2006) suggests that a power equation (c^n x t = k) rather than Haber's Law better defines the severity of the endpoint. They not only noted that the severity of effects plateaued with time, but frequently the severity decreased after awhile. This appeared to be the case with chloropicrin with a slight decrease in the average scores for ocular irritation from minutes 55 to 60. However, there was insufficient information to estimate the exponent on concentration in the power equation to predict the severity beyond 1 hr. Even less is known about whether the increase in NO in expired nasal was concentration dependent. Therefore, rather than estimate an 8-hr or 24-hr NOEL from the 1-hr NOEL in humans, the developmental toxicity study in rabbits was selected as the definitive study to evaluate the 8-hr and 24-hr bystander exposure to chloropicrin (York, 1993). The acute NOEL was 400 ppb (270 $\mu g/m^3$) based on maternal effects observed within the first few days of exposure including nasal discharge, reduced food consumption and body weights and mortalities associated with red discolored lungs. Haber's Law was assumed for these severe effects which appear to involve more than sensory irritation. The 8-hr and 24-hr NOELs were estimated to be 300 ppb (2,000 $\mu g/m^3$) and 100 ppb (670 $\mu g/m^3$), respectively, adjusting for duration of exposure. The 8-hr HECs were 270 ppb and 580 ppb for children and adults, respectively, adjusting for species differences in breathing rates and assuming children had a higher breathing rate (0.59 m^3/kg/day) than adults (0.28 m^3/kg/day). The 24-hr HECs were 92 ppb (610 $\mu g/m^3$) for children and 190 ppb (1,300 $\mu g/m^3$) for adults.

III.A.3. Subchronic Toxicity

The effects observed in laboratory animals after subchronic exposure to chloropicrin are summarized in Table 15. Clinical signs observed in 13-week inhalation studies included eye closure, reddened eyes, labored respiration, reduced activity, emaciation, dehydration, urogenital stains, and hunched posture. Reductions in body weights and food consumption were also seen. Pathological findings observed with subchronic inhalation exposure included changes in hematological (↑ RBCs, Hgb, Hct, eosinophils & monocytes, ↓ MCV and MCH) and clinical chemistry values (↓ cholesterol, ↑ protein, calcium, BUN, & ALP), increased absolute and relative lung weights, and numerous microscopic lesions in the nasal cavity (epithelial hyalin inclusions, respiratory epithelial hyperplasia/dysplasia, rhinitis, mucosal ulceration, goblet cell hyperplasia and catarrhal inflammation of mucosa) and lungs (thickening of the epithelial layer in the larynx, epithelial hypertrophy in the trachea, bronchus and bronchiole, alveolar histiocytosis, bronchitis/bronchiolitis, perivascular infiltrates, interstitial pneumonitis, peribronchial/peribronchiolar fibrosis and muscle hyperplasia, epithelial degeneration/necrosis/-

Table 15. Subacute/Subchronic Effects of Chloropicrin and Their Respective NOELs and LOELs

Species	Exposure	Effect	NOEL	LOEL	Ref.[b]
			ppb (HEC[a])		
Inhalation					
Rat[c]	6 hrs/day, daily for 10 days, WB[d]	Maternal: Clinical signs, ↓ body weights and food consumption	400 (160)	1,200 (490)	1*
Rabbit[c]	6 hrs/day, daily for 14 days, WB	Maternal: Mortalities, clinical signs, ↓ body weights & food consumption, red discoloration and edema in lung	400 (92)	1,200 (270)	2*
Mouse	6 hrs/day, 5 days/wk, 13 weeks, WB	↓ Body weights (M), ↓ food consumption, ↑ lung weights, histopathological lesions in nasal cavity and lungs.	300 (160)	1,030 (560)	3*
Rat	6 hrs/day, 5 days/wk, 13 weeks, WB	Eye closure, ↓ motor activity	370 (110)	670 (190)	4
Rat	6 hrs/day, 5 days/wk, 13 weeks, WB	↑ Lung weights, histopathological lesions in the lung	300 (88)	1,030 (300)	3*
Rat[e]	6 hrs/day, 7 days/wk, 1 generation, WB	Parental: ↓Body weights, ↓ food consumption, ↓ implantation sites	1,000 (410)	2,000 (81)	5
Rat[e]	6 hrs/day, 7 days/wk, 2 generations, WB	Parental: ↓ Body weights, histopathological lesions in lungs (F)	500 (200)	1,000 (410)	6*
Oral[f]					
Rat	Gavage, daily for 10 days	Histopathological lesions in forestomach	---	10	7
Rat	Gavage, daily for 90 days	↓ Body weights, hematological changes, histopathological lesions in forestomach	8	32	7

a HEC (Human Equivalent Concentration) = ppb x RR_a/RR_h x E_a/E_h. RR_a = respiratory rate in animals which was assumed to be 1.8, 0.96 and 0.54 m^3/kg/day for the mouse, rat and rabbit, respectively (Zielhuis and van der Kreek, 1979). RR_h = respiratory rate in humans which was assumed to be 0.59 m^3/kg/day for a child (DPR, 2000). E_a = exposure duration for animals. E_h = exposure duration for humans which was set at 24 hours/day, 7 days/week.
b References: 1. Schardein, 1993; 2. York, 1993; 3. Chun and Kintigh, 1993; 4. Yoshida *et al.*, 1987b; 5. Denny, 1996; 6. Schardein, 1994; 7. Condie *et al.*, 1994.
c Developmental toxicity study: Only maternal effects observed after the first few days were included.
d WB = whole body exposure
e Reproductive toxicity study
f Oral NOELs and LOELs expressed in mg/kg/day.
* Acceptable study based on FIFRA guidelines

desquamation in the bronchus and bronchiole, epithelial hypertrophy of the bronchial gland in the bronchus, thickening of the bronchial wall in the bronchus and bronchiole). Two of the three 13-week inhalation studies met FIFRA guidelines including those in mice and rats conducted by Chun and Kintigh (1993). The lowest NOEL in the subchronic inhalation studies was 300 ppb based on the increased lung weights and histopathological lesions in the lungs of rats and reduced body weights and food consumption, increased lung weights and histopathological lesions in the nasal cavity and lungs of mice (Chun and Kintigh, 1993).

No clinical signs were observed with subchronic oral exposure to chloropicrin. Reductions in body weight were seen as well as changes in absolute and relative organ weights (↑↓ thymus, ↓ liver and spleen weights). Pathological findings with subchronic oral exposure included changes in hematological values (↓↑ RBCs & WBCs, ↑ reticulocytes, ↓ Hgb and Hct) and clinical chemistry values (↓ AST, ↑ phosphate) and histopathological lesions in the forestomach (chronic inflammation, necrosis, acantholysis, hyperkeratosis, epithelial hyperplasia and ulceration). Animals that died after subchronic oral exposure to chloropicrin also had pulmonary inflammation and congestion. There was insufficient information in the published report for the 90-day oral gavage study to determine if it met FIFRA guidelines. The lowest NOEL in subchronic oral studies was 8 mg/kg/day based on reduced body weight, hematological changes and histopathological lesions in the forestomach of rats (Condie *et al.*, 1994).

In addition to the standard subchronic toxicity studies, Table 15 includes two developmental toxicity studies where maternal effects were observed after subacute exposure for 1 to 2 weeks. Maternal signs observed with subacute exposure to chloropicrin included death, gasping, labored breathing, clear nasal discharge, red area around eyes/eyelids, excessive lacrimation, red nasal stains, increased salivation, emaciation, coldness to touch, and reduced activity. Reductions in food consumption and maternal body weights were also seen. Red discoloration and edema were seen in the lungs of pregnant rabbits that died. The lowest maternal NOEL in a developmental toxicity study was 400 ppb (HEC - 92 ppb) based on death, clinical signs, ↓ body weights & food consumption, red discoloration and edema in lung of rabbits (York, 1993).

The effects observed in the two reproductive toxicity studies after subchronic inhalation exposure to chloropicrin for one or two generations were also included in Table 15. No clinical signs were observed in either study. The effects observed in the parental generations included reductions in body weight and food consumption and pathological lesions in the lungs (gross: red discoloration, tan foci, white foci, nodule and adhesions; histological: acute/subacute inflammation). There was no treatment-related effect on reproductive parameters, except a reduction in the number of implantation sites in the 1-generation study (Denny, 1996). The lowest parental NOEL was 500 ppb (HEC - 200 ppb) based on the reduced body weights and pathological lesions in the lungs in the two-generation study. The lowest reproductive NOEL was 1,000 ppb (HEC - 410 ppb) based on the reduced number of implantation sites in the one-generation study.

The NOELs for the 90-day inhalation studies in rats and mice were identical, although mice appear to be more sensitive than rats based on the severity of endpoints at the LOEL. On the other hand, if breathing rate is taken into consideration, the rats appear to be more sensitive. Consequently, a benchmark dose analysis was performed on the more sensitive endpoints observed in these studies, taking into consideration the breathing rate adjustments. The BMDS

software was also used for this analysis, except the models for dichotomous data were used for the histopathological lesions. Because the histological effects were more frank effects, the BMCL at the 5% response level was selected as equivalent to a NOEL. Also, because there appeared to be gender-related differences, the incidences for the males and females were not combined. As with the models for continuous data, AIC scores were generated. In comparing the results from the various models, it was noted that even when the AIC scores and visual fit were similar among the models, the BMCL estimate could vary significantly because of differences in the way the confidence limits were calculated between the models. This made selection of the most sensitive endpoint difficult because it could be very model dependent. Consequently, one model was selected to compare all the endpoints. The probit model was selected for this purpose because it seemed to have a good fit consistently with tight confidence limits among the various data sets. Table 16 summarizes the BMC analysis for the respiratory lesions with non-significant increases at the lowest dose, including their respective BMC and $BMCL_{05}$ estimates. The $BMCL_{05}$ estimates were then converted to HECs for children and adults, adjusting for species differences in breathing rate. The BMC analysis for goblet cell hyperplasia in rats was not shown despite a significant increase in females at the lowest dose. The increase was not significant in males even at the high dose and the trend was also not significant. Meaningful results could not be obtained with the female incidence because of the non-monotonic dose response which resulted in a poor fit with all models. Based on a comparison of

Table 16. Benchmark Dose Analysis of the Most Sensitive Endpoints in the Mouse and Rat Subchronic Inhalation Studies[a]

Species	Endpoint	Sex	BMC (ppb)	$BMCL_{05}$ (ppb)	HEC (ppb)	
					Child	Adult
Mouse[b]	Epithelial Hyalin Inclusions	M	840	360	200	413
		F	180	84	45	96
	Alveolar Histiocytosis	M	370	140	76	161
		F	260	81	44	93
	Rhinitis	M	1,000	650	350	746
		F	500	210	110	241
Rat[c]	**Rhinitis**	M	880	320	93	196
		F	**190**	**120**	**34**	**73**
	Peribronchial/Peribronchiolar Muscle Hyperplasia	M	510	220	64	135
		F	260	160	46	98
	Bronchial/Bronchiolar Epithelial Hyperplasia	M	470	200	58	122
		F	310	180	52	110

a Benchmark dose estimates shown for the probit model only.
b Chun and Kintigh, 1993.
c Chun and Kintigh, 1993.

the HECs in Table 16, the rhinitis in female rats appears to be the most sensitive endpoint with subchronic exposure. Therefore, the 90-day inhalation study conducted by Chun and Kintigh (1993) was selected as the definitive study for evaluating seasonal exposure to chloropicrin in air based on the rhinitis in female rats with a $BMCL_{05}$ of 120 ppb (HEC = 35 ppb for children and 73 ppb for adults).

III.A.4. Chronic Toxicity

The effects observed in laboratory animals with chronic exposure to chloropicrin are summarized in Table 17. Two chronic inhalation studies were conducted with chloropicrin, one in mice and the other in rats. The effects observed with chronic inhalation exposure included reduced survival, reduced body weights and food consumption, increased lung weights and non-

Table 17. Chronic Effects of Chloropicrin and Their Respective NOELs and LOELs

Species	Exposure	Effect	NOEL	LOEL	Ref.[b]
			ppb (HEC[a])		
Inhalation					
Mouse	6 hrs/day, 5 days/wk, 78 weeks, WB[c]	↓ Body weights & food consumption, ↑ lung weights, histopathological lesions in lungs	100 (54)	500 (270)	1*
Rat	6 hrs/day, 5 days/wk, 107 weeks, WB	↓ Survival (M), ↓ body weight gain	100 (29)	500 (150)	2*
Oral[d]					
Mouse	Gavage, daily for 78 weeks	↓ Body weights (F), histopathological lesions in forestomach	---	33	3
Rat	Gavage, 5 days/wk, 78 weeks	↓ Survival, ↓ body weights, clinical signs	---	20	3
Rat	Gavage, daily for 2 years	↓ Body weights, histopathological lesions in liver	0.1	1	4*
Dog	Capsules, daily for 1 year	Clinical signs, ↓ body weights, hematological and clinical chemistry changes	1.0	5.0	5*

a HEC (Human Equivalent Concentration) = ppb x RR_a/RR_h x E_a/E_h. RR_a = respiratory rate in animals which was assumed to be 1.8 and 0.96 m^3/kg/day for the mouse and rat, respectively (Zielhuis and van der Kreek, 1979). RR_h = respiratory rate in humans which was assumed to be 0.59 m^3/kg/day for a child (DPR, 2000). E_a = exposure duration for animals. E_h = exposure duration for humans which was set at 24 hours/day, 7 days/week.
b References: 1. Burleigh-Flayer *et al.*, 1995; 2. Burleigh-Flayer and Benson, 1995; 3. NCI, 1978; 4. Slauter, 1995; 5. Wisler, 1994.
c WB = Whole body exposure
d Oral NOELs and LOELs expressed in mg/kg/day.
* Acceptable study based on FIFRA guidelines

neoplastic and neoplastic changes in the respiratory tract. The non-neoplastic lesions included lesions in the nasal cavity (serous exudate, epithelial hyalin inclusions, rhinitis, olfactory epithelial atrophy) and lungs (alveolar protein deposits, alveolar histiocytosis, peribronchial lymphocytic infiltrates, bronchiectasis, bronchial submucosal fibrosis, bronchioalveolar cell hyperplasia, peribronchial smooth muscle hyperplasia). The only neoplastic change was a slight increase in adenomas in the lungs of females that was not significant by Fisher's exact test, but did have a significant trend. Both of the inhalation studies met FIFRA guidelines. The lowest NOEL among the chronic inhalation studies was 100 ppb based on the reduced survival and rhinitis in male rats and reduced body weights and food consumption, increased lung weights and histopathological lesions in the lungs of mice (Burleigh-Flayer and Benson, 1995; Burleigh-Flyer *et al.*, 1995).

Four chronic oral studies were available for chloropicrin, one in mice, two in rats and one in dogs. In the mouse and both rat studies, chloropicrin was administered by gavage. Chloropicrin was administered in capsules in the dog study. Effects seen in the chronic oral studies for chloropicrin included reduced survival, ptyalism, emesis, diarrhea, hunched posture, squinted or reddened eyes, urogenital stains, reduced body weights, hematological (↓ MCV & MCH) and clinical chemistry (↑↓ calcium, ↑ phosphorus, ↓ASAT, total protein, albumin) changes, non-neoplastic changes in the forestomach/nonglandular stomach (acanthosis, hyperkeratosis, epithelial hyperplasia), and neoplastic changes in the mammary glands (fibroadenoma -female rats) and stomach (papilloma - one male rat). One rat study and the dog study met FIFRA guidelines. The lowest NOEL with chronic oral exposure to chloropicrin was 0.1 mg/kg/day based on reduced body weights and histopathological lesions in the liver of rats (Slauter, 1995).

As with the subchronic inhalation studies, the NOELs for the chronic inhalation studies in rats and mice were identical, although mice appear to be more sensitive than rats based on the severity of endpoints at the LOEL. On the hand, if the NOELs are adjusted for breathing rate, the NOEL in rats appears to be more sensitive. Consequently, a benchmark dose analysis was performed on the more sensitive endpoints observed in these studies, taking into consideration the breathing rate adjustments. As before, the probit model was used to compare endpoints and the default BMR of 5% was used, except for bronchiectasis where a BMR of 2.5% was used due to greater concern about this irreversible pathological lesion. Since the incidence of bronchiectasis was so similar between males and females, the BMCL for this lesion was calculated with the incidence for both sexes combined. Table 18 summarizes the endpoints examined by BMC analysis and their respective BMC, BMCL and HEC estimates. For comparison, the BMCL for bronchiectasis was also calculated for each sex separately and at the 5% response level (in parentheses). Based on a comparison of the HECs, bronchiectasis in mice appears to be the most sensitive endpoint with chronic exposure even at the 5% response level. Therefore, the chronic inhalation study conducted by Burleigh-Flyer *et al.* (1995) was selected as the definitive study for evaluating annual exposure to chloropicrin in air based on the combined incidence of bronchiectasis in male and female mice with a $BMCL_{25}$ of 49 ppb (HEC = 27 ppb for children and 56 ppb for adults).

III.A.5. Carcinogenicity - Weight of Evidence

Chloropicrin is a strong electrophile due to its chlorine and nitro groups. Therefore, it is capable of covalently binding to nucleophiles, such as DNA. Chloropicrin tested positive in a number of tests for genotoxicity. There was evidence of DNA damage in three *in vitro* tests,

Table 18. Benchmark Dose Analysis of the Most Sensitive Endpoints in the Mouse and Rat Chronic Inhalation Studies[a]

Species	Endpoint	Sex	BMC_{05} (ppb)	$BMCL_{05}$ (ppb)	HEC (ppb)	
					Child	Adult
Mouse[b]	**Bronchiectasis[c]**	M	69 (93)	50 (68)	27 (37)	57 (78)
		F	56 (76)	43 (59)	23 (32)	49 (68)
		M/F	**62** (84)	**49** (67)	**27** (36)	**56** (77)
	Epithelial Hyalin Inclusions	M	480	290	160	333
		F	180	100	54	115
	Rhinitis	M	280	130	70	149
		F	150	120	65	138
	Alveolar Histiocytosis	M	300	190	100	218
		F	370	150	82	172
Rat[d]	Rhinitis	M	800	230	67	141

a Benchmark dose estimates shown for the probit model only.
b Burleigh-Flayer *et al.*, 1995
c The BMCL was calculated with a BMR of 2.5% due to greater concern about this irreversible lesion. The BMCL at the 5% response level was also calculated for comparison and is shown in parentheses. The incidence for both sexes was combined since the responses were very similar.
d Burleigh-Flayer and Benson, 1995

including a SOS chromotest with *E. coli*, a single-cell gel electrophoresis (SCGE) assay with Chinese hamster ovary (CHO) cells and a Comet assay with TK6 cells (Giller *et al.*, 1995; Plewa *et al.*, 2004; Liviac *et al.*, 2009). With the Comet assay, the level of DNA damage was reported to be higher than that seen with positive controls, however, this damage appears to be easily repaired based on the repair kinetics that were analyzed with this assay. Since these DNA damage assays are not commonly conducted assays, there is some uncertainty about their relative sensitivity. Furthermore, there are no FIFRA guidelines for these studies. Chloropicrin was also consistently positive in reverse mutation assays with bacterial systems, including eight with *Salmonella typhimurium* and two with *Escherichia coli*, one of which met FIFRA guidelines (Shirasu *et al.*, 1982; Haworth *et al.*, 1983; Moriya et al, 1983; Kawai *et al.*, 1987; San and Wagner, 1990; Sariaslani and Stahl, 1990; Giller *et al.*, 1995; Schneider *et al.*, 1999). In six of these eight studies, the positive responses were seen with S. typhimurium TA100 strain with activation. Schneider *et al.* (1999) reported the dechlorination products, $CHCl_2NO_2$ and CH_2ClNO_2, were also mutagenic with and without GSH. The investigators suggested that the mutagenicity of chloropicrin may be due to its reductive dechlorination or from a reactive intermediate GSH conjugate, such as $GSCCl_2NO_2$ or $GSCHClNO_2$. Two *in vitro* tests for clastogenicity were positive, including an *in vitro* chromosomal aberrations assay with CHO

cells (Putman and Morris, 1990) and a sister chromatid exchange assay with human lymphocytes (Garry *et al.*, 1990). The assay with CHO cells did meet FIFRA guidelines; however, it was unclear if the sister chromatid exchange assay met FIFRA guidelines due to insufficient information. One sex-linked recessive lethal (SLRL) assay in *Drosophila melanogaster* had equivocal results (Valencia *et al.*, 1985), but there was also insufficient information to determine if this study met FIFRA guidelines.

There were a number of negative assays including another SLRL assay with *Drosophila* (Auerbach, 1950), a wing-spot test with *Drosophila* (García-Quispes *et al.*, 2009), a forward mutation assay with L5178Y TK+/- mouse lymphoma cells (San and Sigler, 1990), another chromosomal aberrations assay using cultured human lymphocytes (Garry *et al.* 1990), an *in vitro* micronucleus assay with TK6 cells and human lymphocytes (Liviac *et al.*, 2009), two *in vivo* micronucleus assays, one with *Pleurodeles waltl* newt larvae (Giller *et al.*, 1995) and another with mice (Mehmood, 2003a), two *in vitro* unscheduled DNA synthesis (UDS) assays, one with rat primary hepatocytes (Curren, 1990) and another with TK6 cells (Liviac *et al.*, 2009) and an *in vivo* UDS assay with rats (Mehmood, 2003b). Four of the negative assays met FIFRA guidelines (forward mutation assay, mouse micronucleus assay and both UDS assays), however, it is unclear if the other assays met FIFRA guidelines because there was insufficient information or there were no guidelines for those assays. Although the SLRL assay is an *in vivo* assay for mutagenicity, there is more uncertainty in extrapolating from this invertebrate species to humans than from a mammalian species. The toxicological significance of the *in vivo* micronucleus assay with newt larvae is also uncertain since this amphibian species is not the typical test organism for this assay and it introduces more uncertainty in extrapolating to humans than with a mammalian species. The UDS assays were also not very meaningful since this assay has a reputation for not being very sensitive. The negative results in the forward mutation assay in mouse lymphoma cells could be considered more meaningful than the reverse mutation assays with bacteria because it used mammalian cells, however, this assay was found to not correlate as well as the reverse mutation assay with the results from NTP rodent carcinogenicity studies. A comparison of results from four *in vitro* genotoxicity assays (Tennant *et al.*, 1987; Zeiger *et al.*, 1990) with the results from 114 NTP rodent cancer bioassays found that the reverse mutation assay with *Salmonella* was the most useful based on its positive predictivity and correlation and that the mouse lymphoma assay was the least useful. None of the *in vivo* assays for chloropicrin were positive, however, there was clear evidence of genotoxicity with *in vitro* testing including three assays for DNA damage, all eight reverse mutation assays with *Salmonella*, and two assays for clastogenicity. Therefore, based on this clear evidence of genotoxicity *in vitro*, DPR concluded a genotoxic mode of action for tumor formation was more likely than not.

There was a significant increase in tumors in two carcinogenicity studies for chloropicrin. In a 78-week mouse inhalation study, there was a slight increase in adenomas of the lung in females that was significant by trend analysis ($p < 0.05$) , but not by the Fisher's exact test (Burleigh-Flayer *et al.*, 1995). When combined with the carcinomas the trend was significant at $p < 0.01$ and the p-value for Fisher's exact approached statistical significance (0.053). The combined tumor incidence was further examined using the Poly-3 trend test which takes survival into consideration. This test also includes an pair-wise comparison test similar to the Fisher's exact test. Using this test, not only was the increase in combined tumors significant by trend analysis ($p < 0.01$), but the incidence at the high dose was significant by pair-wise comparison ($p < 0.05$). No historical control data were available from the laboratory where the study was conducted. However, the incidence of the pulmonary adenomas in the female mice at the high

dose (37%) was clearly outside the historical control range reported by the supplier (0-27%) during a similar time period (Giknis and Clifford, 2000). In addition, the number of animals with multiple lung adenomas and/or carcinomas increased in females (3/48, 3/48, 6/47 and 9/49). The average time to tumor was also slightly shorter in the high dose females (554, 562, 564 and 543 days at 0, 100, 500 and 1,000 ppb, respectively). The increase in these lung tumors in males was not significant either by trend analysis or Fisher's exact, but several factors may have contributed to this. The incidence of the pulmonary adenomas in control males (16/49 or 33%) was outside the historical control range (0-28%) and may have masked the increase at the high dose. It has also been reported that the body weight reductions can reduce the incidence of certain tumors in mice and rats, including lung tumors in male mice (Seilkop, 1995). This may be related to reduced caloric intake. Tumor incidence can be seriously diminished when the mean body weights are reduced as little as 10%. Reductions in body weights did not have the same effect on the incidence of lung tumors in female mice according to this study. Another consideration in the interpretation of the findings from the mouse inhalation carcinogenicity study is the length of the study. If the exposure had been longer (e.g., 104 weeks rather than 78 weeks), the increase in tumors might have been more dramatic. A higher incidence in tumors might also have been seen if higher dose levels were tested.

An increase in fibroadenomas was also seen in mammary glands of female rats with oral exposure to chloropicrin (Slauter, 1995). The increase was significant by trend analysis ($p < 0.001$) and by pair-wise comparison with controls at the high dose ($p < 0.05$). The increase at the high dose (34%) was within the historical control range for this laboratory (up to 55%) so there is some uncertainty about the toxicological significance of the increase in these tumors. However, a slight increase in fibroadenomas was also seen in female rats with inhalation exposure (Burleigh-Flayer and Benson, 1995). In this study, the increase was not statistically significant and was within the historical control range for this laboratory. Other evidence of carcinogenicity in the oral studies included the occurrence of a few rare tumors in the stomachs of mice (squamous cell carcinomas in 2 males at 66 mg/kg/day and papilloma in one female at 33 mg/kg/day) (NCI, 1978) and rats (papilloma in one male at 10 mg/kg/day) (Slauter, 1995). Reduced survival was observed in two of the three oral carcinogenicity studies and may have affected the incidence of late-appearing tumors. Due to the high toxicity of chloropicrin, it may be difficult to demonstrate its carcinogenicity or genotoxicity *in vivo* without affecting survival. Also, the evidence from the Comet assay that the DNA damage caused by chloropicrin is readily repaired suggests that an increase in unrepaired genetic damage or tumors may not occur until the DNA repair system is overwhelmed.

Based on the weight of evidence which is summarized in Table 19, it was determined that the tumor data could not be dismissed. Not only was there a significant increase in tumors in two different species in two different laboratories, but chloropicrin is electrophilic and there was clear evidence of DNA damage, gene mutation and clastogenicity in the *in vitro* genotoxicity tests for chloropicrin. Although the increase in tumors was not dramatic in either carcinogenicity study and all of the *in vivo* genotoxicity tests were negative, a health protective assumption was made that a genotoxic mode of action was involved based on the electrophilic structure and the positive *in vitro* genotoxicity tests. Generally, when a genotoxic mode of action is involved the dose response is assumed to be linear when estimating the carcinogenic potency. It should be noted that even when the mode of action is uncertain, the U.S. EPA Guidelines for Carcinogen Risk Assessment recommends that a linear approach be used as a

Table 19. Evidence Supporting a Quantitative Assessment of Carcinogenicity.

1. Chloropicrin is a strong electrophile
2. Chloropicrin tested positive in three in vitro tests for DNA damage a. SOS chromotest with *E. coli*[1] b. SCGE assay with Chinese hamster ovary (CHO) cells[2] c. Comet assay with TK6 cells[3]
3. Chloropicrin was positive in all 8 reverse mutation assays with *Salmonella*[4-11] a. In 6 of 8 studies, the positive responses were seen with TA100 strain with activation
4. Two *in vitro* tests for clastogenicity were positive a. Chromosomal aberrations assay with CHO cells[12] b. Sister chromatid exchange assay with human lymphocytes[13]
5. Female mice exposed to chloropicrin vapors for 78 weeks had an increase in pulmonary adenomas and carcinomas[14] a. Combined incidence was significant by trend analysis ($p < 0.01$) and by pair-wise comparison at the high-dose ($p < 0.05$), when adjusted for survival b. Incidence of adenomas at the high dose (37%) was clearly outside the historical control range reported by the supplier (0-27%) during a similar time period[15] c. Increase in the multiplicity of these tumors was significant by trend analysis d. There was a slight reduction in time to tumors at the high dose e. Tumor incidence might have been higher if: 1) Study duration were 104 weeks rather than 78 weeks 2) Dose levels were higher 3) Body weights and caloric intake were not reduced
6. Female rats administered chloropicrin daily for 2 years by oral gavage had an increase mammary fibroadenomas[16] a. Increase was significant by trend analysis ($p < 0.05$) and by pair-wise comparison at the high dose ($p < 0.05$)
1. Giller *et al.*, 1995; 2. Plewa *et al.*, 2004; 3. Liviac *et al.*, 2009; 4. Shirasu *et al.*, 1982; 5. Haworth *et al.*, 1983; 6. Moriya et al, 1983; 7. Kawai *et al.*, 1987; 8. San and Wagner, 1990; 9. Sariaslani and Stahl, 1990; 10. Giller *et al.*, 1995; 11. Schneider *et al.*, 1999; 12. Putman and Morris, 1990; 13. Garry *et al.*, 1990; 14. Burleigh-Flayer *et al.*, 1995; 15. Giknis and Clifford, 2000; 16. Slauter, 1995

default (U.S. EPA, 2005). Consequently, a linear dose response was assumed in evaluating the carcinogenic potential of chloropicrin even considering the uncertainty regarding the mode of action.

III.A.5.a. Quantitative Assessment of Carcinogenic Effects

The combined incidence of lung adenomas and carcinomas in female mice in the carcinogenicity study conducted by Burleigh-Flayer *et al.* (1995) was used to estimate the carcinogenic potency of chloropicrin. The adjusted incidence from the Poly-3 trend test was used to estimate potency with the Multistage Cancer model in the BMDS software. The air concentrations from the mouse study were first converted to mg/kg/day (mg/kg/day = ppm x

M.Wt./M.Vol. x RR_a x 6 hrs/24 hrs x 5 days/7days) and then converted to human equivalent dose by multiplying by an interspecies scaling factor of body weight to the 3/4 power $[(BWt_A/BWt_H)^{0.25} = (0.030\ kg/70\ kg)^{0.25} = 0.144]$ (U.S. EPA, 2005). The resulting adjusted dosages were 0, 0.031, 0.155 and 0.311 mg/kg/day. The estimated carcinogenic potency for chloropicrin ranged from 1.3 $(mg/kg/day)^{-1}$ (maximum likelihood estimate or MLE) to 2.2 $(mg/kg/day)^{-1}$ (95% upper bound or 95% UB).

III.A.6. Reference Concentrations

The reference concentration (RfC) is the air concentration at which no adverse effects are expected to occur in humans. RfCs were calculated for chloropicrin for acute, seasonal and chronic exposures. Generally, the RfCs are calculated by dividing the NOEL or BMC (after conversion to a HEC) by a default uncertainty factor of 100 when the NOEL is from an animal study to account for interspecies and intraspecies variation in sensitivity. When the NOEL is from a human study the NOEL was divided by a default uncertainty factor of 10 for intraspecies variation.

$$RfC\,(ppb) = \frac{HEC\,(ppb)}{uncertainty\ factor\ (e.g., 100)}$$

$$RfC\ (\mu g/m^3) \quad = \quad RfC\ (ppb)\ x\ \frac{M.Wt.\ (164.38\,g)}{M.Vol.\ (24.45L\ @\ 25^o\,C)}$$

The critical endpoints, HECs and reference concentrations selected for use in this risk assessment are summarized in Table 20. A $BMCL_{05}$ of 44 ppb (299 $\mu g/m^3$) was selected as the NOEL for evaluating acute 1-hr exposures to chloropicrin based on the increase in NO in expired nasal air in humans after a 1-hour exposure (Cain, 2004). No adjustment was made for differences in breathing rate for this endpoint since it was observed in humans and involved only the upper respiratory tract. An uncertainty factor of 10 was applied to the NOEL for increase NO in expired nasal air in humans; therefore, the 1-hr RfC for chloropicrin is 4.4 ppb (30 $\mu g/m^3$) for both children and adults.

Due to the uncertainty about the application of Haber's Law to the more sensitive endpoints in the human study, 8-hr and 24-hr NOELs were derived from a developmental toxicity study in rabbits in which the does were exposed for 6 hours/day (York, 1993). The acute maternal effects observed at the LOEL in this study included nasal discharge, reduced food consumption and body weights and mortalities associated with red discolored lungs during the first few days of exposure. Since these severe effects appear to be more than local effects, Haber's Law was assumed to estimate 8-hr and 24-hr NOELs. The 8-hr and 24-hr NOELs were estimated to be 300 ppb (2,000 $\mu g/m^3$) and 100 ppb (670 $\mu g/m^3$), respectively. The 8-hr HECs were 270 ppb (1,800 $\mu g/m^3$) and 580 ppb (3,900 $\mu g/m^3$) for children and adults, respectively. The 24-hr HECs were 92 ppb (610 $\mu g/m^3$) and 190 ppb (1,300 $\mu g/m^3$) for children and adults, respectively. An uncertainty factor of 100 was applied to the HECs derived from the animal studies to allow for interspecies and intraspecies variation in sensitivity; therefore, the 8-hr RfCs are 2.7 ppb (18 $\mu g/m^3$) and 5.8 ppb (39 $\mu g/m^3$) for children and adults, respectively. The 24-hr RfCs are 0.92 ppb (6.1 $\mu g/m^3$) and 1.9 ppb (13 $\mu g/m^3$) for children and adults, respectively.

Table 20. DPR Critical Endpoints, Human Equivalent Concentrations and Reference Concentrations for Chloropicrin

Exposure Scenario	Critical Endpoints	HEC		RfC	
		Children	Adults	Children	Adults
Acute - 1 hr	↑ NO in nasal air in humans	44 ppb	44 ppb	4.4 ppb UF[a] = 10	4.4 ppb UF = 10
Acute - 8 hr & 24 hr	Mortalities (days 2-4), nasal discharge (onset day 0), ↓ body weights & food consumption (days 0-6), red discoloration in lungs of pregnant rabbits.	8-hr 270 ppb 24-hr 92 ppb	8-hr 580 ppb 24-hr 190 ppb	8-hr 2.7 ppb 24-hr 0.92 ppb UF = 100	8-hr 5.8 ppb 24-hr 1.9 ppb UF = 100
Seasonal	Rhinitis in female rats	35 ppb	73 ppb	0.35 ppb UF = 100	0.73 ppb UF = 100
Chronic	Bronchiectasis in male and female mice	27 ppb	56 ppb	0.27 ppb UF = 100	0.56 ppb UF = 100
Lifetime	Lung tumors in female mice	Potency = 2.2 $(mg/kg/day)^{-1}$		-------	0.24 ppt[b]

[a] UF = Uncertainty factor used to derive RfC.
[b] RfC for cancer is the air concentration corresponding to a negligible risk level (i.e., one in a million excess cancer cases)

The 90-day inhalation study in rats was selected as the definitive study for evaluating seasonal inhalation exposure with a critical NOEL of 120 ppb (807 $\mu g/m^3$) based on the $BMCL_{05}$ for rhinitis in females (Chun and Kintigh, 1993). The subchronic HECs were 35 ppb (230 $\mu g/m^3$) for children and 73 ppb (490 $\mu g/m^3$) for adults. The subchronic RfCs are 0.35 ppb (2.3 $\mu g/m^3$) and 0.73 ppb (4.9 $\mu g/m^3$) for children and adults, respectively.

The 78-wk inhalation study in mice was selected as the definitive study for evaluating chronic inhalation exposure to chloropicrin with a critical NOEL of 43 ppb (289 $\mu g/m^3$) based on the $BMCL_{25}$ for bronchiectasis in males and females (Burleigh-Flayer *et al.*, 1995). The chronic HECs were 27 ppb (179 $\mu g/m^3$) for children and 56 ppb (378 $\mu g/m^3$) for adults. The chronic RfCs are 0.27 ppb (1.8 $\mu g/m^3$) and 0.56 ppb (3.8 $\mu g/m^3$) for children and adults, respectively.

Generally, RfDs/RfCs are not calculated for carcinogenicity since it is assumed there is no threshold for this endpoint. However, it is possible to calculate a dose or air concentration at which the carcinogenic risk is negligible. To do this, the negligible risk level (1×10^{-6}) is divided by the 95% UB estimate of carcinogenic potency (2.2 $(mg/kg/day)^{-1}$). For chloropicrin, the exposure dosage or RfD corresponding to a negligible carcinogenic risk is 0.45 ng/kg/day. The exposure dosage was converted to an air concentration by dividing by the estimated breathing rate for an adult male (0.28 m^3/kg/day). The air concentration below which there would be no regulatory concern for carcinogenic effects is 0.24 ppt (1.6 ng/m^3).

III.B. EXPOSURE ASSESSMENT

III.B.1. Occupational Exposure

III.B.1.a. Soil Fumigation

Occupational exposure monitoring was conducted during and following soil fumigation using air samplers in the breathing zone of handlers and reentry workers (Beard *et al.*, 1996; Rotondaro, 2004) which is described in detail in the Exposure Assessment Document addressing occupational exposure to chloropicrin (Beauvais, 2011). Only shallow shank applications were monitored. It was assumed that the handler exposures with deep shank applications would be equal or less than with shallow shank applications. Air concentrations were corrected for recoveries less than 90%. For some scenarios such as soil shapers, tarp punchers and pipe layers, 1-hour and 4-hour samples were collected in the study conducted by Rotondoro (2004) (see Tables 20, 25, 29, 33, and 35 in the EAD). The 1-hr samples were only used for 1-hour exposure estimates if the 95th percentile was higher for the 1-hour samples than the 4-hour samples. Otherwise, both 1-hour and 8-hour estimates were based on the 95th percentile of the 4-hour samples. For short-term exposures (1-hour and 8-hr) when chloropicrin was used as an active ingredient (greater than 15% of the formulation), the air concentrations were adjusted for a maximum application rate of 350 lbs/acre for all application methods except for broadcast with Tri-Con 33/67 (266 lbs/acre), all bedded/non-tarped (175 lbs/acre), all drip irrigation (300 lbs/acre), most handwand replant (431 lbs/acre), and handwand replant with Pic-Brom 25 (163 lbs/acre). When chloropicrin was used as a warning agent, the maximum application rate was based on the maximum application rate for methyl bromide. For the 10.5% formulation, the maximum application rate for chloropicrin was 46.7, 29.3, 26.4, 68.6, and 45.7 lbs/acre for broadcast, bedded/tarped, drip irrigation, handwand replant and potting soil applications, respectively. For the formulations with less 2% chloropicrin, the maximum application rate for chloropicrin was estimated to be 8.16, 5.10, 4.59, 13.1 and 64.5 lbs/acre for broadcast, bedded/tarped, drip irrigation, handwand replant and potting soil applications, respectively. When chloropicrin was 100% of the formulation, the reentry interval was 10 days. For formulations with methyl bromide, the reentry interval was assumed to be 5 days based on new labels. 1,3-Dichloropropene product labels specify that soil should be left undisturbed for 7 days. Short-term exposure estimates were set at the 95th percentile using lognormal methods. Some short-term exposure estimates exceeded 100 ppb, however, labels require that a respirator be worn when air concentrations exceed 100 ppb.

The 1-hour exposure estimates for all application methods with soil fumigation are summarized in Table 21. With most application methods, the handlers involved in the application had the highest exposure. When chloropicrin was an active ingredient (i.e., > 15% of formulation), most of the workers involved in the application and aeration with broadcast, tarped application had 95th percentile estimates that exceeded 100 ppb, except for shovelers and soil shapers. The tarp splitters had the highest estimates at 2,310 ppb. In contrast, exposure estimates for workers involved in broadcast, untarped application were all less than 100 ppb, except for soil shapers using Tri-Con 33/67. The exposure estimates for soil shapers are higher with methyl bromide formulations due to the shorter reentry intervals. It was 7 days with Tri-Form 40/60 and 5 days with Tri-Con 33/67. Workers with the lowest 1-hour exposures (< 10 ppb) when chloropicrin was an active ingredient were soil shapers with broadcast, non-tarped application, pipe layers with bedded, non-tarped application, and tarp punchers with drip

Table 21. Estimated One-Hour Occupational Exposures to Chloropicrin Associated with Soil Fumigation[a]

Exposure Scenarios	Concentration (ppb)		
	Active Ingredient >15%	**Warning Agent 10.5%**	**Warning Agent < 2%**
Broadcast, tarped[b] Driver	196[b]	26.2	4.57
Copilot	205[b]	27.4	4.78
Shoveler	81.0	10.8	1.89
Tarp splitter	1,220[b]	162[b]	28.3
Tarp remover	2,310[b]	307[b]	53.8
Soil shaper	41.4	9.02	1.57
Soil shaper - Tri-Form 40/60	106[b]	NA	NA
Soil shaper - Tri-Con 33/67	77.3	NA	NA
Broadcast, non-tarped Driver	66.3	11.1	1.93
Soil sealer	37.7	6.35	1.10
Soil shaper - shallow	6.55	NA	NA
Soil shaper - shallow (Tri-Form 40/60)	39.3	NA	NA
Soil shaper - deep	10.7	39.1	6.80
Soil shaper - deep (Tri-Form 40/60)	56.3	NA	NA
Soil shaper - deep (Tri-Con 33/67)	356[b]	NA	NA
Bedded, tarped Driver	23.7	1.98	0.345
Copilot	39.7	3.32	0.578
Shoveler	15.5	1.30	0.226
Tarp puncher	31.0	2.60	0.452
Bedded, non-tarped Driver	56.4	NA	NA
Pipe layer	5.19	NA	NA
Pipe layer - Tri-Con 33/67	7.89	NA	NA
Drip irrigation Applicator - tarped	20.9	1.84	0.320
Tarp puncher	7.79	0.684	0.119
Applicator - non-tarped	45.4	NA	NA
Handwand replant Applicator	96.3	15.3	2.93
Applicator, Telone C-35	97.4	NA	NA
Applicator, Pic-Brom 25	36.4	NA	NA
Potting soil Tarp remover	NA	74.9	94.5

a From Tables 21, 23, 24, 26-28, 30-32, 34, 36-38, 40, and 41 in the occupational exposure assessment document (EAD) for chloropicrin (Beauvais, 2011). The estimates were derived from exposure monitoring data from Rotendoro (2004) and Beard *et al.* (1996) . When used as an active ingredient, the maximum application rate was 350 lbs/acre for all application methods except for broadcast with Tri-Con 33/67 (266 lbs/acre), all bedded/non-tarped (175 lbs/acre), all drip irrigation (300 lbs/acre), most handwand replant (431 lbs/acre), and handwand replant with Pic-Brom 25 (163 lbs/acre). For the 10.5% formulation, the maximum application rate for chloropicrin was 46.7, 29.3, 26.4, 68.6, and 45.7 lbs/acre for broadcast, bedded tarped, drip irrigation, handwand replant and potting soil applications, respectively. When chloropicrin was used as a warning agent the maximum application rate was based on the maximum application rate for methyl bromide. For the 2% formulations, the maximum application rate for chloropicrin was estimated to be 8.16, 5.10, 4.59, 13.1 and 64.5 lbs/acre for broadcast, bedded tarped, drip irrigation, handwand replant and potting soil applications, respectively. When chloropicrin was 100% of the formulation, the reentry interval was 5 days for aeration and pipe laying and 10 days for activities involving soil disturbance. For formulations with methyl bromide and 1,3-dichloropropene, the reentry interval for activities involving soil disturbance was assumed to be 5 and 7 days, respectively, based on their labels. Primarily shallow shank applications were monitored. Handler exposures for deep shank applications were assumed to be equal or less than with shallow shank application. One-hour exposures were upper bound estimates based on the 95th percentile calculated using lognormal methods. The exposure estimates were rounded to three significant figures.

b Labels require a respirator whenever chloropicrin air concentrations exceed 100 ppb. If a respirator is worn, exposure would be reduced by 90-99.99% depending on the type of respirator worn.

application with 1-hr exposure estimates ranging from 5.19 to 7.89 ppb. The 1-hour exposure estimates were all less than 100 ppb when chloropicrin was only used as a warning agent, either at 10.5% or 2%, except for tarp splitters and removers with broadcast, tarped fumigation. Generally, when chloropicrin was used as a warning agent the exposure estimates were proportionately lower compared to when it was used as an active ingredient based on the maximum application rate for chloropicrin in the formulation. The 1-hour and 8-hour exposures were the same except for when 4-hr samples were available and the 95th percentile air concentrations were lower. Therefore, the statements regarding 1-hr exposure estimates also apply to the 8-hour exposure estimates which are summarized in Table 22.

For seasonal, annual and lifetime exposure, the application rate was adjusted to the 50th percentile rate of 190, 20, and 3.8 lbs/acre when used as an active ingredient, a warning agent at 10.5% and a warning agent at 2%, respectively. The arithmetic mean of daily exposure was used for seasonal exposure. The seasonal exposure estimates for workers are summarized in Table 23. The mean air concentrations never exceeded 100 ppb even when chloropicrin was used as an active ingredient. The highest seasonal exposure estimates were around 50 ppb for copilots, tarp splitters and tarp removers for broadcast, tarped fumigation when chloropicrin was used as an active ingredient. Reentry workers for bedded applications (tarp punchers and pipe layers) had some of the lowest seasonal exposures ranging from about 0.5 to 1.0 ppb. As with short-term exposure estimates, the seasonal exposure estimates were proportionately lower when chloropicrin was used as a warning agent, depending on the maximum application rate assumed. When used as a warning agent at 2% or less, many of the seasonal exposures were less than 1 ppb, including all of the bedded application scenarios.

Annual exposure was calculated by assuming there were five high-use months in a season (i.e., annual exposure = seasonal exposure x 5 months/12months). The annual exposure estimates for workers are summarized in Table 24. When chloropicrin was used as an active ingredient the highest annual exposures were around 20 ppb for copilots, tarp splitters and tarp removers with broadcast, tarped fumigation. Some of the lowest annual exposures when chloropicrin was an active ingredient were between 0.2 and 0.5 ppb for tarp punchers and pipe layers with bedded application. When chloropicrin was used as a warning agent, the annual exposures were proportionately lower depending on the maximum application rate assumed. They ranged from 0.00824 ppb for tarp punchers with bedded, tarped application with the 2% formulations to 2.24 ppb for copilots with broadcast, tarped application with the 10.5% formulation.

For lifetime exposure, it was assumed that workers were exposed for 40 years of a 75-year lifetime (i.e., lifetime exposure = annual exposure x 40 years/75 years). Lifetime exposures were converted from air concentrations to µg/kg/day since cancer potency in expressed per mg/kg/day. The lifetime exposure estimates for workers are summarized in Table 25 in µg/kg/day. The lifetime exposure estimates ranged from 0.207 µg/kg/day for tarp punchers with bedded, tarped application to 21.3 µg/kg/day for copilots with broadcast, tarped application when chloropicrin was an active ingredient. When used as a warning agent at less than 2%, lifetime exposure estimates were proportionately lower based on the maximum application rate, ranging from 0.00826 to 0.429 µg/kg/day. Coincidently, the lifetime exposure estimates in µg/kg/day are similar to the annual exposure estimates in ppb.

Table 22. Estimated Eight-Hour Occupational Exposures to Chloropicrin Associated with Soil Fumigation[a]

Exposure Scenarios	Concentration (ppb)		
	Active Ingredient >15%	**Warning Agent 10.5%**	**Warning Agent < 2%**
Broadcast, tarped[b] Driver	196[b]	26.2	4.57
Copilot	205[b]	27.4	4.78
Shoveler	81.0	10.8	1.89
Tarp splitter	1,220[b]	162[b]	28.3
Tarp remover	2,310[b]	307[b]	53.8
Soil shaper	41.4	9.02	1.57
Soil shaper - Tri-Form 40/60	106[b]	NA	NA
Soil shaper - Tri-Con 33/67	77.3	NA	NA
Broadcast, non-tarped Driver	66.3	11.1	1.93
Soil sealer	37.7	6.34	1.10
Soil shaper - shallow	4.29	NA	NA
Soil shaper - shallow (Tri-Form 40/60)	25.7	NA	NA
Soil shaper - deep	4.59	16.7	2.92
Soil shaper - deep (Tri-Form 40/60)	24.2	NA	NA
Soil shaper - deep (Tri-Con 33/67)	152[b]	NA	NA
Bedded, tarped Driver	23.7	1.98	0.345
Copilot	39.7	3.32	0.578
Shoveler	15.5	1.30	0.226
Tarp puncher	8.17	0.682	0.119
Bedded, non-tarped Driver	56.4	NA	NA
Pipe layer	1.22	NA	NA
Pipe layer - Tri-Con 33/67	1.85	NA	NA
Drip irrigation Applicator - tarped	20.9	1.84	0.320
Tarp puncher	7.27	0.639	0.111
Applicator - non-tarped	45.4	NA	NA
Handwand replant Applicator	96.3	15.3	2.93
Applicator - Telone C-35	97.4	NA	NA
Applicator - Pic-Brom 25	36.4	NA	NA
Potting soil Tarp remover	NA	74.9	94.5

a From Tables 21, 23, 24, 26-28, 30-32, 34, 36-38, 40, and 41 in the occupational exposure assessment document (EAD) for chloropicrin (Beauvais, 2011). The estimates were derived from exposure monitoring data from Rotendoro (2004) and Beard *et al.* (1996) . When used as an active ingredient, the maximum application rate was 350 lbs/acre for all application methods except for broadcast with Tri-Con 33/67 (266 lbs/acre), all bedded/non-tarped (175 lbs/acre), all drip irrigation (300 lbs/acre), most handwand replant (431 lbs/acre), and handwand replant with Pic-Brom 25 (163 lbs/acre). For the 10.5% formulation, the maximum application rate for chloropicrin was 46.7, 29.3, 26.4, 68.6, and 45.7 lbs/acre for broadcast, bedded tarped, drip irrigation, handwand replant and potting soil applications, respectively. When chloropicrin was used as a warning agent the maximum application rate was based on the maximum application rate for methyl bromide. For the 2% formulations, the maximum application rate for chloropicrin was estimated to be 8.16, 5.10, 4.59, 13.1 and 64.5 lbs/acre for broadcast, bedded tarped, drip irrigation, handwand replant and potting soil applications, respectively. When chloropicrin was 100% of the formulation, the reentry interval was 5 days for aeration and pipe laying and 10 days for activities involving soil disturbance. For formulations with methyl bromide and 1,3-dichloropropene, the reentry interval for activities involving soil disturbance was assumed to be 5 and 7 days, respectively, based on their labels. Primarily shallow shank applications were monitored. Handler exposures for deep shank applications were assumed to be equal or less than with shallow shank application. Eight-hour exposures were upper bound estimates based on the 95th percentile calculated using lognormal methods. The exposure estimates were rounded to three significant figures.

b Labels require a respirator whenever chloropicrin air concentrations exceed 100 ppb. If a respirator is worn, exposure would be reduced by 90-99.99% depending on the type of respirator worn.

Table 23. Estimated Seasonal Occupational Exposures to Chloropicrin Associated with Soil Fumigation[a]

Exposure Scenarios	Concentration (ppb)		
	Active Ingredient >15%	**Warning Agent 10.5%**	**Warning Agent < 2%**
Broadcast, tarped			
Driver	40.9	4.29	0.818
Copilot	51.2	5.38	1.02
Shoveler	17.9	1.88	0.358
Tarp splitter	49.5	5.20	0.990
Tarp remover	50.0	5.25	1.00
Soil shaper	5.76	0.605	0.115
Soil shaper - Tri-Form 40/60	3.46	NA	NA
Soil shaper - Tri-Con 33/67	3.84	NA	NA
Broadcast, non-tarped			
Driver	19.7	2.07	0.394
Soil sealer	8.65	0.908	0.173
Soil shaper - shallow	2.62	NA	NA
Soil shaper - shallow (Tri-Form 40/60)	1.57	NA	NA
Soil shaper - deep	1.64	0.172	0.0328
Soil shaper - deep (Tri-Form 40/60)	0.984	NA	NA
Soil shaper - deep (Tri-Con 33/67)	1.09	NA	NA
Bedded, tarped			
Driver	4.92	0.517	0.0984
Copilot	6.22	0.653	0.124
Shoveler	3.55	0.373	0.0710
Tarp puncher	0.495	0.052	0.0198
Bedded, non-tarped			
Driver	23.0	NA	NA
Pipe layer	1.17	NA	NA
Pipe layer - Tri-Con 33/67	0.850	NA	NA
Drip irrigation			
Applicator - tarped	6.20	0.651	0.124
Tarp puncher	1.86	0.195	0.0372
Applicator - non-tarped	8.29	NA	NA
Handwand replant			
Applicator	9.72	1.02	0.194
Applicator - Telone C-35	3.37	NA	NA
Applicator - Pic-Brom 25	2.43	NA	NA
Potting soil			
Tarp remover	NA	5.25	1.00

a From Tables 21, 23, 24, 26-28, 30-32, 34, 36-38, 40, and 41 in the occupational exposure assessment document (EAD) for chloropicrin (Beauvais, 2011). The estimates were derived from exposure monitoring data from Rotendoro (2004) and Beard *et al.* (1996) assuming a 50th percentile application rate of 190, 20, and 3.8 lbs/acre when used as an active ingredient, warning agent at 10.5% and warning agent at 2%, respectively. Primarily shallow shank applications were monitored. Handler exposures for deep shank applications were assumed to be equal or less than with shallow shank application. Seasonal exposures were based on the arithmetic mean rather than the geometric mean because the arithmetic mean gives it weight in proportion to their probability. The exposure estimates were rounded to three significant figures.

Table 24. Estimated Annual Occupational Exposures to Chloropicrin Associated with Soil Fumigation[a]

Exposure Scenarios	Dose (µg/kg/day)		
	Active Ingredient >15%	**Warning Agent 10.5%**	**Warning Agent < 2%**
Broadcast, tarped			
Driver	17.1	1.79	0.341
Copilot	21.3	2.24	0.427
Shoveler	7.46	0.783	0.149
Tarp splitter	20.7	2.17	0.414
Tarp remover	20.8	2.19	0.417
Soil shaper	2.41	0.252	0.0480
Soil shaper - Tri-Form 40/60	1.44	NA	NA
Soil shaper - Tri-Con 33/67	1.60	NA	NA
Broadcast, non-tarped			
Driver	8.19	0.860	0.164
Soil sealer	3.60	0.378	0.0720
Soil shaper - shallow	1.09	NA	NA
Soil shaper - shallow (Tri-Form 40/60)	0.655	NA	NA
Soil shaper - deep	0.683	0.0718	0.0137
Soil sahper - deep (Tri-Form 40/60)	0.410	NA	NA
Soil shaper - deep (Tri-Con 33/67)	0.455	NA	NA
Bedded, tarped			
Driver	2.05	0.215	0.0410
Copilot	2.59	0.272	0.0518
Shoveler	1.48	0.155	0.0296
Tarp puncher	0.207	0.0217	0.00824
Bedded, non-tarped			
Driver	9.58	NA	NA
Pipe layer	0.488	NA	NA
Pipe layer - Tri-Con 33/67	0.354	NA	NA
Drip irrigation			
Applicator - tarped	2.59	0.272	0.0518
Tarp puncher	0.773	0.0812	0.0155
Applicator - non-tarped	3.45	NA	NA
Handwand replant			
Applicator	2.42	0.254	0.0484
Applicator - Telone C-35	0.840	NA	NA
Applicator - Pic-Brom 25	0.605	NA	NA
Potting soil			
Tarp remover	NA	1.75	NA

a From Tables 21, 23, 24, 26-28, 30-32, 34, 36-38, 40, and 41 in the occupational exposure assessment document (EAD) for chloropicrin (Beauvais, 2011). The estimates were derived from exposure monitoring data from Rotendoro (2004) and Beard *et al.* (1996) assuming a 50th percentile application rate of 190, 20, and 3.8 lbs/acre when used as an active ingredient, warning agent at 10.5% and warning agent at 2%, respectively. Primarily shallow shank applications were monitored. Handler exposures for deep shank applications were assumed to be equal or less than with shallow shank application. Annual exposures were estimated assuming a 5-month high-use season (i.e., annual exposure = seasonal exposure x (5 months/12 months)). The exposure estimates were rounded to three significant figures.

Table 25. Estimated Lifetime Occupational Exposures to Chloropicrin Associated with Soil Fumigation[a]

Exposure Scenarios	Dose (µg/kg/day)		
	Active Ingredient >15%	**Warning Agent 10.5%**	**Warning Agent < 2%**
Broadcast, tarped			
Driver	17.2	1.80	0.343
Copilot	21.3	2.24	0.429
Shoveler	7.51	0.787	0.150
Tarp splitter	20.7	2.18	0.416
Tarp remover	20.9	2.20	0.418
Soil shaper	2.41	0.252	0.0482
Soil shaper - Tri-Form 40/60	1.45	NA	NA
Soil shaper - Tri-Con 33/67	0.852	NA	NA
Broadcast, non-tarped			
Driver	8.23	0.864	0.165
Soil sealer	3.61	0.380	0.0723
Soil shaper - shallow	1.10	NA	NA
Soil shaper - shallow (Tri-Form 40/60)	0.657	NA	NA
Soil shaper - deep	0.685	0.0721	0.0137
Soil shaper - deep (Tri-Form 40/60)	0.412	NA	NA
Soil shaper - deep (Tri-Con 33/67)	0.243	NA	NA
Bedded, tarped			
Driver	2.05	0.216	0.0412
Copilot	2.60	0.273	0.0520
Shoveler	1.48	0.156	0.0297
Tarp puncher	0.207	0.0218	0.00826
Bedded, non-tarped			
Driver	9.62	NA	NA
Pipe layer	0.489	NA	NA
Pipe layer - Tri-Con 33/67	0.356	NA	NA
Drip irrigation			
Applicator - tarped	2.60	0.273	0.0520
Tarp puncher	0.776	0.0815	0.0155
Applicator - non-tarped	3.46	NA	NA
Handwand replant			
Applicator	2.43	0.256	0.0486
Applicator - Telone C-35	0.843	NA	NA
Applicator - Pic-Brom 25	0.606	NA	NA
Potting soil			
Tarp remover	NA	1.87	0.335

a Derived from Tables 21, 23, 24, 26-28, 30-32, 34, 36-38, 40, and 41 in the occupational exposure assessment document (EAD) for chloropicrin (Beauvais, 2011) converting lifetime exposure in ppb to µg/kg/day. The estimates were derived from exposure monitoring data from Rotendoro (2004) and Beard *et al*. (1996) assuming a 50th percentile application rate of 190, 20, and 3.8 lbs/acre when used as an active ingredient, warning agent at 10.5% and warning agent at 2%, respectively. Primarily shallow shank applications were monitored. Handler exposures for deep shank applications were assumed to be equal or less than with shallow shank application. Lifetime exposures were estimated assuming they worked 40 years in a 75-year lifetime (i.e., lifetime exposure = annual exposure x (40 years /75 years)). The exposure estimates were rounded to three significant figures.

III.B.1.b. Structural Fumigation

Four monitoring studies of structural fumigation where chloropicrin was used as a warning agent were considered in estimating occupational exposure to chloropicrin (Beauvais, 2011). Maddy *et al.* (1986) monitored structural fumigation of seven houses with methyl bromide where chloropicrin was used as a warning agent. In addition to monitoring indoor air concentrations during fumigation, workers wore personal air samplers during tarp removal and aeration. This study had the highest indoor air concentration of chloropicrin during the first two-hour interval of fumigation, so it was used to estimate occupational exposure during fumigation introduction. Also, the air concentrations from the personal air samplers in this study were used to estimate exposure during tarp removal, testing for clearance and reentry. Lee and Liscombe (1993) measured air concentrations of chloropicrin inside houses and under tarps during fumigation of ten houses with methyl bromide or sulfuryl fluoride. However, the structures were not supposed to be occupied during this time and no post-aeration samples were collected, so this study was not used to evaluate occupational exposure. ARB conducted air monitoring for chloropicrin during fumigation and 24 hours following aeration of three houses with sulfuryl fluoride (2003d and 2005a&b), however, indoor air concentrations were not monitored in one study (2005b), so that study was not considered in estimating occupational exposure to chloropicrin. The other two ARB studies were ultimately not used either, because air concentrations in other studies were higher. Barnekow and Byrne (2006) monitored indoor air concentrations during and following fumigation of eight houses with sulfuryl fluoride for up to 36 hours following aeration. This study had the highest air concentrations outside the house during the first 2-hours of fumigation and during aeration, so these air concentrations were used to estimate occupational exposure during tarp inspection and during aeration. For details on the air concentrations and assumptions used to estimate occupational exposure for structural fumigation see Table 43 of the EAD (Beauvais, 2011). Exposures were adjusted assuming a maximum application rate of 0.0107 lbs/ft^3. A survey by Contardi and Lambesis (1996) was used to estimate the amount of time each worker spent on various activities related to structural fumigation. Table 26 in this document summarizes the occupational exposure estimates for chloropicrin associated with structural fumigation. The 1-hr and 8-hr exposures for applicators, aerators and fumigators all exceeded 100 ppb which requires a respirator be worn. The 1-hr exposures ranged from 43.7 ppb for tarp removers during aeration to 4,760 ppb for applicators and fumigators. The 8-hr exposures were the same as the 1-hr exposures for tarp removers and reentry workers, but applicators and aerators were not expected to work on any one site more than 1 hour and fumigators were assumed to work 1 hour as an applicator, 1 hr as a aerator and 6 hours as a tarp remover resulting in a lower exposure (723 ppb) when averaged over an 8-hr period. Seasonal, annual and lifetime exposure for workers involved in structural fumigation continued to be fairly high because it was assumed their exposure was 180 days/year for tarp removers and reentry workers and 196 days/year for fumigators. Seasonal exposures ranged from 15.8 ppb for tarp removers to 62.2 ppb for fumigators. Annual was approximately half of seasonal exposure ranging from 7.79 to 33.4 ppb. Lifetime exposure estimates were about one quarter of seasonal when expressed in ppb, however, the lifetime exposure estimates for structural fumigation are expressed in µg/kg/day in Table 26 ranging from 7.83 to 33.5 µg/kg/day.

Table 26. Occupational Exposure Estimates for Structural Fumigation with Chloropicrin[a]

Exposure Scenario	Dose (ppb)				
	1-Hour[b]	8-Hour[b]	Seasonal[c]	Annual[d]	Lifetime[e]
Applicator	4,760[f]	NA[g]	NA	NA	NA
Tarp Remover	43.7	43.7	15.8	7.79	7.83
Aerator	758[f]	NA	NA	NA	NA
Fumigator	4,760[f]	723[f]	62.2	33.4	33.5
Reentry	123[f]	123[f]	35.9	17.7	17.8

a Summarized from Table 44 of the occupational exposure assessment document (EAD) for chloropicrin (Beauvais, 2011). Occupational exposure estimates were based on monitoring conducted by Maddy *et al.* (1986) and Barnekow and Byrne (2006) during fumigation of houses with methyl bromide or sulfuryl fluoride where chloropicrin was a warning agent at 0.0107 lbs/1,000 ft^3.
b Short-term exposure estimates represent the highest realistic exposure estimates covering 1 hour to 1 week.
c Seasonal exposure represents the average daily exposure estimates.
d Assumes 180 days/year for tarp removers and reentry workers and 196 days/year for fumigators (e.g., seasonal exposure x 180 days/365 days).
e Assumes 40 years of work exposure over a 75-year lifetime (i.e., annual exposure x 40 years/75 years). Dose expressed in µg/kg/day.
f Labels require a respirator whenever chloropicrin air concentrations exceed 100 ppb. If a respirator is worn, exposure would be reduced by 90-99.99% depending on the type of respirator worn.
g NA=Not applicable

III.B.2. Bystander Exposure

III.B.2.a. Soil Fumigation

Individuals might be exposed to chloropicrin if they are working or standing adjacent to fields that are being treated or have recently been treated (i.e., bystander exposure). Two types of air monitoring studies were conducted following soil fumigation with chloropicrin where air samples were collected either on-site for direct estimation of field volatility or flux or off-site (See Barry (2008) and Beauvais (2011) for detailed description of these studies). Preliminary studies of off-site air concentrations were conducted by DPR in 1982 and 1983 in Orange County (Maddy *et al.*, 1983 & 1984). However, the application rate and percentage of chloropicrin in the methyl bromide/chloropicrin mixture were not reported, so these studies were not used. Off-site monitoring was conducted by the Air Resources Board (ARB) in 1986, 2001, 2003 and 2005. The 1986 study monitored off-site air concentrations following a tarped broadcast application in Monterey County (ARB, 1987). However, the methyl bromide/-chloropicrin formulation, field size and application rate were not reported. Due to insufficient information, this study was not used in analyzing the off-site air concentrations for chloropicrin. The ARB monitoring in 2001 was conducted in Monterey County following a shank tarped bed application of a methyl bromide/chloropicrin 50:50 mixture (ARB, 2003c). In 2003, ARB monitored off-site air concentrations in Santa Cruz County after a shallow shank tarped bed application of a methyl bromide/chloropicrin 50:50 mixture (ARB, 2004). In 2005, off-site air concentrations were monitored by ARB in Santa Barbara County following a drip tarped bed application of 94% chloropicrin (ARB, 2006). Two off-site monitoring studies were also

conducted by registrants (Beard *et al.*, 1996; Rotondaro, 2004). Beard *et al.* (1996) monitored off-site air concentrations in Washington (broadcast tarped application), Florida (broadcast tarped application) and Phoenix, Arizona (broadcast tarped, broadcast non-tarped, bedded tarped and bedded non-tarped applications) following the application of 99.4% chloropicrin. Rotondaro (2004) monitored off-site air concentrations after field and greenhouse surface drip applications of 99.1% chloropicrin in California.

The two off-site air monitoring studies conducted by the registrants also characterized the flux for chloropicrin on-site following the soil fumigation (Beard *et al.*, 1996; Rotondaro, 2004). Flux (expressed as $\mu g/m^2/sec$) is the rate at which a chemical moves out from the ground into the air. Direct measurement of flux measures air concentrations on a mast in the center of the field. Since off-site air concentrations were dependent on environmental conditions, it is unlikely that the highest possible air concentrations were encountered during a particular study. Therefore, the flux data along with air modeling were used to estimate off-site air concentrations for a worse case scenario. The flux following the applications in Washington and Florida was lower than that following the applications in Arizona in the study conducted by Beard *et al.* (1996) and, therefore, was not further considered in the exposure assessment. From the on-site monitoring, DPR estimated the maximum 6-hour and 24-hour time-weighted average (TWA) chloropicrin flux (Barry, 2008). From these maximum 6-hr and 24-hr flux estimates, DPR then calculated rate adjusted air concentrations for 1.2 m (4 ft) above ground (breathing zone) and 3 m (10 ft) from the edge of a 40-acre square field using the Industrial Source Complex Short Term model, Version 3 (ISCT3). The model generated downwind centerline estimates of reasonable worst-case air concentrations for the different application methods at the maximum application rate for 6-hours and 24-hours (TWA). Table 27 summarizes highest exposure estimates for bystanders using the different application methods based on the reasonable worst case air concentrations from modeling. The highest day or night 6-hr air concentration with each application method was used for their respective 1-hr and 8-hr exposure estimates. Since 6 hours was the shortest monitoring interval for flux, 1-hr exposure estimates were calculated using a peak-to-mean ratio as described in Barry (2008). The 1-hr exposure estimates ranged from 11,000 to 75,000 $\mu g/m^3$ (1,600 to 11,000 ppb)[20]. The 6-hr air concentrations were not adjusted for time for the 8-hr exposure estimates. The 8-hr exposure estimates were between 4,700 and 31,000 $\mu g/m^3$ (700 to 4,600 ppb). The 24-hr exposure estimates ranged from 1,100 to 5,400 $\mu g/m^3$ (160 to 800 ppb). For periods of 24 hours or less, it was assumed a bystander was located downwind throughout the entire exposure period. For the subchronic and chronic exposure, this assumption was unrealistic since wind direction would change. Therefore, the seasonal exposure was estimated from 2-week TWA air concentrations which were calculated by first taking a 24-hr average flux over 2 weeks and then adjusting with a time-scaling factor using the peak-to-mean theory. In addition, the air concentrations were adjusted for the typical application rate instead of the maximum application rate. The seasonal exposure estimates were between 29 and 230 $\mu g/m^3$ (4.3 to 34 ppb). The annual exposure was estimated from the 2-week average air concentration assuming it was used 5 months out of the year. The annual exposure estimates ranged from 12 to 96 $\mu g/m^3$ (1.8 and 14 ppb). The highest estimates for 1-hr to 24-hr exposures were for broadcast, non-tarped application. Bedded, tarped application had the highest seasonal and annual exposure estimates.

20 The exposure estimates were rounded to two significant figures for both $\mu g/m^3$ and ppb.

Table 27. Estimated Bystander Exposure to Chloropicrin Following Soil Fumigation[a]

Exposure Duration Scenarios	Concentration (µg/m^3)	Concentration (ppb)
Acute - 1 hour[b,c]		
Broadcast, non-tarped	**75,000**	**11,000**
Bedded, non-tarped	47,000	7,000
Bedded, tarped	54,000	8,000
Broadcast, tarped	28,000	4,200
Bedded, drip, tarped	11,000	1,600
Acute - 8 hour[c]		
Broadcast, non-tarped	**31,000**	**4,600**
Bedded, non-tarped	19,000	2,800
Bedded, tarped	22,000	3,300
Broadcast, tarped	12,000	1,800
Bedded, drip, tarped	4,700	700
Acute - 24 hr		
Broadcast, non-tarped	**5,400**	**800**
Bedded, non-tarped	3,500	520
Bedded, tarped	5,200	770
Broadcast, tarped	3,000	450
Bedded, drip, tarped	1,100	160
Seasonal[d]		
Broadcast, non-tarped	120	18
Bedded, non-tarped	120	18
Bedded, tarped	**230**	**34**
Broadcast, tarped	74	11
Bedded, drip, tarped	29	4.3
Annual[e]		
Broadcast, non-tarped	50	7.4
Bedded, non-tarped	50	7.4
Bedded, tarped	**96**	**14**
Broadcast, tarped	31	4.6
Bedded, drip, tarped	12	1.8

a Reasonable worst case exposure estimates for bystanders were generated using the Industrial Complex Short Term, Version 3 (ISCST3) air dispersion model and flux data from application site monitoring studies in Arizona (Beard *et al.*, 1996) and California (Rotendoro, 2004) adjusting for the maximum application rate and assuming the bystander was downwind, 10 ft (3.0 m) from the edge of a square, 40-acre field and the breathing zone was 4 ft (1.2 m) above ground (Beauvais, 2011). The maximum application rate was assumed to be 350 lbs/acre for all application methods except, bedded non-tarped which was 175 lbs/acre. The exposure estimates were rounded to two significant figures for both µg/m^3 and ppb. Values in bold are the application method with highest exposure estimates for each exposure duration.

b The 1-hr exposure was estimated from the highest 6-hr concentration for the different application methods (using the peak-to-mean ratio: $C_p = C_m(t_p/t_m)^{½}$ where C_p is the peak concentration over the peak period of interest, t_p, and C_m is the mean concentration over mean measurement period, t_m.

c The highest day or night 6-hr air concentration for each application method was used for their respective 1-hr and 8-hr exposure estimates.

d Seasonal exposure was estimated by calculating an average 24-hr flux over 2 weeks, then adjusted using a time-scaling factor based on the peak-to-mean theory. The application rate was adjusted from a maximum application rate to typical application rate. The typical application rate was assumed to be 190 lbs/acre for all application methods.

e Annual exposure was assumed 5 months of seasonal exposure per year.

For ease in calculation of cancer risk, the reasonable worse case lifetime exposure estimates for bystanders was calculated from annual exposures in μg/m^3 from Table 27 and converted to μg/kg/day by multiplying by the breathing rate for adult humans (Table 28). The lifetime exposure for residential bystanders was assumed to be the same as their annual exposure (i.e., 190 lb A.I./acre). The lifetime exposure for occupational bystanders was the same as residential bystanders except that it was assumed they were only exposed for 40 years in a 70-year life span. The lifetime exposure estimates for residential bystanders ranged from 3.4 to 26 μg/kg/day. The lifetime exposure estimates for occupational bystanders ranged from 1.9 to 15 μg/kg/day. The lifetime exposure estimates were highest for bedded tarped applications for both residential and occupational bystanders.

Table 28. Estimated Lifetime Bystander Exposure to Chloropicrin Following Soil Fumigation[a,b]

Application Method	Residential		Occupational	
	ppb	μg/kg/day	ppb	μg/kg/day
Broadcast, non-tarped	7.4	14	4.2	7.9
Bedded, non-tarped	7.4	14	4.2	7.9
Bedded, tarped	14	26	8.0	15
Broadcast, tarped	4.6	8.7	2.6	4.9
Bedded, drip, tarped	1.8	3.4	1.0	1.9

a Reasonable worst case exposure estimates for bystanders were generated using the Industrial Complex Short Term, Version 3 (ISCST3) air dispersion model and flux data from application site monitoring studies in Arizona (Beard *et al.*, 1996) and California (Rotendoro, 2004) adjusting for the maximum application rate and assuming the bystander was downwind, 10 ft (3.0 m) from the edge of a square, 40-acre field and the breathing zone was 4 ft (1.2 m) above ground (Beauvais, 2011).

b Lifetime exposure estimates were calculated from the annual exposure in μg/m^3 from Table 27 adjusting from the typical application rate to the 50th percentile rate (190 lbs/acre) and multiplying by the breathing rate for adults which was assumed to be 0.28 m^3/kg/day. Residential bystanders were assumed to be exposed every year throughout their lifetime. Occupational bystanders were assumed to be exposed for only 40 years in 70-year lifespan.

Ambient air monitoring was conducted by ARB in four counties (Monterey, Santa Cruz, Santa Barbara and Kern County) in four studies (ARB, 1987, 2003a &b; Wofford *et al.*, 2003). These studies confirm that exposure to chloropicrin can occur through ambient air in individuals living in communities near where there is high use, but who do not actually live or work next to an application site. The highest air concentration, 14.3 μg/m^3, was observed at the La Joya Elementary School site in Salinas (Monterey County) during monitoring conducted from early September to early November of 2001 which was a time when high chloropicrin use was anticipated (Pan-Huang, 2003b). DPR's Pesticide Use data for this county showed that September and October were the two highest use months in Monterey county (Beauvais, 2011). These monitoring studies support the assumption that exposures to chloropicrin in ambient air are equal to or less than bystander exposures near the application site. Therefore, the bystander exposure estimates for application site air were assumed to be health protective estimates for ambient air, also, and no separate exposure estimates were calculated for ambient air.

III.B.2.b. Structural Fumigation

DPR monitored chloropicrin concentrations during structural fumigation of seven houses with methyl bromide (Maddy et al., 1986). The Structural Pest Control Board also monitored chloropicrin concentrations during structural fumigation of ten houses with methyl bromide or

sulfuryl fluoride (Lee and Liscombe, 1993). However, neither of these studies was used to evaluate bystander exposure to chloropicrin since off-site air concentrations of chloropicrin were not measured.

ARB conducted several studies in which off-site air concentrations of chloropicrin were monitored following structural fumigations with sulfuryl fluoride. One study was conducted in Sacramento County during a fumigation of a single-story home with an estimated fumigation volume of 22,000 ft^3 (ARB, 2003d). A second study was conducted in Nevada county during a fumigation of a two-story house with a fumigation volume of 81,000 ft^3 (ARB, 2005a). The third study was conducted in Placer County during a fumigation of another two-story house with a fumigation volume of 45,000 ft^3 (ARB, 2005b). As might be expected, the highest off-site air concentrations were found in the second study with the house that had the highest fumigation volume. The highest air concentrations occurred at 1.5 m northwest of the house during the mechanical ventilation.

Dow AgroSciences, LLC, submitted a study to DPR in support of the registration for sulfuryl fluoride in which chloropicrin was used as a warning agent at 0.0107 lbs/1,000 ft^3 (Barnekow and Byrne, 2006). Off-site chloropicrin air concentrations were monitored in this study along with the air concentrations for sulfuryl fluoride. Chloropicrin air concentrations from this study was selected to estimate acute exposures since the air concentrations were monitored at more frequent intervals allowing for more accurate estimates of 1-hour exposures than in the ARB studies. Furthermore, the chloropicrin air concentrations found in this study were higher than those in the ARB studies. In this study, four houses were fumigated twice such that Replicates 1-2, 3-4, 5-6, and 7-8 are the fumigations for the houses in Ojai (32,000 ft^3), Homeland (53,000 ft^3), Reedley (25,000 ft^3) and Reedley (40,000 ft^3), respectively. Off-site air concentrations were monitored at 32 samplers placed at various distances on all four sides of the house. During fumigation, approximately one 4-hr sample followed by two 8-hr samples were collected. During aeration, four 1-hr samples were collected followed by two 4-hr sample. The estimated exposure for bystanders following structural fumigation are summarized in Table 29. The 1-hr exposure for bystanders was based on the highest outdoor air concentration which occurred during aeration in Interval 7 of Replicate 2. The 8-hr exposure for bystanders was

Table 29. Estimated Bystander Exposure to Chloropicrin Following Structural Fumigation[a]

Exposure Duration	Concentraion ($\mu g/m^3$)	Concentration (ppb)
Acute - 1 hr[b]	244	36.2
Acute - 8 hr[c]	67.7	10.1
Acute - 24 hr[d]	49.7	7.39

a Exposure estimates for bystanders were based on the highest air concentrations found during and following structural fumigation of four houses with sulfuryl fluoride where chloropicrin was a warning agent at 0.0107 lbs/1,000 ft^3 (Barnekow and Byrne, 2006). Each house was fumigated twice such that Replicates 1-2, 3-4, 5-6, and 7-8 are the fumigations for the houses in Ojai (32,000 ft^3), Homeland (53,000 ft^3), Reedley (25,000 ft^3) and Reedley (40,000 ft^3), respectively. Outdoor air concentrations were monitored at 32 samplers placed at various distances on all four sides of the house. During fumigation, one 4-hr samples followed by two 8-hour samples. During aeration, four 1-hr samples were collected followed by two 4-hr sample.

b The 1-hr exposure for bystanders was based on the highest air concentration which occurred during aeration in Interval 7 of Replicate 2.

c The 8-hr exposure for bystanders was based on the highest rolling time-weighted average that occurred during aeration in Intervals 4-8 of Replicate 2 that spanned 8 hours.

d The 24-hr exposure for bystanders was based on the highest rolling time-weighted average which occurred during fumigation and aeration in Intervals 2-8 of Replicate 2 that spanned 23 hours.

based on the highest rolling time-weighted average for outdoor air concentrations that occurred during aeration in Intervals 4-8 of Replicate 2 that spanned 8 hours. The 24-hr exposure for bystanders was based on the highest rolling time-weighted average for outdoor air concentrations which occurred during fumigation and aeration in Intervals 2-8 of Replicate 2 that spanned 23 hours. Multiple structural fumigations are not anticipated in the same area; therefore, no seasonal or annual exposure estimates were calculated for structural fumigation.

III.B.3. Residential Reentry Exposure

Residents could potentially be exposure to chloropicrin following clearance of structures that have been fumigated with methyl bromide or sulfuryl fluoride where chloropicrin is used as a warning agent. Post-clearance indoor air concentrations of chloropicrin were monitored in the studies conducted by ARB (2003d and 2005a) and Barnekow and Byrne (2006). The highest indoor air concentrations were reported by Barnekow and Byrne (2006) in which chloropicrin was applied as a warning agent at 0.0107 lbs/1,000 ft^3 along sulfuryl fluoride. As discussed previously, four houses were fumigated twice such that Replicates 1-2, 3-4, 5-6, and 7-8 are the fumigations for the houses in Ojai (32,000 ft^3), Homeland (53,000 ft^3), Reedley (25,000 ft^3) and Reedley (40,000 ft^3), respectively. Following clearance, four indoor samplers were placed in the attic, crawlspace, utility area and living room or bedroom for four 1-hr intervals followed by four 8-hr intervals (see Beauvais, 2011, for detailed discussion). The estimated exposure for residents to chloropicrin in indoor air following clearance with structural fumigation are summarized in Table 30. The 1-hr indoor exposure was based on the highest indoor concentration which occurred in the crawl space during clearance in Interval 11 of Replicate 4. The 8-hr indoor exposure was based on the highest 8-hr indoor concentration which occurred in the living room during the clearance in Interval 14 of Replicate 5. The 24-hr indoor exposure was based on the highest rolling time-weighted average for indoor air that occurred in the living room during clearance in Intervals 10-15 of Replicate 5 and spanned 20 hours. Multiple structural fumigations are not anticipated in the same house; therefore, no seasonal or annual exposure estimates were calculated for structural fumigation.

Table 30. Estimated Residential Reentry Exposure to Chloropicrin in Indoor Air Following Structural Fumigation[a]

Exposure Duration	Concentration	
	(µg/m³)	(ppb)
Acute - 1 hr[b]	3,060	456
Acute - 8 hr[c]	1,230	183
Acute - 24 hr[d]	1,160	172

a Exposure estimates for indoor air were based on the highest air concentrations found following structural fumigation of four houses with sulfuryl fluoride where chloropicrin was a warning agent at 0.0107 lbs/1,000 ft^3 (Barnekow and Byrne, 2006). Each house was fumigated twice such that Replicates 1-2, 3-4, 5-6, and 7-8 are the fumigations for the houses in Ojai (32,000 ft^3), Homeland (53,000 ft^3), Reedley (25,000 ft^3) and Reedley (40,000 ft^3), respectively. Following clearance, four indoor samplers were placed in the attic, crawlspace, utility are and living room or bedroom for four 1-hr intervals followed by four 8-hour intervals (Beauvais, 2011).

b The 1-hr indoor exposure was based on the highest indoor concentration which occurred in the crawl space during clearance in Interval 11 of Replicate 4.

c The 8-hr indoor exposure was based on the highest 8-hour indoor concentration which occurred in the living room during the clearance in Interval 14 of Replicate 5.

d The 24-hr indoor exposure was based on the highest rolling time-weighted average for indoor air that occurred in the living room during clearance in Intervals10-15 of Replicate 5 that spanned 20 hours.

III.C. RISK CHARACTERIZATION

The risk for non-carcinogenic human health effects is expressed as a margin of exposure (MOE). The MOE is the ratio of the NOEL from experimental animal studies to the human exposure dosage.

$$Margin\,of\ Exposure = \frac{NOEL}{Exposure\,Dosage}$$

The risk for carcinogenic effects was calculated by multiplying the carcinogenic potency by the exposure dosage.

$$Carcinogenic\,Risk = Carcinogenic\,Potency\ x\ Exposure\,Dosage$$

III.C.1. Occupational Exposure

III.C.1.a. Soil Fumigation

The 1-hr exposures for workers involved in soil fumigation were evaluated using the 1-hr NOEL of 44 ppb based on increased NO in nasal air in humans and the 1-hr exposure estimates from Table 21. The 1-hr MOEs for these workers are summarized in Table 31. When chloropicrin was an active ingredient, all of the MOEs were less than 10. The lowest MOEs were seen in tarp splitters with broadcast, tarped and potting soil fumigation. The highest MOE was 5.0 which was seen in pipe layers with bedded, non-tarped application using a 100% formulation. The MOEs were slightly lower for the same scenario when 60% or 67% formulations are used due to the shorter reentry interval (5-7 days vs. 10 days) with the methyl bromide/chloropicrin formulations. The MOEs were at least an order of magnitude higher when chloropicrin was used as only a warning agent. Only a few scenarios still had MOEs less than one with these lower concentration formulations, including tarp splitters with broadcast application of the 10.5% formulation and tarp removers with broadcast and potting soil application of both the 10.5% and 2% formulations.

Similar patterns were seen in the 8-hr MOEs for workers involved in soil fumigation which are summarized in Table 32. These MOEs were estimated using the 8-hr exposure estimates from Table 22 and the 8-hr HEC of 580 ppb for adults based on mortalities, nasal discharge, decreased body weights and food consumption, red discoloration in lungs in pregnant female rabbits and skeletal variations in their fetuses. As with 1-hr MOEs, the 8-hr MOEs were lowest for tarp splitters and removers with broadcast and potting soil application. When chloropicrin was used as an active ingredient, most of the 8-hr MOEs were less than 1. The highest 8-hr MOE was 470 for pipe layers with bedded, tarped application when a 100% formulation was used. When chloropicrin was used as a warning agent, nearly all of the 8-hr MOEs were greater than 10. Many of these MOEs were greater than 100, especially with the 2% formulation.

The seasonal MOEs for workers involved in soil fumigation are summarized in Table 33. A subchronic HEC of 73 ppb for adults based on rhinitis in female rats and the seasonal exposure estimates from Table 23 were used to calculate these MOEs. All of the seasonal MOEs for soil fumigation are greater than one. Unlike with acute MOEs, the seasonal MOEs are not

Table 31. Estimated One-Hour Margins of Exposure for Workers Involved in Soil Fumigation with Chloropicrin[a]

Exposure Scenarios	Margin of Exposure		
	Active Ingredient >15%	**Warning Agent 10.5%**	**Warning Agent < 2%**
Broadcast, tarped Driver	0.22[b]	1.7	9.6
Copilot	0.21[b]	1.6	9.2
Shoveler	0.54	4.1	23
Tarp splitter	0.036[b]	0.27	1.6
Tarp remover	0.019[b]	0.14	0.82
Soil shaper	1.1	4.9	28
Soil shaper - Tri-Form 40/60	0.28[b]	NA[c]	NA
Soil shaper - Tri-Con 33/67	0.57[b]	NA	NA
Broadcast, non-tarped Driver	0.66	4.0	23
Soil sealer	1.2	6.9	40
Soil shaper - shallow	6.7	NA	NA
Soil shaper - shallow (Tri-Form 40/60)	1.1	NA	NA
Soil shaper - deep	4.1	1.1	6.5
Soil shaper - deep (Tri-Form 40/60)	0.78	NA	NA
Soil shaper - deep (Tri-Con 33/67)	0.12[b]	NA	NA
Bedded, tarped Driver	1.9	22	130
Copilot	1.1	13	76
Shoveler	2.8	34	190
Tarp puncher	1.4	17	97
Bedded, non-tarped Driver	0.78	NA	NA
Pipe layer	8.5	NA	NA
Pipe layer - Tri-Con 33/67	5.6	NA	NA
Drip irrigation Applicator - tarped	2.1	5.8	140
Tarp puncher	5.6	1.2	370
Applicator - non-tarped	0.97	NA	NA
Handwand replant Applicator	0.46	2.9	15
Applicator - Telone C-35	0.46	NA	NA
Applicator - Pic-Brom 25	1.2	NA	NA
Potting soil Tarp remover	NA	0.59	0.47

a Margin of Exposure (MOE) = NOEL or HEC / Exposure Dosage. NOEL= No-Observed-Effect Level. HEC = Human Equivalent Concentration. Acute 1-hr NOEL = 44 ppb (humans, ↑ NO in nasal air) for children and adults. Exposure estimates from Table 21. Values rounded to two significant figures.

b If a respirator is worn when exposure exceeds 100 ppb, the MOEs would increase 10 to 1,000-fold depending on the type of respirator worn.

c NA = Not applicable

Table 32. Estimated Eight-Hour Margins of Exposure for Workers Involved in Soil Fumigation with Chloropicrin[a]

Exposure Scenarios	Margin of Exposure		
	Active Ingredient >15%	**Warning Agent 10.5%**	**Warning Agent < 2%**
Broadcast, tarped Driver	3.0[b]	22	130
Copilot	2.8[b]	21	120
Shoveler	7.1	54	310
Tarp splitter	0.47[b]	3.6[b]	20
Tarp remover	0.25[b]	1.9[b]	11
Soil shaper	14	64	370
Soil shaper - Tri-Form 40/60	5.5[b]	NA[c]	NA
Soil shaper - Tri-Con 33/67	7.5	NA	NA
Broadcast, non-tarped Driver	8.7	52	300
Soil sealer	15	91	530
Soil shaper - shallow	130	NA	NA
Soil shaper - shallow (Tri-Form 40/60)	23	NA	NA
Soil shaper - deep	130	35	200
Soil shaper - deep (Tri-Form 40/60)	24	NA	NA
Soil shaper - deep (Tri-Con 33/67)	3.8[b]	NA	NA
Bedded, tarped Driver	24	290	1,700
Copilot	15	170	1,000
Shoveler	37	450	2,600
Tarp puncher	71	850	4,900
Bedded, non-tarped Driver	10	NA	NA
Pipe layer	470	NA	NA
Pipe layer - Tri-Con 33/67	310	NA	NA
Drip irrigation Applicator - tarped	28	310	1,800
Tarp puncher	80	910	5,200
Applicator - non-tarped	13	NA	NA
Handwand replant Applicator	6.0	NA	NA
Applicator - Telone C-35	5.9	NA	NA
Applicator - Pic-Brom 25	16	NA	NA
Potting soil Tarp remover	NA	7.7	6.1

a Margin of Exposure (MOE) = NOEL or HEC / Exposure Dosage. NOEL= No-Observed-Effect Level. HEC = Human Equivalent Concentration. Acute 8-hr HEC = 580 ppb for adults (rabbits - mortalities, nasal discharge, ↓body weights & food consumption, red discoloration in lungs in does and skeletal variations in fetuses). Exposure estimates from Table 22. Values rounded to two significant figures.

b If a respirator is worn when exposure exceeds 100 ppb, the MOEs would increase 10 to 1,000-fold depending on the type of respirator worn.

c NA = Not applicable

Table 33. Estimated Seasonal Margins of Exposure for Workers Involved in Soil Fumigation with Chloropicrin[a]

Exposure Scenarios	Margin of Exposure		
	Active Ingredient >15%	**Warning Agent 10.5%**	**Warning Agent < 2%**
Broadcast, tarped[b]			
Driver	1.8	17	90
Copilot	1.4	14	72
Shoveler	4.1	39	210
Tarp splitter	1.5	14	74
Tarp remover	1.5	14	73
Soil shaper	13	120	640
Soil shaper - Tri-Form 40/60	21	NA[b]	NA
Soil shaper - Tri-Con 33/67	19	NA	NA
Broadcast, non-tarped			
Driver	3.7	35	190
Soil sealer	8.5	81	420
Soil shaper - shallow	28	NA	NA
Soil shaper - shallow (Tri-Form 40/60)	47	NA	NA
Soil shaper - deep	45	430	2,200
Soil shaper - deep (Tri-Form 40/60)	75	NA	NA
Soil shaper - deep (Tri-Con 33/67)	67	NA	NA
Bedded, tarped			
Driver	15	140	750
Copilot	12	110	590
Shoveler	21	200	1,000
Tarp puncher	150	1,400	3,700
Bedded, non-tarped			
Driver	3.2	NA	NA
Pipe layer	63	NA	NA
Pipe layer - Tri-Con 33/67	86	NA	NA
Drip irrigation			
Applicator - tarped	12	110	590
Tarp puncher	39	380	2,000
Applicator - non-tarped	8.9	NA	NA
Handwand replant			
Applicator	7.6	72	380
Applicator - Telone C-35	22	NA	NA
Applicator - Pic-Brom 25	30	NA	NA
Potting soil			
Tarp remover	NA	14	73

a Margin of Exposure (MOE) = NOEL or HEC / Exposure Dosage. NOEL= No-Observed-Effect Level. HEC = Human Equivalent Concentration. Subchronic HEC = 73 ppb for adults (female rats - rhinitis). Exposure estimates from Table 23. Values rounded to two significant figures.

b NA = Not applicable

significantly lower for tarp splitters and removers with broadcast, tarped and potting soil fumigation. However, the seasonal MOEs were generally lower with broadcast, tarped application when chloropicrin was 100% of the formulation, ranging from 1.4 to 13. The highest MOE was 150 for tarp punchers with bedded, tarped application when chloropicrin was an active ingredient. The seasonal MOEs were all greater than 10 when chloropicrin was used as a warning agent. Most of the seasonal MOEs were greater than 100 when a 2% chloropicrin formulation was used.

The annual exposures to chloropicrin for workers involved in soil fumigation were evaluated using the chronic HEC of 56 ppb for adults based on bronchiectasis in male and female mice and the annual exposure estimates in Table 24. The annual MOEs for these workers are summarized in Table 34. The annual MOEs were generally about twice as large as the seasonal MOEs. As with seasonal exposure, the annual MOEs were lowest with broadcast, tarped fumigation when chloropicrin was 100% of the formulation, ranging from 2.6 to 23. The highest annual MOE when chloropicrin was an active ingredient was 270 for tarp punchers with bedded, tarped application. When chloropicrin was used as a warning agent, the annual MOEs were all greater than 20 when 10.5% of the formulation and greater than 100 when 2% of the formulation.

The cancer risk estimates for workers involved in soil fumigation are summarized in Table 35. The cancer risk for these workers was calculated using the maximum likelihood estimate (MLE - 1.3 $(mg/kg/day)^{-1}$) and the 95th upper bound estimate (95% UB - 2.2 $(mg/kg/day)^{-1}$) for cancer potency for chloropicrin and the lifetime exposure estimates in Table 25. The highest cancer risk estimates were for broadcast, tarped applications when chloropicrin was 100% of the formulation. With this application methods, the MLE risk ranged from 3.1 x 10^{-3} to 2.8 x 10^{-2} while the 95% UB risk ranged from 5.3 x 10^{-3} to 4.7 x 10^{-2}. The lowest cancer risk estimates when chloropicrin is an active ingredient are for reentry workers (tarp punchers and pipe layers) with bedded application, ranging from 2.7 x 10^{-4} to 6.4 x 10^{-4} for the MLE and from 4.6 x 10^{-4} to 1.1 x 10^{-3} for the 95% UB. When chloropicrin is used as a warning agent, the cancer risk estimates were all less than 4.9 x 10^{-3} with 10.5% formulation and 9.4 x 10^{-4} for the 2% formulations. The lowest cancer risk estimates were seen for reentry workers with bedded and drip irrigation application, ranging from 1.1 x 10^{-5} to 6.0 x 10^{-4}

III.C.1.b. Structural Fumigation

The MOEs for workers involved in structural fumigation are summarized in Table 36. The 1-hr MOEs were calculated with the 1-hr NOEL of 44 ppb based on increased nitric oxide in expired nasal air in humans and the 1-hr exposure estimates from Table 26. The 1-hr MOEs were 1 or lower, with the lowest MOE being 0.0092 for applicators and fumigators. The 8-hr MOEs were calculated using the 8-hr exposure estimates from Table 26 and the 8-hr HEC of 580 ppb for adults based on mortalities, nasal discharge, decreased body weights and food consumption, red discoloration in lungs in pregnant rabbits and skeletal variations in their fetuses. The 8-hr MOEs were larger ranging from 0.80 to 13 with fumigators having the lowest MOE. The seasonal MOEs were estimated using the subchronic HEC of 73 ppb for adults based on rhinitis in female rats and the seasonal exposure estimates from Table 26. The seasonal MOEs ranged from 1.2 for fumigators to 4.6 for tarp removers. The annual MOEs were calculated using the chronic HEC of 56 ppb for adults based on bronchiectasis in male and female mice and the annual exposure dosages from Table 26. The annual MOEs were similar to

Table 34. Estimated Annual Margins of Exposure for Workers Involved in Soil Fumigation with Chloropicrin[a]

Exposure Scenarios	Margin of Exposure		
	Active Ingredient >15%	**Warning Agent 10.5%**	**Warning Agent < 2%**
Broadcast, tarped[b]			
Driver	3.3	31	160
Copilot	2.6	25	130
Shoveler	7.5	72	380
Tarp splitter	2.7	26	140
Tarp remover	2.7	26	130
Soil shaper	23	220	1,200
Soil shaper - Tri-Form 40/60	39	NA[b]	NA
Soil shaper - Tri-Con 33/67	35	NA	NA
Broadcast, non-tarped			
Driver	6.9	65	340
Soil sealer	16	150	780
Soil shaper - shallow	52	NA	NA
Soil shaper - shallow (Tri-Form 40/60)	86	NA	NA
Soil shaper - deep	82	780	4,100
Soil shaper - deep (Tri-Form 40/60)	140	NA	NA
Soil shaper - deep (Tri-Con 33/67)	120	NA	NA
Bedded, tarped			
Driver	27	260	1,400
Copilot	22	210	1,100
Shoveler	38	360	1,900
Tarp puncher	270	2,600	6,800
Bedded, non-tarped			
Driver	5.9	NA	NA
Pipe layer	120	NA	NA
Pipe layer - Tri-Con 33/67	160	NA	NA
Drip irrigation			
Applicator - tarped	22	210	1,100
Tarp puncher	73	690	3,600
Applicator - non-tarped	21	NA	NA
Handwand replant			
Applicator	30	220	1,200
Applicator - Telone C-35	87	NA	NA
Applicator - Pic-Brom 25	120	NA	NA
Potting soil			
Tarp remover	NA	32	170

a Margin of Exposure (MOE) = NOEL or HEC / Exposure Dosage. NOEL= No-Observed-Effect Level. HEC = Human Equivalent Concentration. Annual HEC = 56 ppb for adults (male and female mice - bronchiectasis). Exposure estimates from Table 24. Values rounded to two significant figures.

b NA = Not applicable

Table 35. Estimated Cancer Risk For Workers Involved in Soil Fumigation with Chloropicrin[a]

Exposure Scenarios	Cancer Risk					
	Active Ingredient >15%		Warning Agent 10.5%		Warning Agent < 2%	
	MLE[b]	95% UB[c]	MLE	95% UB	MLE	95% UB
Broadcast, tarped						
Driver	$2.2x10^{-2}$	$3.8x10^{-2}$	$2.3x10^{-3}$	$4.0x10^{-3}$	$4.5x10^{-4}$	$7.5x10^{-4}$
Copilot	$2.8x10^{-2}$	$4.7x10^{-2}$	$2.9x10^{-3}$	$4.9x10^{-3}$	$5.6x10^{-4}$	$9.4x10^{-4}$
Shoveler	$9.8x10^{-3}$	$1.7x10^{-2}$	$1.0x10^{-3}$	$1.7x10^{-3}$	$2.0x10^{-4}$	$3.3x10^{-4}$
Tarp splitter	$2.7x10^{-2}$	$4.6x10^{-2}$	$2.8x10^{-3}$	$4.8x10^{-3}$	$5.4x10^{-4}$	$9.2x10^{-4}$
Tarp remover	$2.7x10^{-2}$	$4.6x10^{-2}$	$2.9x10^{-3}$	$4.8x10^{-3}$	$5.4x10^{-4}$	$9.2x10^{-4}$
Soil shaper	$3.1x10^{-3}$	$5.3x10^{-3}$	$3.3x10^{-4}$	$5.5x10^{-4}$	$6.3x10^{-5}$	$1.1x10^{-4}$
Soil shaper - Tri-Form 40/60	$1.9x10^{-3}$	$3.2x10^{-3}$	NA[d]	NA	NA	NA
Soil shaper - Tri-Con 33/67	$2.1x10^{-3}$	$3.5x10^{-3}$	NA	NA	NA	NA
Broadcast, non-tarped						
Driver	$1.1x10^{-2}$	$1.8x10^{-2}$	$1.1x10^{-3}$	$1.9x10^{-3}$	$2.1x10^{-4}$	$3.6x10^{-4}$
Soil sealer	$4.7x10^{-3}$	$7.9x10^{-3}$	$4.9x10^{-4}$	$8.4x10^{-4}$	$9.4x10^{-5}$	$1.6x10^{-4}$
Soil shaper - shallow	$1.4x10^{-3}$	$2.4x10^{-3}$	NA	NA	NA	NA
Soil shaper - Tri-Form 40/60[e]	$8.5x10^{-4}$	$1.4x10^{-3}$	NA	NA	NA	NA
Soil shaper - deep	$8.9x10^{-4}$	$1.5x10^{-3}$	$9.4x10^{-5}$	$1.6x10^{-4}$	$1.8x10^{-5}$	$3.0x10^{-5}$
Soil shaper - Tri-Form 40/60[f]	$5.4x10^{-4}$	$9.1x10^{-4}$	NA	NA	NA	NA
Soil shaper - Tri-Con 33/67[f]	$5.9x10^{-4}$	$1.0x10^{-3}$	NA	NA	NA	NA
Bedded, tarped						
Driver	$2.7x10^{-3}$	$4.5x10^{-3}$	$2.8x10^{-4}$	$4.8x10^{-4}$	$5.4x10^{-5}$	$9.1x10^{-5}$
Copilot	$3.4x10^{-3}$	$5.7x10^{-3}$	$3.5x10^{-4}$	$6.0x10^{-4}$	$6.8x10^{-5}$	$1.1x10^{-4}$
Shoveler	$1.9x10^{-3}$	$3.3x10^{-3}$	$2.0x10^{-4}$	$3.4x10^{-4}$	$3.9x10^{-5}$	$6.5x10^{-5}$
Tarp puncher	$2.7x10^{-4}$	$4.6x10^{-4}$	$2.8x10^{-5}$	$4.8x10^{-5}$	$1.1x10^{-5}$	$1.8x10^{-5}$
Bedded, non-tarped						
Driver	$1.3x10^{-2}$	$2.1x10^{-2}$	NA	NA	NA	NA
Pipe layer	$6.4x10^{-4}$	$1.1x10^{-3}$	NA	NA	NA	NA
Pipe layer - Tri-Con 33/67	$4.6x10^{-4}$	$7.8x10^{-4}$	NA	NA	NA	NA
Drip irrigation						
Applicator - tarped	$3.4x10^{-3}$	$5.7x10^{-3}$	$3.5x10^{-4}$	$6.0x10^{-4}$	$6.8x10^{-5}$	$1.1x10^{-4}$
Tarp puncher	$1.0x10^{-3}$	$1.7x10^{-3}$	$1.1x10^{-4}$	$1.4x10^{-4}$	$2.0x10^{-5}$	$3.4x10^{-5}$
Applicator - non-tarped	$4.5x10^{-3}$	$7.6x10^{-3}$	NA	NA	NA	NA
Handwand replant						
Applicator	$3.4x10^{-3}$	$5.7x10^{-3}$	$3.3x10^{-4}$	$5.6x10^{-4}$	$6.3x10^{-5}$	$1.1x10^{-4}$
Applicator - Telone C-35	$1.0x10^{-3}$	$1.7x10^{-3}$	NA	NA	NA	NA
Applicator - Pic-Brom 25	$7.9x10^{-4}$	$1.3x10^{-3}$	NA	NA	NA	NA
Potting soil						
Tarp remover	NA	NA	$2.4x10^{-3}$	$4.1x10^{-3}$	$4.4x10^{-4}$	$7.4x10^{-4}$

a Carcinogenic Risk = Carcinogenic Potency x Exposure Dosage. The exposure dosages were the lifetime exposure estimates in Table 25. The maximum likelihood estimate for carcinogenic potency was 1.3 $(mg/kg/day)^{-1}$. The 95% upper bound estimate for carcinogenic potency was 2.2 $(mg/kg/day)^{-1}$.
b MLE = Maximum Likelihood Estimate
c 95% UB = 95th percentile upper bound
d NA = Not applicable
e Shallow
f Deep

Table 36. Estimated Margins of Exposure and Cancer Risk for Workers Involved in Structural Fumigation with Chloropicrin

Exposure Scenario	Margin of Exposure[a]				Cancer Risk[b]	
	1-Hour	8-Hour	Seasonal	Annual	MLE	95% UB
Applicator	0.0092[c]	NA[d]	NA	NA	NA	NA
Tarp Remover	1.0	13	4.6	7.2	1.0×10^{-2}	1.7×10^{-2}
Aerator	0.058[c]	NA	NA	NA	NA	NA
Fumigator	0.0092[c]	0.80[c]	1.2	1.7	4.4×10^{-2}	7.4×10^{-2}
Reentry	0.36[c]	4.7[c]	2.0	3.2	2.3×10^{-2}	3.9×10^{-2}

a Margin of Exposure (MOE) = NOEL or HEC / Exposure Dosage. NOEL= No-Observed-Effect Level. HEC = Human Equivalent Concentration. Acute 1-hr NOEL = 44 ppb (humans, ↑ NO in nasal air) for children and adults. Acute 8-hr HEC = 580 ppb for adults (rabbits - mortalities, nasal discharge, ↓ body weights & food consumption, red discoloration in lungs in does and skeletal variations in fetuses). Subchronic HEC = 73 ppb for adults (female rats - rhinitis). Chronic HEC = 56 ppb for adults (male and female mice - bronchiectasis). Exposure estimates from Table 26. Values rounded to two significant figures.

b Carcinogenic Risk = Carcinogenic Potency x Exposure Dosage. The maximum likelihood estimate for carcinogenic potency was 1.3 $(mg/kg/day)^{-1}$. The 95% upper bound estimate for carcinogenic potency was 2.2 $(mg/kg/day)^{-1}$. MLE = Maximum Likelihood Estimate. 95% UB = 95th percentile upper bound.

c If a respirator is worn when exposure exceeds 100 ppb, the MOEs would increase 10 to 1,000-fold depending on the type of respirator worn.

d NA=Not applicable

the seasonal MOEs ranging from 1.7 to 7.2. The cancer risk for workers involved in structural fumigation were calculated using the MLE and 95% UB estimates for cancer potency (1.3 and 2.2 $(mg/kg/day)^{-1}$) and the lifetime exposure estimates from Table 26. The MLE risk estimates ranged from 1.0×10^{-2} to 4.4×10^{-2}. The 95% UB risk estimates ranged from 1.7×10^{-2} to 7.4×10^{-2}. Fumigators had the highest cancer risk estimates.

III.C.2. Bystander Exposure

III.C.2.a. Soil Fumigation

The acute MOEs for 1-hr exposure to chloropicrin were calculated for adults and children using the $BMCL_{10}$ for increased NO in expired nasal air (44 ppb) and the worse case 1-hr bystander exposure estimates for the different application methods in Table 27. The 1-hr acute MOE for increased NO ranged from 0.028 to 0.0040 for both children and adults (Table 37). The 1-hr exposure represents 36,000% to 250,000% of the 1-hr RfC for increased NO. The 8-hr acute MOE for chloropicrin was calculated using the 8-hr HECs of 270 ppb for children and 580 ppb for adults and the worse case 8-hr bystander exposure estimates from Table 27. The 8-hr MOEs ranged from 0.060 to 0.39 for children and from 0.13 to 0.83 for adults. The 8-hr exposure represent between 25,000% and 170,000% of the RfC for children and between 12,000% and 79,000% of the RfC for adults. The 24-hr MOEs were calculated using the 24-hr HECs of 92 ppb for children and 190 ppb for adults and the 24-hr worse case bystander exposure estimates for the different application methods from Table 27. The 24-hr MOEs ranged from 0.12 to 0.58 for children and from 0.24 to 1.2 for adults. The 24-hr exposures represented

Table 37. Estimated Margins of Exposure for Bystanders Exposed to Chloropicrin Following Soil Fumigation[a]

Exposure Scenarios	Children		Adults	
	MOE	% RfC[b]	MOE	% RfC
Acute - 1 hr				
Broadcast, non-tarped	**0.0040**	**250,000**	**0.0040**	**250,000**
Bedded, non-tarped	0.0063	160,000	0.0063	160,000
Bedded, tarped	0.0055	180,000	0.0055	180,000
Broadcast, tarped	0.010	95,000	0.010	95,000
Bedded, drip, tarped	0.028	36,000	0.028	36,000
Acute - 8 hr				
Broadcast, non-tarped	**0.060**	**170,000**	**0.13**	**79,000**
Bedded, non-tarped	0.098	100,000	0.21	48,000
Bedded, tarped	0.083	120,000	0.18	57,000
Broadcast, tarped	0.15	65,000	0.32	31,000
Bedded, drip, tarped	0.39	25,000	0.83	12,000
Acute - 24 hr				
Broadcast, non-tarped	**0.12**	**87,000**	**0.24**	**41,000**
Bedded, non-tarped	0.18	57,000	0.37	27,000
Bedded, tarped	0.12	84,000	0.25	40,000
Broadcast, tarped	0.20	49,000	0.43	23,000
Bedded, drip, tarped	0.58	17,000	1.2	8,300
Seasonal				
Broadcast, non-tarped	1.9	5,100	4.1	2,500
Bedded, non-tarped	1.9	5,100	4.1	2,500
Bedded, tarped	**1.0**	**9,700**	**2.1**	**4,700**
Broadcast, tarped	3.2	3,100	6.6	1,500
Bedded, drip, tarped	8.1	1,200	17	590
Chronic				
Broadcast, non-tarped	3.6	2,700	7.6	1,300
Bedded, non-tarped	3.6	2,700	7.6	1,300
Bedded, tarped	**1.9**	**5,200**	**4.0**	**2,500**
Broadcast, tarped	5.9	1,700	12	820
Bedded, drip, tarped	15	670	31	320

a Margin of Exposure (MOE) = NOEL or HEC / Exposure Dosage. NOEL= No-Observed-Effect Level. HEC = Human Equivalent Concentration. Acute 1-hr NOEL = 44 ppb (humans - ↑NO in nasal air) for children and adults. Acute 8-hr HEC = 270 ppb for children and 580 ppb for adults (rabbits - mortalities, nasal discharge, ↓body weights & food consumption, red discoloration in lungs in does and skeletal variations in fetuses). Acute 24-hr HEC = 92 ppb for children and 190 ppb for adults (rabbits - mortalities, nasal discharge, ↓body weights & food consumption, red discoloration in lungs in does and skeletal variations in fetuses). Subchronic HEC = 35 ppb for children and 73 ppb for adults (female rats - rhinitis). Chronic HEC = 27 ppb for children and 56 ppb for adults (male and female mice - bronchiectasis). Exposure estimates from Table 27 assuming the bystander was downwind, 10 ft (3.0 m) from the edge of a square, 40-acre field and the breathing zone was 4 ft (1.2 m) above ground. Values rounded to two significant figures.

b % RfC = Percentage of Reference Concentration. The 1-hr, 8-hr, 24-hr, seasonal and chronic RfCs for chloropicrin for children are 4.4 ppb, 2.7 ppb, 0.92 ppb, 0.35 ppb and 0.27 ppb, respectively. The respective RfCs for adults are 4.4 ppb, 5.8 ppb, 1.9 ppb, 0.73 ppb and 0.56 ppb. See Table 20 for more details. Values rounded to two significant figures.

between 17,000 and 87,000% of the RfC for children and between 8,300% and 41,000% of the RfC for adults. The seasonal MOEs for chloropicrin were calculated using the subchronic HECs from the 90-day inhalation study in rats (children: 35 ppb, adults: 73 ppb) and the worse case seasonal bystander exposure estimates for the different application methods from Table 27. The seasonal MOEs for chloropicrin ranged from 1.0 to 8.1 for children and from 2.1 to 17 for adults. The seasonal exposure represented between 1,200 and 9,800% of the seasonal RfCs for children and between 590% and 4,700% of the RfC for adults. The MOEs for annual exposure were calculated using the chronic HECs of 27 ppb for children and 56 ppb for adults and the worse case annual bystander exposure estimates for the different application methods in Table 27. The annual MOEs for bystanders following soil fumigation were slightly larger than the seasonal MOEs, ranging from 1.9 to 15 for children and from 4.0 to 31 for adults. The annual exposure represented between 670% and 5,200% of the chronic RfCs for children and between 320% and 2,500% of the RfC for adults.

The carcinogenic risk was calculated using the reasonable worse case lifetime exposure estimates in Table 28 and the cancer potency estimates based on lung adenomas and carcinomas in female mice [1.3 $(mg/kg/day)^{-1}$ for MLE or 2.2 $(mg/kg/day)^{-1}$ for 95% UB]. The carcinogenic risk estimates are shown in Table 38. For the residential bystanders, the carcinogenic risk estimates ranged from 4.4×10^{-3} to 3.4×10^{-2} for the maximum likelihood estimate (MLE) and from 7.5×10^{-3} to 5.7×10^{-2} for the 95th percentile upper bound (95% UB). The estimated carcinogenic risk from lifetime exposure for occupational bystanders to chloropicrin following soil fumigation ranged from 2.5×10^{-3} to 2.0×10^{-2} for the MLE and from 4.2×10^{-3} to 3.3×10^{-2} for the 95% UB.

Table 38. Estimated Cancer Risk for Bystanders Exposed to Chloropicrin Following Soil Fumigation[a]

Application Method	Residential		Occupational	
	MLE[b]	95% UB[c]	MLE	95% UB
Broadcast, non-tarped	1.8×10^{-2}	3.1×10^{-2}	1.0×10^{-2}	1.7×10^{-2}
Bedded, non-tarped	1.8×10^{-2}	3.1×10^{-2}	1.0×10^{-2}	1.7×10^{-2}
Bedded, tarped	3.4×10^{-2}	5.7×10^{-2}	2.0×10^{-2}	3.3×10^{-2}
Broadcast, tarped	1.1×10^{-2}	1.9×10^{-2}	6.4×10^{-3}	1.1×10^{-2}
Bedded, drip, tarped	4.4×10^{-3}	7.5×10^{-3}	2.5×10^{-3}	4.2×10^{-3}

a Carcinogenic Risk = Carcinogenic Potency x Exposure Dosage. The exposure dosage was the lifetime exposure estimates in Table 28. The maximum likelihood estimate for carcinogenic potency was 1.3 $(mg/kg/day)^{-1}$. The 95% upper bound estimate for carcinogenic potency was 2.2 $(mg/kg/day)^{-1}$.
b MLE = Maximum Likelihood Estimate
c 95% UB = 95th percentile upper bound

MOEs were not calculated for ambient air since it was assumed that exposure in ambient air would be less than bystander exposure at the application site and, therefore, any mitigation needed for application site exposure would also mitigate ambient air exposure.

II.C.2.b. Structural Fumigation

The MOEs for 1-hr bystander exposure following structural fumigation where chloropicrin was used as a warning agent were calculated for adults and children using the acute $BMCL_{10}$ for increased NO in expired nasal air (44 ppb) and the 1-hr bystander exposure estimate (36.2 ppb) from Table 29. The 1-hr acute MOE for bystanders of structural fumigation is 1.2 for both children and adults (Table 39). The 1-hr exposure estimate represents 820% of the 1-hr RfC for chloropicrin. The 8-hr acute MOE for structural fumigation was calculated using the 8-hr HECs of 270 ppb for children and 580 ppb for adults and the 8-hr exposure estimate (10.1 ppb). The 8-hr MOEs were 27 and 57 for children and adults, respectively. The 8-hr exposure represent 370% and 170% of the RfC for children and adults, respectively. The 24-hr MOEs were calculated using the 24-hr HECs of 92 ppb for children and 190 ppb for adults and a 24-hr exposure estimate for structural fumigation (7.39 ppb). The 24-hr MOEs were 12 and 26 for children and adults, respectively. The 24-hr exposures for structural fumigation represented 800% and 380% of the RfC for children and adults, respectively.

Table 39. Estimated Margins of Exposure for Bystanders Exposed to Chloropicrin Following Structural Fumigation[a]

Exposure Scenarios	Children		Adults	
	MOE	% RfC[b]	MOE	% RfC
Acute - 1 hr	1.2	820	1.2	820
Acute - 8 hr	27	370	57	170
Acute - 24 hr	12	800	26	380

a Margin of Exposure (MOE) = NOEL or HEC / Exposure Dosage. NOEL= No-Observed-Effect Level. HEC = Human Equivalent Concentration. Acute 1-hr NOEL = 44 ppb (humans, ↑ NO in nasal air) for children and adults. Acute 8-hr HEC = 270 ppb for children and 580 ppb for adults (rabbits, mortalities, nasal discharge, ↓ body weights & food consumption, red discoloration in lungs in does and skeletal variations in fetuses). Acute 24-hr HEC = 92 ppb for children and 190 ppb for adults (rabbits - mortalities, nasal discharge, ↓ body weights & food consumption, red discoloration in lungs in does and skeletal variations in fetuses). Exposure estimates from Table 29. Values rounded to two significant figures.

b % RfC = Percentage of Reference Concentration. The 1-hr, 8-hr, and 24-hr RfCs for chloropicrin for children are 4.4 ppb, 2.7 ppb, and 0.92 ppb, respectively. The respective RfCs for adults are 4.4 ppb, 5.8 ppb, and 1.9 ppb. See Table 20 for more details. Values rounded to two significant figures.

III.C.3. Residential Reentry Exposure

Table 40 summarizes the MOEs for indoor exposures following aeration with structural fumigation using chloropicrin as a warning agent. The 1-hr MOEs were calculated for children and adults using the acute $BMCL_{10}$ for increased NO in expired nasal air (44 ppb) and the 1-hr indoor exposure estimate (456 ppb) from Table 30. The 1-hr acute MOE for indoor exposure with structural fumigation is 0.096 for both children and adults. The 1-hr exposure estimate represents 10,000% of the 1-hr RfC for chloropicrin. The 8-hr acute MOE for indoor exposure was calculated using the 8-hr HECs of 270 ppb for children and 580 ppb for adults and the 8-hr exposure estimate (183 ppb). The 8-hr MOEs were 1.5 and 3.2 for children and adults, respectively. The 8-hr exposure represent 6,700% and 3,200% of the RfC for children and adults, respectively. The 24-hr MOEs for indoor exposure with structural fumigation were calculated using the 24-hr HEC (92 ppb for children and 190 ppb for adults) and the highest adjusted 24-hr indoor air concentrations (172 ppb). The 24-hr MOEs for indoor air were estimated to be 0.54 (19,000% RfC) for children and 1.1 (8,900% RfC) for adults.

Table 40. Estimated Margins of Exposure for Residents Exposed to Chloropicrin in Indoor Air Following Structural Fumigation[a]

Exposure Scenarios	Children		Adults	
	MOE	% RfC[b]	MOE	% RfC
Acute - 1 hr	0.096	10,000	0.096	10,000
Acute - 8 hr	1.5	6,700	3.2	3,200
Acute - 24 hr	0.54	19,000	1.1	8,900

a Margin of Exposure (MOE) = NOEL or HEC / Exposure Dosage. NOEL= No-Observed-Effect Level. HEC = Human Equivalent Concentration. Acute 1-hr NOEL = 44 ppb (humans, ↑NO in nasal air) for children and adults. Acute 8-hr HEC = 270 ppb for children and 580 ppb for adults (rabbits, mortalities, nasal discharge, ↓body weights & food consumption, red discoloration in lungs in does and skeletal variations in fetuses). Acute 24-hr HEC = 92 ppb for children and 190 ppb for adults (rabbits - mortalities, nasal discharge, ↓body weights & food consumption, red discoloration in lungs in does and skeletal variations in fetuses). Exposure estimates from Table 30. Values rounded to two significant figures.

b % RfC = Percentage of Reference Concentration. The 1-hr, 8-hr, and 24-hr RfCs for chloropicrin for children are 4.4 ppb, 2.7 ppb, and 0.92 ppb, respectively. The respective RfCs for adults are 4.4 ppb, 5.8 ppb, and 1.9 ppb. See Table 20 for more details. Values rounded to two significant figures.

IV. RISK APPRAISAL

Risk assessment is the process used to evaluate the potential for human exposure and the likelihood that the adverse effects observed in toxicity studies with laboratory animals will occur in humans under the specific exposure conditions. Every risk assessment has inherent limitations on the application of existing data to estimate the potential risk to human health. Therefore, certain assumptions and extrapolations are incorporated into the hazard identification, dose-response assessment, and exposure assessment processes. These, in turn, result in uncertainty in the risk characterization which integrates all the information from the previous three processes. Qualitatively, risk assessments for all chemicals have similar uncertainties. However, the degree or magnitude of the uncertainty can vary depending on the availability and quality of the data, and the types of exposure scenarios being assessed. Specific areas of uncertainty associated with this risk assessment for chloropicrin are delineated in the following discussion.

Following the discussion of the uncertainties related to the different components of DPR's risk assessment is a comparison with the endpoints and exposure estimates used in U.S. EPA's risk assessment for chloropicrin. In addition, there is a discussion of the information available for chloropicrin related to Food Quality Protection Act including potential increased pre- and post-natal sensitivity in infants and children, endocrine effects, cumulative toxicity and aggregate exposure. Both the uncertainties in the risk estimates and the information related to FQPA can be used in determining the adequacy of the MOEs for chloropicrin.

IV.A. HAZARD IDENTIFICATION

One source of uncertainty in selecting the acute 1-hr NOEL for chloropicrin was in the BMC analysis. Since there was wide inter-individual variation in sensitivity to chloropicrin, one approach considered for converting continuous data to quantal data was setting individual thresholds based on their response during exposure to blank air. All of the subjects were exposed to blank air as well as the two different air concentrations of chloropicrin, so the upper confidence limit (UCL) on a subject's response during the exposure to the blank air was used to define that individual's threshold, rather than using one threshold value for all subjects. The UCL was defined as follows:

$$UCL = mean + \frac{1.645 x SD}{\sqrt{n}}$$

where the mean is the mean of the four daily averages and SD is the standard deviation of the four daily averages and n is the number of daily averages. Any subject with an overall mean score greater than their UCL during exposure was considered a responder. Using this approach for increased NO in expired nasal air, there were 9 responders at 100 ppb and 13 responders at 150 ppb. Several models had good fits with an average $BMCL_{05}$ of 11 ppb. Since this is a fairly novel approach which had not been fully vetted, these estimates were not used.

Consultants for the CMTF considered an increase in NO in expired nasal air greater than 25% to be clinically significant (Haber *et al.*, 2005). Using this single threshold to convert the continuous data into quantal, there were 2, 4 and 6 responders at 0, 100 and 150 ppb,

respectively. The $BMCL_{05}$ using this approach was 56 ppb which is slightly higher than the $BMCL_{05}$ estimated with the hybrid approach (44 ppb).

Although increased NO in expired nasal air is the first step in the development of more severe respiratory irritation, some might argue that this level of irritation is so mild that a $BMCL_{10}$ is sufficiently health protective. Using the hybrid approach, the $BMCL_{10}$ for increased NO in nasal air was 75 ppb. If the $BMCL_{10}$ had been used, the 1-hr MOEs would be about 70% higher.

Others might argue that increased NO in expired nasal air is a subclinical effect since the subjects in the human study did not report any nasal or throat irritation. A more overt sign of respiratory irritation is the reduction in nasal air flow due to the swelling of the mucus membrane which was seen at 150 ppb in the Cain (2004) study. An attempt was made to estimate a BMDL for this endpoint, but the combination of non-homogeneous variation and small number of dose groups made it impossible to obtain any meaningful results. Consequently, the lowest dose level of 100 ppb was used as the NOEL. Using this NOEL, the 1-hr RfC would be 10 ppb assuming a default uncertainty factor of 10 since toxicokinetic variation is possible and the most sensitive sub-population (e.g., people with chronic rhinitis and asthma) was not tested in this study. Even using this NOEL, the 1-hr MOEs would only be about 2.25 times larger as shown in Table 41 and would still be orders of magnitude from the target MOE of 10.

Table 41. Estimated Acute One-Hour Margins of Exposure for Potential Bystander Exposure to Chloropicrin Following Soil Fumigation Based on Decreased Nasal Airflow[a]

Exposure Scenarios	Children and		Adults	
	MOE	% RfC[b]	MOE	% RfC
Acute - 1 hr - nasal airflow Broadcast, non-tarped	**0.0091**	**110,000**	**0.0091**	**110,000**
Bedded, non-tarped	0.014	70,000	0.014	70,000
Bedded, tarped	0.013	80,000	0.013	80,000
Broadcast, tarped	0.024	42,000	0.024	42,000
Bedded, drip, tarped	0.063	16,000	0.063	16,000

a Margin of Exposure (MOE) = NOEL or HEC / Exposure Dosage. NOEL= No-Observed-Effect Level. HEC = Human Equivalent Concentration. Acute 1-hr NOEL = 100 pbb (humans, decreased nasal airflow) for children and adults. Exposure estimates from Table 27. Values rounded to two significant figures.

b % RfC = Percentage of Reference Concentration. The 1-hr RfC based on decreased nasal airflow is 10 ppb for both children and adults.

The eye irritation from the human study appears to be a more sensitive endpoint in the human study based on a lower $BMCL_{10}$ of 26 ppb. A smaller intraspecies uncertainty factor of 3 is recommended for this endpoint since no toxicokinetic variation is anticipated. Consequently, the 1-hr RfC for eye irritation is actually 2-fold higher (8.7 ppb) than that for increased NO in nasal air (4.4 ppb). However, if the $BMCL_{10}$ for eye irritation had been used to evaluate 1-hr exposures, the acute 1-hr MOEs would be approximately 60% lower than estimated as shown in Table 42. This is somewhat misleading since the % RfC would also be 50% lower due to the higher RfC.

Table 42. Estimated Acute One-Hour Margins of Exposure for Potential Bystander Exposure to Chloropicrin Following Soil Fumigation Based on Eye Irritation[a]

Exposure Scenarios	Children		Adults	
	MOE	% RfC[b]	MOE	% RfC
Acute - 1 hr - Eye irritation Broadcast, non-tarped	**0.0024**	**130,000**	**0.0024**	**130,000**
Bedded, non-tarped	0.0037	81,000	0.0037	81,000
Bedded, tarped	0.0033	92,000	0.0033	92,000
Broadcast, tarped	0.0062	48,000	0.0062	48,000
Bedded, drip, tarped	0.016	18,000	0.016	18,000

a Margin of Exposure (MOE) = NOEL or HEC / Exposure Dosage. NOEL= No-Observed-Effect Level. HEC = Human Equivalent Concentration. Acute 1-hr NOEL = 26 ppb (humans, eye irritation) for children and adults using hybrid approach. Exposure estimates from Table 27. Values rounded to two significant figures.

b % RfC = Percentage of Reference Concentration. The 1-hr RfC based on eye irritation is 8.7 ppb for both children and adults.

If individual thresholds were used to convert the continuous data to quantal data for eye irritation, 22 and 27 subjects would be considered responders at 100 and 150 ppb, respectively. Five of the quantal models had good fits with an average $BMCL_{10}$ of 7.1 ppb. As with NO data, this novel approach was not used since it was not fully vetted.

Other approaches to converting the eye irritation data to quantal data were considered. The highest average score with exposure to blank air during the plateau period (minutes 31-55 of exposure) over the 4 days of exposure for any subject was 0.87. Therefore, 1.0 seemed like a logical threshold for identifying subjects as responders. Using this threshold, the number of responders were 0, 6 and 15 at 0, 100 and 150 ppb, respectively. Four of the quantal models had good fits with an average $BMCL_{10}$ of 33 ppb. Since only one subject had an average score greater than 0.5 over the 4 days of exposure during the plateau period, the use of this threshold was also examined. Using this threshold, there were 1, 12 and 15 responders at 0, 100 and 150 ppb, respectively. The model with the best fit had a $BMCL_{10}$ of 13 ppb. Consultants for the CMTF also did a BMC analysis of these data using an average score of 1.5 during the plateau period as the threshold (Haber *et al.*, 2005). The rationale for the cutoff of 1.5 was based on chloropicrin being used as a warning agent so that a certain amount of mild eye irritation would be acceptable. This resulted in an incidence of 0, 2, and 9 responders at 0, 100 and 150 ppb, respectively. The average $BMCL_{10}$ for the best fitting models was 73 ppb. Using this less health protective threshold for eye irritation, the MOEs were still orders of magnitude below the target MOE even if one assumed an uncertainty factor of one was adequate (Table 43).

Regardless of the approach used for the BMC analysis, the estimates were higher for increased nasal NO production than the $BMCL_{10}$ for eye irritation, indicating eye irritation is the more sensitive endpoint even using a higher BMR. However, the RfCs for increased NO in nasal air were always lower than the RfCs for eye irritation when using the same approach for BMC analysis since a smaller uncertainty factor of 3 was used with eye irritation.

Table 43. Estimated Acute One-Hour Margins of Exposure for Potential Bystander Exposure to Chloropicrin Following Soil Fumigation Based on Average Eye Irritation > 1.5[a]

Exposure Scenarios	Children		Adults	
	MOE	% RfC[b]	MOE	% RfC
Acute - 1 hr - Eye irritation > 1.5 Broadcast, non-tarped	**0.0066**	**15,000**	**0.0066**	**15,000**
Bedded, non-tarped	0.010	9,600	0.010	9,600
Bedded, tarped	0.0091	11,000	0.0091	11,000
Broadcast, tarped	0.017	5,800	0.017	5,800
Bedded, drip, tarped	0.046	2,200	0.046	2,200

a Margin of Exposure (MOE) = NOEL or HEC / Exposure Dosage. NOEL= No-Observed-Effect Level. HEC = Human Equivalent Concentration. Acute 1-hr NOEL = 73 pbb (humans, average eye irritation score > 1.5) for children and adults. Exposure estimates from Table 27. Values rounded to two significant figures.

b % RfC = Percentage of Reference Concentration. The 1-hr RfC based on eye irritation is 73 ppb for both children and adults assuming an uncertainty factor of 1.

The Office of Environmental Health Hazard Assessment (OEHHA) in the California Environmental Protection Agency (Cal/EPA) derived a 1-hour Reference Level Exposure (REL) for chloropicrin using the RD_{50} study in mice conducted by Kane *et al.* (1979), but this was before the human sensory irritation study was available (OEHHA, 1999). They did a BMC analysis to derive a BMC_{05} of 790 ppb (5,300 $\mu g/m^3$) for the respiratory depression. Applying Haber's Law to adjust from the 10 minute exposure to a 1-hour exposure, the 1-hr BMC_{05} became 132 ppb. It is interesting to note that OEHHA applied Haber's Law to estimate the 1-hr REL since some think that sensory irritation is more concentration dependent. However, looking at the human study, during the first 30 minutes of exposure the severity of the eye irritation does appear to increase with time. Therefore, this assumption appears to be appropriate for extrapolating from time periods less than an hour up to an hour. OEHHA used an interspecies factor of only 3 due to the greater degree of certainty or precision in estimating a threshold in animals using a BMC analysis instead of the NOAEL approach. However, OEHHA did not think that the increased precision with the BMC analysis reduced the human variability, therefore, a standard intraspecies uncertainty factor of 10 was applied. This resulted in a 1-hr REL for chloropicrin of 4.4 ppb which is coincidentally identical to the 1-hr RfC that DPR derived based on increased NO in expired nasal air in humans.

The inhalation developmental toxicity study in rabbits conducted by York (1993) was selected as the definitive study for evaluating acute exposures of 8 and 24 hours. The endpoints observed at the LOEL in this study (maternal: death, nasal discharge, reduced body weights and food consumption, red discoloration of lungs) were more severe than those measured in the human study (increased NO in nasal air and eye irritation). The NOEL might have been higher if only a single dose had been administered since most effects, except the nasal discharge were not seen until after more than one dose was administered. Also, the respiratory effects in this study could also be local effects that were concentration dependent and not time dependent, in which case Haber's Law would not apply and the 8-hr and 24-hr NOEL would be same as the 6-hr NOEL. On the other hand, the NOEL might have been lower in this study if sensory irritation had been evaluated in the animals. It is interesting to note that the 8-hour RfC based on this study is very similar to the 1-hour RfC based on the sensory irritation in humans and the 1-hr REL that OEHHA derived based on sensory irritation in mice. If Haber's Law does not apply to the increased NO in nasal air or eye irritation, the 1-hr RfC could also be used for the 8-hour and

24-hour RfCs. If the 1-hr RfC for increased NO in nasal air was used for evaluating all acute exposures, the 8-hr RfCs would increase by 60% for children, but would be 30% lower for adults. The 24-hr RfCs would increase 5-fold for children and 2.3-fold for adults. If the 1-hr RfC for eye irritation had been used for evaluating all acute inhalation exposures, the 8-hr RfCs would increase 3.2-fold for children and 1.5-fold for adults. The 24-hr RfCs would increase approximately 9.5-fold for children and 4.6-fold for adults.

The 90-day inhalation study in rats was selected as the definitive study for evaluating seasonal exposure to chloropicrin with a critical NOEL of 120 ppb based on $BMCL_{05}$ for rhinitis in females rats (Chun and Kintigh, 1993). A NOEL of 300 ppb was observed in this study and in the 90-day inhalation study in mice, although the mice appeared to be more sensitive based on more severe effects at the LOEL including reduced body weights and food consumption, increased lung weights and histopathological lesions in the nasal cavity and lungs (Chun and Kintigh, 1993). The lowest $BMCL_{05}$ values were found in female mice for alveolar histiocytosis (81 ppb) and epithelial hyalin inclusions (84 ppb). However, after converting to an HEC taking species differences in breathing rate into consideration, the HEC for rhinitis in female rats was lower than the HECs for alveolar histiocytosis (44 ppb) and epithelial hyalin inclusions (45 ppb). If these HECs for alveolar histiocytosis or epithelial hyalin inclusions in female mice had been used instead of the one for rhinitis, the subchronic MOEs would be about 25-30% higher than calculated. Alternatively, if the observed NOEL of 300 ppb in rats (HEC = 87 ppb) was used, subchronic MOEs would be 2.5 times larger than estimated.

A similar situation occurred in the selection of the definitive study for evaluating chronic exposure to chloropicrin. A NOEL of 100 ppb was observed in both rats and mice. The lesions were more severe in mice, but if breathing rate was taken into consideration the NOEL in rats was lower. Therefore, DPR performed a BMC analysis on the more sensitive endpoints in the chronic inhalation studies and found the bronchiectasis in both sexes of mice to be the most sensitive endpoint with a $BMCL_{25}$ of 49 ppb. Even with adjusting for breathing rate, the HECs for this endpoint (27 and 56 ppb for children and adults, respectively) were the lowest. If the NOEL had been used instead of the $BMCL_{25}$, the lowest HECs would have been in rats (29 and 62 ppb for children and adults, respectively). If these HECs had been used, the chronic MOEs would have been higher by about 9%.

In calculating the cancer potency factor for chloropicrin, the adjusted number of animals at risk was taken from the Poly-3 trend test. An argument has been made that this test is not the appropriate test to use because survival is not affected and the test has not been validated in CD-1 mouse strain which has a natural life span of less than 2 years (CMTF, 2009a). However, the increase in tumors at the high dose could still be considered biologically significant even though by the Fisher's exact test it was just outside the statistical significance level ($p = 0.053$) because of the electrophilic structure of chloropicrin and the positive *in vitro* genotoxicity tests showing DNA damage, mutations and clastogenicity. Based on results from a Comet assay which showed the DNA damage caused by chloropicrin was easily repaired, an argument might also be made that no tumors would be expected until the DNA repair capabilities of an individual are overwhelmed suggesting there is a threshold for carcinogenicity. This argument seems to be supported by the fact that none of the *in vivo* genotoxicity tests were positive for chloropicrin despite the positive *in vitro* tests. Assuming there is a threshold, an alternative approach to evaluating the carcinogenic risk might be to calculate a $BMCL_{01}$ for the lung tumors in female mice. Given the adversity of the endpoint, a 1% BMR seems appropriate. The $BMCL_{01}$ for

lung tumors in female mice was estimated to be 14 ppb using the multistage model. The corresponding HEC for this endpoint would be 16 ppb. Given the uncertainty regarding carcinogenicity, an additional uncertainty factor of 10 seems appropriate for deriving the carcinogenicity RfC. This would result in a carcinogenicity RfC of 16 ppt which is 67-fold higher than the carcinogenicity RfC calculated assuming there is no threshold (0.24 ppt).

IV.B. EXPOSURE ASSESSMENT

IV.B.1. Occupational Exposure

The uncertainties associated with occupational exposure estimates for chloropicrin were discussed in the Exposure Appraisal section of the Exposure Assessment Document for chloropicrin (Beauvais, 2011) and just briefly summarized here. Occupational exposure estimates were based on monitoring Beard *et al.* (1996) and Rotondaro (2004). There was some uncertainty regarding the protection provided with respirators. Consequently, if the exposure estimates were greater than 100 ppb, they were not adjusted for wearing a respirator even though regulations require a respirator be worn when air concentrations were greater than 100 ppb because there is no consensus on the degree of protection provided by various respirators. Uncertainties related to adjustments to exposure estimates based on recoveries, application rates and fields size were also discussed in the Exposure Appraisal section in the Exposure Assessment Document.

IV.B.2. Bystander Exposure

As with occupational exposure estimates, the bystander estimates were based on air monitoring conducted by Beard *et al.* (1996) and Rotondaro (2004). Most of the uncertainties associated with bystander exposure estimates were also discussed in the Exposure Appraisal section of the Exposure Assessment Document for chloropicrin (Beauvais, 2011) and will not be repeated here. Other uncertainties were discussed in the Risk Appraisal section of the Risk Characterization Document evaluating chloropicrin as a potential toxic air contaminant (Lewis, 2010) and will not be repeated here. It should be noted that the bystander estimates were worse case scenarios based on a deterministic approach in the air modeling. Probabilistic modeling of the bystander exposures will be done in mitigation phase for chloropicrin and should result is more typical exposure estimates.

IV.C. RISK CHARACTERIZATION

Generally, a MOE of at least 100 is considered sufficiently protective of human health when the NOEL for an adverse effect is derived from an animal study. The MOE of 100 allows for humans being 10 times more sensitive than animals and for a 10-fold variation in sensitivity between the lower range of the normal distribution in the overall population and the sensitive subgroup (Dourson *et al.*, 2002). When the NOEL is derived from a human study, an MOE of 10 or greater is generally considered sufficiently protective allowing for intraspecies variation in sensitivity. For the increased NO in expired nasal air in humans, the standard 10-fold variation in intraspecies sensitivity was assumed. However, it should be noted that MOEs less than these targets does not necessarily mean there will be illnesses. A number of health protective assumptions were made in the endpoints selected, in the relative sensitivity of animals to humans

and in the variation in sensitivity within the human population which may not be correct. Furthermore, the exposure estimates were worse case scenarios which assumed rare combinations of high application rate, large field size, bystander standing downwind at field edge, and stable environmental conditions. But the likelihood of illnesses does increase as the MOE decreases below the target and, in fact, there are a number of illness reports associated with the use of chloropicrin.

For eye irritation in humans, the CMTF has suggested that the toxicokinetic component of the intraspecies uncertainty factor for sensory irritation could be reduced to one because of the mechanism of action (CMTF, 2009b). The inter- and intraspecies uncertainty factors is sometimes further divided into toxicokinetic and toxicodynamic components of 3.16 ($10^{0.5}$) each (Renwick and Lazarus, 1998). The mechanism of action for chloropicrin with respect to sensory irritation involves the direct interaction of the compound with the free trigeminal nerve endings in the respiratory mucosa. Consequently, toxicokinetics should not play a significant role in the development of this effect. The guidelines of the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances recommends an intraspecies uncertainty factor of 3 when the "response involves a direct acting mechanism of action where metabolic and physiologic differences are unlikely to play a major role" (NAC/AEGL Committee, 2001). An argument was also made to reduce the toxicodynamic component (variation in the interaction of the toxicant with the receptor) to 1 based on two assumptions: 1) the variation in the population was taken into consideration with the use of a benchmark dose analysis and 2) the subjects in the study represented the more sensitive human population subgroup (i.e, young adults). There was a large variation in sensitivity among the subjects of this study and this was taken into consideration in the use of the benchmark dose analysis to set the threshold. However, there is some uncertainty whether the most sensitive individuals were tested in this study. For one, subjects with asthma, allergic rhinitis, respiratory allergies, and chronic sinusitis were purposely excluded from the chloropicrin human sensory irritation study. Shusterman *et al.* (2003) reported that individuals with allergic rhinitis were more sensitive to sensory irritation due to various biochemical mediators, such as, histamine, prostaglandin E_2, and nerve growth factor that are known to augment the sensitivity of airway nerves to physical and chemical stimuli. Secondly, children have rarely been tested for sensory irritation so it is unclear if they are more or less sensitive than young adults. Children appear to be less able to detect odor than young adults, but this was attributed to a lack of odor-specific knowledge rather than a reduction in olfactory nerve sensitivity (Cain *et al.*, 1995). For these reasons, an intraspecies uncertainty factor of at least 3 is still desirable for eye irritation given the uncertainties regarding the toxicodynamic variation.

The 1-hr MOEs for occupational exposure with soil fumigation were less than 10 for all application methods when chloropicrin was an active ingredient in the formulation (> 15%) and, therefore, of concern. With the 10.5% formulation, the 1-hr MOEs were also less than 10, except for workers involved in bedded and drip irrigation applications. With the 2% formulations, many of the 1-hr MOEs were greater than 10, especially with bedded and drip irrigation application. The 8-hr MOEs with soil fumigation were less than 100 for most worker scenarios when chloropicrin was an active ingredient. However, when chloropicrin was 10% or less of the formulation, many of the 8-hr MOEs were over 100, especially with bedded and drip irrigation application. The seasonal MOEs were similar to the 8-hr MOEs with most being less than 100 when chloropicrin was an active ingredient, but when 10% or less of the formulation, the seasonal MOEs were often greater than 100 especially with bedded and drip irrigation

application. The annual MOEs for workers involved in soil fumigation were about twice as large as the seasonal MOEs, but were still less than 100 for most scenarios when chloropicrin was an active ingredient. All of the annual MOEs were greater than 100 when chloropicrin was less than 2% of the formulation.

The MOEs for workers involved in structural fumigation are smaller than those involved in soil fumigation for similar exposure durations. All the MOEs were less than their target MOEs (10 for 1-hr and 100 for longer exposure durations), usually by a couple of orders of magnitude.

Bystander exposure to chloropicrin following soil fumigation is of concern since all of the MOEs were less than 100 for both children and adults. The acute MOEs are of great concern since they are all less than 1, except for the 24-hr MOEs for adults with the drip irrigation application. With the 1-hr exposure, the MOEs are orders of magnitude lower than the benchmark that would be considered adequate based on the increased NO in nasal air in the human study (i.e., 10). Even if the intraspecies uncertainty factor had been reduced to 1X, the bystander exposure would still be of concern. The seasonal and chronic MOEs for soil fumigation air were greater than or equal to 1, but still less than 100 which is the target MOE for these exposure durations since the NOELs were based on animal studies.

The bystander MOEs for chloropicrin following structural fumigation are higher than those for soil fumigation, but the 1-hr bystander MOEs for structural fumigation are still lower than the target MOE of 10, thus this acute exposure scenario for structural fumigation is of concern. The 8-hr and 24-hr bystander MOEs for structural fumigation are less than target MOE of 100 and, therefore, these acute exposure scenarios are of some health concern. The indoor air concentrations following structural fumigation were of even greater health concern with the 1-hr MOEs being less than 0.1 and the 8-hr and 24-hr MOEs being less than 10.

A carcinogenic risk level less than 10^{-6} is generally considered negligible. For workers involved in soil fumigation, the cancer risks estimates were all greater than the negligible risk level. When chloropicrin was used as an active ingredient, the occupational risk estimates were all greater than 2.7×10^{-4}. When chloropicrin was used as a warning agent at 10.5%, the risk estimates for workers were all greater than 2.8×10^{-5}. When chloropicrin was used as a warning agent at 2%, the occupational risk estimates were all greater than 1.1×10^{-5}. For workers involved in structural fumigation, the cancer risk estimates were higher than for workers involved in soil fumigation. The occupational risk estimates for structural fumigation were all greater than 1.0×10^{-2} for scenarios where repeated exposure is anticipated. The carcinogenic risk estimates for residential and occupational bystanders for soil fumigation were significantly greater (10^{-3} to 10^{-2}) than the negligible risk level. However, it should be noted that if there is a threshold for the carcinogenicity, the cancer risk estimates derived in this risk assessment could be overestimated by several orders of magnitude. Given the widespread use of chloropicrin, one would expect an association between exposure to chloropicrin and lung cancer would have been noticed by now if the cancer potency is as high as estimated.

IV.D. U.S. EPA'S HUMAN HEALTH RISK ASSESSMENT FOR CHLOROPICRIN

U.S. EPA completed a Human Health Risk Assessment for chloropicrin in June 2008 (Reaves and Smith, 2008). U.S. EPA then revised this risk assessment in April 2009 to include new flux data and revised air modeling (Reaves and Smith, 2009). U.S. EPA evaluated occupational and residential exposure to chloropicrin in the air using inhalation NOELs. U.S. EPA did not evaluate dietary exposure to chloropicrin since no residues are anticipated on food based on its volatility and results from metabolism studies on soil and plants. Therefore, there are no food tolerances for chloropicrin. U.S. EPA evaluated acute (1-24 hours) non-occupational and occupational exposure to chloropicrin using the human sensory irritation study. This study was evaluated by U.S. EPA's Human Studies Review Board (HSRB) which concluded it was conducted in an ethical manner and was scientifically sound. U.S. EPA adopted the benchmark dose analysis of the human study performed by consultants for the CMTF (Haber *et al.*, 2005). The $BMCL_{10}$ of 73 ppb was selected as the NOAEL or point of departure to evaluate all short-term exposures up to 24 hours. In their analysis, Haber *et al.* converted the eye irritation scores which were continuous data to quantal data by selecting a cut-off of 1.5 for the average score during the plateau period to define adversity. This assumes that some level of mild eye irritation is acceptable given its use as a warning agent. This is in contrast to DPR's approach that used a different endpoint (increased NO in expired nasal air) and method to define the threshold (hybrid approach) whereby the standard deviation in the response to blank air was used to define the threshold. This approach for selecting a threshold to define adversity was more objective and did not consider its use as a warning agent which was a risk management decision. However, the use of chloropicrin as a warning agent will be taken into consideration by DPR in their risk mitigation for chloropicrin. Due to differences in endpoints selected and approach used for selecting the threshold, the $BMCL_{05}$ that DPR used to evaluate 1-hr exposures was 44 ppb which was approximately 1.7-fold lower than that used by U.S. EPA (73 ppb). Furthermore, DPR used the full 10-fold intraspecies uncertainty factor with the increased NO in nasal air to estimate the 1-hr RfC while U.S. EPA reduced the intraspecies uncertainty factor for eye irritation to 1 resulting in an acute RfC that was 17-fold higher than DPR's. In addition, DPR only used the human study to evaluate exposures up to 1-hr due to uncertainties about the applicability of Haber's Law to the more sensitive endpoints in the human study while U.S. EPA used the $BMCL_{10}$ for eye irritation in humans to evaluate exposures up to 24 hours. Instead DPR used the acute NOEL from a rabbit developmental toxicity study (York, 1993) to evaluate 8-hr and 24-hr exposures assuming Haber's Law applied to the more severe acute effects seen in this study (maternal deaths with red discolored lungs, nasal discharge, and reduced body weights and food consumption). Since this NOEL was derived from an animal study, an uncertainty factor of 100 was used to estimate the 8-hr and 24-hr RfCs. Consequently, DPR's 8-hr and 24-hr RfCs for children were approximately 27-fold and 79-fold lower than U.S. EPA's acute RfC. Therefore, despite DPR and U.S. EPA both using a benchmark dose analysis to analyze the acute endpoints in the same human study, they derived very different acute RfCs based on 1) different endpoints selected, 2) different assumptions in setting the threshold for the benchmark dose analysis, 3) different assumptions about the applicability of Haber's Law for exposures longer than 1 hour and 4) different assumptions about the variability of the response in selecting uncertainty factors for setting the RfC.

Unlike DPR, U.S. EPA did not do a BMC analysis on the subchronic studies. Instead they used the observed NOELs and converted them to HECs using a regional gas dose ratio (RGDR) which adjusts for interspecies differences in not only breathing rate, but also regional

surface area, if the effects were local. The RGDR for respiratory effects is basically the ratio of the minute volume to the regional surface area in animals divided by the ratio of the minute volume to the regional surface area in humans. For this purpose, the respiratory tract was divided into three regions: extrathoracic, tracheobronchial and pulmonary. Using the RGDR for extrathoracic effects, U.S. EPA calculated a HEC of 8 ppb for the 90-day mouse inhalation study, which it used to evaluate seasonal non-occupational exposure to chloropicrin. U.S. EPA's HEC for seasonal occupational exposure was 35 ppb assuming exposure was limited to 8 hrs/day, 5 days/wk. DPR did not calculate different HECs for occupational and residential exposure, but did calculate different HECs for adults and children based on differences in their breathing rates. DPR's subchronic HEC for children was 35 ppb and for adults was 73 ppb.

U.S. EPA assumes that pharmacokinetic differences are taken into consideration in the RGDR adjustment and, consequently, only use an uncertainty factor of 3 for interspecies differences to account for pharmacodynamic differences. DPR has not adopted the use of the RGDR adjustment in the HEC calculation because there are insufficient data and experience for an adjustment of the dose estimate for respiratory effects based on surface area, especially on a regional basis, that would adequately account for the pharmacokinetic differences between species. Instead, DPR prefers to make adjustments for species differences in intake based on their breathing rate and not make any assumption about the concentration of the chemical in different regions of the respiratory tract. For this reason, DPR retains the use of the default uncertainty factor of 10 for interspecies variation to account for both pharmacokinetic and pharmacodynamic differences. So despite the differences in the subchronic HECs, the subchronic RfCs for residential exposure are fairly similar between DPR (0.35 ppb - children) and U.S. EPA (0.27 ppb).

A similar situation occurred with the chronic endpoints. U.S. EPA used the chronic NOEL from the mouse inhalation study and estimated an HEC of 4 ppb for long-term non-occupational exposure and 15 ppb for long-term occupational exposure. OEHHA also calculated an HEC for the chronic mouse inhalation study using an RGDR factor, however, OEHHA's HEC for the chronic mouse study (1.6 ppb) was 2.5-fold lower than U.S. EPA's HEC because OEHHA used a BMC_{05} of 42 ppb for this study instead of the observed NOAEL of 100 ppb. EPA's and OEHHA's HECs for the chronic mouse study are about 8-fold and 20-fold lower, respectively. However, because DPR applied a larger uncertainty factor to estimate the chronic RfC, DPR's chronic RfC (0.27 ppb for children) was only about 2-fold higher than U.S. EPA's chronic RfC (0.13 ppb - residential) and about 5-fold higher than OEHHA's chronic REL (0.05 ppb).

U.S. EPA acknowledged that there may be a carcinogenic risk with oral exposure to chloropicrin based on the increase in fibroadenomas in female rats in one study with oral exposure, but they did not think chloropicrin was a carcinogen by the inhalation exposure based on the inhalation studies which, in their evaluation, did not indicate an increase in neoplasm incidence. The National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee) apparently also did not consider chloropicrin carcinogenic by the inhalation route since they did not mention the increase in adenomas and carcinomas in lungs of female mice in their summary of the inhalation carcinogenicity studies for chloropicrin (NAC/AEGL Committee, 2008). The conclusions of these agencies is in contrast with DPR's evaluation of the lung tumors in female mice which relied on the use of the Poly-3 trend test to determine statistical significance rather than the more traditional Fisher's

exact test. The CMTF argued that the Poly-3 trend test was not appropriate with this data because survival was not affected and this test had not been validated in CD-1. However, NTP does use this test as their default trend test even when survival is not affected. Furthermore, it seems unlikely that the distribution curves for these lung tumors in CD-1 would be significantly different from those in B6C3F1 mice since their historical control ranges are very similar (CD-1: 0-27% vs. B6C3F1: 0-24%). Therefore, DPR considered it an appropriate, if not preferred, trend test for analyzing this data. Table 44 summarizes the critical endpoints, HECs and RfCs that U.S. EPA used in its risk assessment for chloropicrin.

Table 44. Comparison of DPR's and U.S. EPA's Critical Endpoints, Human Equivalent Concentrations and Reference Concentrations for Chloropicrin

Exposure Duration/ Agency	Critical Endpoints	HEC		RfC	
Acute/ DPR	↑ NO in nasal air in humans	Child 44 ppb	Adult 44 ppb	Child 4.4 ppb UF[a] = 10	Adult 4.4 ppb UF = 10
Acute/ U.S. EPA	Ocular irritation in humans	Resident. 73 ppb	Occupat. 73 ppb	Resident. 73 ppb UF = 1[b]	Occupat. 73 ppb UF = 1
Seasonal/ DPR	Rhinitis in female rats	Child 35 ppb	Adult 73 ppb	Child 0.35 ppb UF=100[c]	Adult 0.73 ppb UF=100
Seasonal/ U.S. EPA	Nasal and lung damage, increased lung weights in mice	Resident. 8 ppb	Occupat. 35 ppb	Resident. 0.27 ppb UF = 30[d]	Occupat. 1.2 ppb UF=30
Chronic/ DPR	Bronchiectasis in male and female mice	Child 27 ppb	Adult 56 ppb	Child 0.27 ppb UF=100	Adult 0.56 ppb UF = 100
Chronic/ U.S. EPA	Nasal discharge, nasal and lung damage, increased lung weight, body weight loss in mice	Resident. 4 ppb	Occupat. 15 ppb	Resident. 0.13 ppb UF = 30	Occupat. 0.50 ppb UF =30

a UF = Uncertainty factor used to derive RfC.
b U.S. EPA reduced the intraspecies uncertainty factor to 1 due to the mechanism of action for this endpoint and the most sensitive population was tested.
c DPR did not use the RGDR adjustment in the calculation of their HECs due to insufficient data and experience supporting the adjustment of the dose estimate for respiratory effects based on surface area. Therefore, DPR used a default interspecies uncertainty factor at 10.
d U.S. EPA reduced the interspecies uncertainty factor to 3 because of the use of the RGDR factor in their HEC calculations.

U.S. EPA evaluated occupational exposure for workers involved in soil fumigation using worker breathing zone air sampler data from the same studies that DPR used which were conducted by Beard *et al.* (1996) and Rotondaro (2004). Unlike DPR, U.S. EPA's evaluations

were limited to acute and short-/intermediate-term exposures. For acute exposures, they used the maximum air concentrations from these studies which they reported as ranging 0.00066 ppm for tarp punchers with drip irrigation, tarped application to 0.654 ppm for tarp removers with broadcast, tarped application. DPR's 1-hr and 8-hr exposure estimates were higher since they were based on the 95th percentile concentrations reported and adjusting for the maximum application rate. DPR's 1-hr and 8-hr estimates when chloropicrin was more than 15% of the formulation were 0.0166 ppm for tarp punchers with drip irrigation, tarped application and 3.140 ppm for tarp removers with broadcast, tarped application. Given U.S. EPA's lower acute exposure estimates and higher acute NOEL, their acute MOEs were significantly higher than DPR's for occupational exposure. Most of their acute MOEs exceeded their target MOE of 1. For short- and intermediate-term occupational exposure estimates, U.S. EPA used the geometrical mean air concentration. Their lowest exposure estimate for this duration were 0.0006 ppm for tarp punchers with drip irrigation, tarped application while their highest estimate was 0.099 ppm for tarp removers with broadcast, tarped application. DPR calculated seasonal occupational exposure using the arithmetic mean air concentrations and assumed an average application rate of 190 lbs/acre. Consequently, DPR's seasonal exposure estimates were more similar to U.S. EPA's estimates with 0.00186 ppm for tarp punchers with drip irrigation, tarped application and 0.0495 ppm for tarp removers with broadcast, tarped application. Since U.S. EPA's target MOE for their short- and intermediate-term exposures was 30, most of their MOEs were below the target. However, use of a PF10 respirator mitigated most of these exposures, except with broadcast (tarped and untarped) and bedded, tarped application. Unlike DPR, U.S. EPA did not estimate occupational exposure for structural fumigation.

Both U.S. EPA and DPR estimated bystander exposure to chloropicrin following soil fumigation using the flux data from the studies conducted by Beard *et al.* (1996) and Rotondaro (2004) and the ISCST3 model. However, DPR used a deterministic approach with screening level meteorological conditions to provide a single downwind centerline of off-site air concentrations representing reasonable worst case exposure. U.S. EPA used the PERFUM model, which has the ISCST3 model as the core processor, and applied a variety of meteorological conditions to produce buffer zones in a distributional format so that their approach is more probabilistic. U.S. EPA ran analyses with PERFUM assuming a variety of field sizes from 5 to 120 acres and application rates of 2 to 100%. The 2% application rate was selected to evaluate the use of chloropicrin as a warning agent. Meteorological data from six weather stations were used by U.S. EPA (Ventura, CA, Bakersfield, CA, Flint, MI, Tallahassee, FL, Bradenton, FL, and Yakima, WA). Nineteen flux profiles were analyzed by U.S. EPA including broadcast/tarped, broadcast/untarped, bedded/tarped, and bedded/untarped applications in Phoenix (AZ), broadcast/tarped, broadcast/untarped, deep broadcast/untarped, and strip/tarped applications in Wasco (CA), buried drip irrigation at 10" deep/tarped and untarped and at 6" deep/untarped in Yuma (AZ), bedded/tarped applications in Dover (FL), Bainbridge (GA), and Hart (MI) with three different tarps, broadcast/tarped applications in Bradenton (FL) and Yakima (WA), and drip irrigation/tarped applications in Douglas (GA) and Salinas (CA, 2 volatility studies with different tarps). In comparison, DPR limited its exposure estimates to seven flux profiles, including broadcast/tarped, broadcast/untarped, bedded/tarped, and bedded/untarped applications in Phoenix (AZ), broadcast/tarped applications in Bradenton (FL) and Yakima (WA), and a drip irrigation/tarped application in Salinas (CA). While U.S. EPA estimated downwind air concentrations at several application rates, DPR estimated air concentrations only at the maximum application rate at a distance of 3.04 m (10 ft) as part of their deterministic approach. Since U.S. EPA only reported the size of the buffer zone needed to mitigate the risk

and not specific air concentrations, a direct comparison of U.S. EPA's and DPR's bystander exposure estimates was difficult.

DPR found the highest 1-hour and 8-hour exposure estimates with the broadcast/non-tarped application and the highest 24-hour exposure estimates with the bedded/tarped application. U.S. EPA only estimated buffer zones for 24-hour exposure periods. U.S. EPA found that the buffer zones needed to meet the target MOE exceeded 1440 meters (the maximum buffer zone distance calculated by PERFUM) for a 40 acre field using the flux data from the bedded/tarped, bedded/untarped and broadcast/untarped applications in Phoenix, AZ, at the 95th to 99.9th percentiles, regardless of the meteorological data used. The buffer zones also exceeded 1440 meters at the 99.9th percentile using the flux data from the broadcast applications in Wasco, CA. U.S. EPA calculated whole field buffer zones distances as well as the maximum buffer zone distances while DPR only calculated maximum buffer zone distances. DPR did not calculate whole field buffer zones because it is not possible to know the percentile of protection for any particular whole field buffer zone.

To estimate bystander exposure following structural fumigation, U.S. EPA used air concentrations using air monitoring data that ARB performed in 2004 (ARB, 2005a &b). DPR used the highest air concentrations from these same data to estimate exposure for structural fumigation. The highest air concentration U.S. EPA estimated from these data was 0.79 ppb (5.3 $\mu g/m^3$) which presumably was treated as a 24-hr exposure estimate. DPR estimated the highest 1-hr, 8-hr and 24-hr air concentrations to be 11, 2.4 and 0.92 ppb (73, 16 and 6.2 $\mu g/m^3$), respectively, after adjusting for recovery and maximum application rate.

U.S. EPA also estimated exposures for greenhouse fumigation. The exposures for this use were also estimated using the PERFUM model assuming aeration with no stack. Assuming only 25% of the amount applied (300 lbs/acre) is released, the maximum buffer zone distances were less than 135 ft with greenhouses up to 50,000 sq. ft. Assuming 50-75% were released, the maximum buffer zone distances increased up to 455 ft. DPR did not estimate greenhouse fumigation so no comparison was possible.

U.S. EPA did not specifically evaluate the need for an additional uncertainty factor for infants and children based on the Food Quality and Protection Act since there are no tolerances for chloropicrin. However, they noted that the incident reports for chloropicrin suggest that children and asthmatics respond similarly to other individuals. Furthermore, they also recommended that an intraspecies uncertainty factor of 10 is not warranted. They cited a 2005 WHO International Programme on Chemical Safety (IPCS) guidance document on deriving chemical specific adjustment factors which divided the intraspecies uncertainty factor into two components, toxicokinetics and toxicodynamics. Sensory irritation is a local effect so absorption, distribution, metabolism and excretion are not involved. Therefore, they argued that the toxicokinetic component can be reduced to 1X. The toxicodynamic component is defined as the determination and quantification of the sequence of events at the cellular and molecular levels leading to a toxic response. The IPCS guidance document listed three questions to consider in the determination of the adequacy of the experimental data for refinement of the toxicodynamic component: relevance of population, adequacy of concentration-response data and adequacy of number of subjects/samples. U.S. EPA considered the population tested to be the most sensitive, there was a clear dose-response evaluation in the third phase of the human study and the number of subjects tested (127 for all 3 phases) adequate. Consequently, they

argued the toxicodynamic component could also be reduced to 1X. Therefore, an MOE of 1 defined U.S. EPA's level of concern for acute exposure. DPR recommended an intraspecies uncertainty factor of 10 be used for eye irritation since there appears to be a large variation in sensitivity among the subjects of the human study based on their eye irritation scores.

IV.E. ISSUES RELATED TO THE FOOD QUALITY PROTECTION ACT

The Food Quality Protection Act of 1996 mandated U.S. EPA to "upgrade its risk assessment process as part of the tolerance setting procedures" (U.S. EPA, 1997a and b). The improvements to risk assessment were based on the recommendations from the 1993 National Academy of Sciences report, "Pesticides in the Diets of Infants and Children" (NAS, 1993). The Act required an explicit finding that tolerances are safe for children. U.S. EPA was required to use an extra 10-fold safety factor to take into account potential pre- and post-natal developmental toxicity and the completeness of the data unless U.S. EPA determined, based on reliable data, that a different margin would be safe. In addition, U.S. EPA must consider available information on: 1) aggregate exposure from all non-occupational sources; 2) effects of cumulative exposure to the pesticide and other substances with common mechanisms of toxicity; 3) the effects of *in utero* exposure; and 4) the potential for endocrine disrupting effects. U.S. EPA did not recommend an FQPA factor for chloropicrin since there are no food tolerances for chloropicrin and, therefore, FQPA does not apply. However, the issues addressed under FQPA could still be potentially of concern for chloropicrin and warrant further discussion.

IV.E.1. Prenatal and Postnatal Sensitivity

Two developmental toxicity studies (one with rats and another with rabbits) were available for chloropicrin (Schardein, 1993; York, 1993). Both studies were acceptable based on FIFRA guidelines. Fetal effects in rats included reduced fetal body weights and various skeletal variations (reduced ossification of skull bone, less than 13 rib pairs, 14th rudimentary ribs, bent ribs, unossified 5th and 6th sternebrae). Developmental effects in rabbits included increased pre- and post-implantation losses, late-term abortions, reduced fetal body weights, visceral (left carotid arising from the innominate) and skeletal variations (unossified hyoid body and unossified tail). In both studies, the developmental NOEL was equal or greater than the NOEL for maternal effects. Based on these two studies, there is no evidence of increased prenatal sensitivity to chloropicrin.

There were two reproductive toxicity studies in rats for chloropicrin, a one-generation range-finding study and a standard two-generation study (Denny, 1996; Schardein, 1994). Only the two-generation study met FIFRA guidelines. No developmental effects were seen in the pups in either study. The only reproductive effect was a reduced number of implantation sites in the range-finding study at 2 ppm which was higher than the top dose in the main study (1.5 ppm). The pup/reproductive NOELs were equal to or greater than the parental NOELs in these studies. Based on these reproductive toxicity studies, there is no evidence of increased postnatal sensitivity to chloropicrin. While not required by FIFRA guidelines, the neonates in this study were not exposed directly to chloropicrin vapors until day 28, so theoretically they could have been more sensitive during this developmental period.

Based on the absence of ossification and reduced ossification seen in the two developmental studies, OEHHA concluded that the fetus is impacted by inhalation exposure to chloropicrin (OEHHA, 2009). They note that the octanol/water partition coefficient suggests that it is likely to cross the placenta and be present in breast milk. They suggested a toxicokinetic safety factor of 10 should be applied to protect for this. They also suggest that chloropicrin may impact development by binding with sulfhydryl groups during critical phases of development, leading to possible functional deficits later in life. They note that chloropicrin has a similar mechanism of action to that of arsenic, methylene chloride and a few other chemicals which have been shown to affect critical enzymes during development. This may also be true for chloropicrin, but there is no evidence that this is occurring in fetuses at doses below those which cause maternal or parental toxicity. Furthermore, chloropicrin appears to be a fairly reactive chemical and is most likely reacting primarily with sulfhydryl groups at the site of first contact (i.e, the respiratory tract). For this reason, it seems unlikely that a sufficient amount of chloropicrin would get into the blood stream to affect the developing fetus or nursing pup. Most of the effects seen in the adults were in the respiratory tract, supporting the theory that very little of it reaches the blood stream. In addition, the effects seen in available developmental and reproductive toxicity studies were non-specific signs of delayed development including reduced implantation sites, late-term abortions, reduced pup weights and visceral and skeletal variations. Since these fetal or pup effects were seen at doses that also caused maternal toxicity, it is possible that they are indirect effects from maternal toxicity, such as reduced maternal body weight. There was nothing to suggest any functional losses, either physiological or neurological, although a developmental neurotoxicity study had not been conducted. Generally, DPR and U.S. EPA do not require developmental neurotoxicity studies for chemicals unless there is evidence of neurotoxicity in adults. Although there was no evidence of increased pre- and postnatal sensitivity from the available developmental and reproductive toxicity studies which met FIFRA guidelines, theoretically it is possible that the neonates could be more sensitive to direct exposure to chloropicrin vapors due to a higher breathing rate or the immaturity of their respiratory system, immune system and/or metabolic enzymes. For this reason, it may be appropriate to consider an additional uncertainty factor for infants and children.

V.E.2. Endocrine Effects

The Food Quality Protection Act (FQPA) of 1996 required U.S. EPA to develop a screening program to determine the endocrine disruption potential of pesticides. In 1997, the Risk Assessment Forum of the U.S. EPA published a report that reviewed the current state of science relative to environmental endocrine disruption (U.S. EPA, 1997c). U.S. EPA formed the Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC) to develop a strategy for screening and testing of pesticides for their potential to produce endocrine disruption. The EDSTAC members include various stakeholders and scientific experts. This screening and testing process was to be implemented by August of 1999 as required by FQPA.

Environmental chemicals can interact with the endocrine system, resulting in cancer, reproductive and/or developmental anomalies (EDSTAC, 1998). It may produce these effects by affecting hormonal production and synthesis, binding directly to hormone receptors or interfering with the breakdown of hormones (U.S. EPA, 1997c). The interim science policy stated in U.S. EPA's 1997 report is that "*the Agency does not consider endocrine disruption to be an adverse endpoint per se, but rather to be a mode or mechanism of action leading to other outcomes*." The only possible endocrine related effects seen in the available animal studies for

chloropicrin were reduced number of implantation sites, increased pre- and post-implantation losses and later-term abortions observed in the developmental and reproductive toxicity studies (York, 1993; Denny, 1996). However, it is unclear from these studies if any of these effects are mediated through endocrine disruption or some other mechanism. U.S. EPA has stated that once its Endocrine Disruptor Screening Program (EDSP) has been developed and vetted, chloropicrin may be subject to additional screening and/or testing to better characterize its endocrine disruption potential (U.S. EPA, 2008a). It should be noted that U.S. EPA concluded in its human health assessment for chloropicrin that there was no evidence of endocrine disruption from the available data (Reaves and Smith, 2008).

IV.E.3. Cumulative Toxicity

Chloropicrin kills common root destroying fungi, nematodes, soil insects and other plant pests. Chloropicrin causes sensory irritation and respiratory toxicity in animals which may be related to its reaction with thiol groups in proteins. U.S. EPA evaluated the mode of action for chloropicrin and noted that its potential to cause eye irritation was similar to methyl isocyanate (MITC) (U.S. EPA, 2008b). U.S. EPA described the mode of action for chloropicrin as sensory irritation. This may describe the mode of action for the effects in the upper respiratory tract at low concentrations, but obviously the respiratory effects, especially in the lower respiratory tract, go beyond the irritation of sensory trigeminal nerves seen at higher concentrations. Irritation may still be a key part of its initial mode of action in the lower respiratory tract. However, there is insufficient information about the mode of action for chloropicrin and other fumigants which also cause sensory irritation and/or respiratory toxicity to know if they have similar modes of action.

V. CONCLUSIONS

The risks for potential adverse human health effects with bystander exposure to chloropicrin after soil and structural fumigation were evaluated using margin of exposure (MOE) estimates. The MOEs for acute, subchronic and chronic exposure were calculated using no-observed-effect levels (NOELs) or benchmark concentration (BMC) estimates from the available guideline and literature toxicity studies for chloropicrin. In selecting the NOELs/BMCs to evaluate exposure, the greatest weight was given to studies which met FIFRA guidelines. Generally, an MOE greater than 100 is considered sufficiently protective of human health when the NOEL/BMC for an adverse effect is derived from an animal study. The MOE of 100 allows for humans being 10 times more sensitive than animals and for a 10-fold variation in sensitivity between the lower distribution of the overall human population and the sensitive subgroup. When the NOEL/BMC is derived from a human study generally an MOE of 10 is considered sufficiently protective, allowing for intraspecies variation. A carcinogenic risk level less than one in a million or 10^{-6} is generally considered negligible.

The estimated health risks for workers involved in soil fumigation are of concern when chloropicrin is an active ingredient since the MOEs were less than their target for most scenarios. Broadcast applications had the lowest MOEs. There is less concern for occupational exposure with soil fumigation when chloropicrin was used only as a warning agent, especially at a concentration of 2% or less. The MOEs for most of the scenarios at this concentration were above their target. The potential health risks from bystander exposure to chloropicrin following soil fumigation are of also concern since all of the MOEs were less than their target MOE for both children and adults based on reasonable worse case exposure estimates. The acute bystander exposure is of particular concern since the MOEs were all less than their target MOEs by orders of magnitude. The seasonal and chronic MOEs for soil fumigation were greater than or equal to1.0, but they were still less than the target MOE of 100.

There is concern about the potential health risks for workers involved in structural fumigation since all of the MOEs were less than their target MOEs. The off-site air concentrations of chloropicrin following structural fumigation were lower than those following soil fumigation, but the acute bystander exposure is still of concern since the MOEs were less than their target. The indoor air concentrations after complete aeration with structural fumigation are of greater concern with 1-hr MOEs less than 0.01 and the 8-hr and 24-hr MOEs less than 10. No seasonal or chronic bystander exposures are expected for structural fumigation.

Lifetime exposure for chloropicrin soil fumigation workers is a concern since their calculated cancer risk estimates were all greater than the negligible risk level, even when chloropicrin was used only as a warning agent at 2%. The lifetime exposures for structural fumigation workers are also a concern since their cancer risk estimates were all well above the negligible risk level. The lifetime exposure for bystanders of chloropicrin soil fumigation are of particular concern since their cancer risk estimates were greater than the negligible risk level by several orders of magnitude. However, cancer risks may have been overestimated due to uncertainties related to the carcinogenicity potential of chloropicrin (see pages 58, 92 and 97 in the Hazard Identification and Risk Appraisal sections for further discussion).

Based on the low MOEs and high cancer risk estimates for most occupational and bystander exposure scenarios mitigation should be considered.

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