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MEMORANDUM

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DATE: November 24, 2009

SUBJECT: FINDINGS ON THE HEALTH EFFECTS OF THE ACTIVE INGREDIENT CHLOROPICRIN

Enclosed please find a copy of the Office of Environmental Health Hazard Assessment's (OEHHA) findings for the active ingredient chloropicrin. These findings were prepared in response to the risk characterization document (RCD) for chloropicrin prepared by the Department of Pesticide Regulation (DPR). OEHHA comments on the draft exposure assessment document and draft risk characterization document for chloropicrin were sent to you in a previous memorandum dated March 23, 2009.

The comments were prepared in response to the DPR's Chloropicrin Draft Exposure Assessment Document (EAD), Part A (dated November 14, 2008); and Chloropicrin Draft Risk Characterization Document, Part B (dated December 2, 2008). The Findings were prepared after discussions with DPR and in response to DPR's revised draft chloropicrin report released November 2009 (Draft Report for the Scientific Review Panel. Part A - Chloropicrin Environmental Fate Review and Exposure Assessment. Part B - Chloropicrin Human Health Assessment.). The information contained in these documents serves to identify chloropicrin as a candidate toxic air contaminant (TAC).

Pursuant to Food and Agricultural Code sections 14022 and 14023, OEHHA provides review, consultation and comments to DPR on the evaluation of the health effects of candidate TACs. As part of its statutory responsibility, OEHHA also prepares findings on the health effects of candidate TACs. This documentation is to be included as part of the DPR report.

Should you have any questions regarding OEHHA's findings on the health effects of chloropicrin, please contact Dr. Charles Salocks at (916) 323-2605, Dr. Melanie Marty at (510) 622-3154, or Dr. Anna M. Fan at (510) 622-3165.

Attachment

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Office of Environmental Health Hazard Assessment's Findings on the Health Effects of Chloropicrin

Pursuant to Food and Agriculture Code Sections 14022 and 14023, the Office of Environmental Health Hazard Assessment (OEHHA) of the California Environmental Protection Agency (Cal/EPA) provides consultation and technical assistance to the Department of Pesticide Regulation (DPR) on the evaluation of health effects of candidate toxic air contaminants (TAC) and prepared health-based findings. OEHHA previously reviewed and commented on earlier draft documents prepared by DPR on the evaluation of human health risks associated with potential exposure to chloropicrin. These documents are used by DPR in considering whether to list chloropicrin as a TAC. As part of its statutory responsibility, OEHHA has also prepared these findings on the health effects of chloropicrin which are to be included as part of DPR's Risk Characterization/Toxic Air Contaminant (RC/TAC) documents.

Documents Reviewed

Evaluation of Chloropicrin as a Toxic Air Contaminant. Part A: Environmental Fate and Exposure Assessment (Final Draft, November 2009; prepared by Worker Health and Safety Branch, DPR) and *Part B: Human Health Assessment* (Draft, November 9, 2009; prepared by Medical Toxicology Branch, DPR).

Chemical Identification

1. Chloropicrin (trichloronitromethane) is a fumigant pesticide that is used to completely fill an area, such as a building or soil in a field, to control targeted pests or soil pathogens, certain weeds, and nematodes that adversely affect crops. In addition to its use as a pesticide active ingredient, chloropicrin is also added as a warning agent to other fumigants due to its low odor threshold and ability to cause sensory irritation at very low concentrations.

Usage and Reported Illnesses

2. Chloropicrin use in California has increased from 2,494,606 pounds in 1993 to 5,494,541 pounds in 2007, with the total number of acres treated averaging 53,974 during this 15-year interval. As of May 2009, there are 54 registered products containing chloropicrin in California, including 7 products intended solely for manufacturing or reformulation use and 8 products where chloropicrin is used as a warning agent. The majority of use was for pre-plant fumigation of strawberry fields, which accounted for an average of 68% of pounds applied from 1993-2007. Other crops for which some chloropicrin-containing products are registered as pre-plant fumigants include asparagus, broccoli, cauliflower, eggplant, grapes, lettuce, melons, onions, peppers, pineapple, tomatoes, floral crops, nursery crops, and fruit and nut crops.

3. Between 1992 and 2007, the Pesticide Illness Surveillance Program of DPR recorded 1,015 illness cases that were definitely, probably, or possibly related to chloropicrin exposure, or that were associated with or indirectly related to fumigants with chloropicrin as a warning agent. Most of the illnesses involved eye and respiratory symptoms but systemic and skin effects were also reported. Additionally, various smaller incidents were reported in the open literature.

Environmental Fate

4. Chloropicrin rapidly diffuses through the soil in all directions following application, and then dissipates quickly, with half-lives ranging from approximately one hour to several days. Volatilization is reported to be the major pathway through which chloropicrin dissipates from soil, but it also undergoes chemical degradation and microbial decomposition. Chloropicrin can persist in water for several days in the absence of light, but degrades rapidly when subjected to light of suitable wavelengths, with half-lives ranging from 6 hours to 3 days. Chloropicrin also reacts quickly and undergoes reductive dechlorinations under reducing conditions. The potential for chloropicrin to bioconcentrate in aquatic organisms is anticipated to be low. In the air, chloropicrin is reactive and photodegrades to phosgene and nitrosyl chloride with an estimated half-life of 18 hours.

5. Although chloropicrin has been reported to dissipate rapidly from soil under many conditions, Guo et al. (2003) report a case in Maine in which the soil beneath a former chloropicrin manufacturing facility contained residues as high as 500 mg/kg seven years after manufacturing ceased and the facility was abandoned. Chloropicrin concentrations in groundwater beneath the facility ranged from 10-150 mg/l. In the same report, results of follow-up soil column studies suggested that under conditions of high water movement through soil and limited microbial activity, substantial amounts of chloropicrin could potentially leach into ground water.

6. The results reported by Guo et al. (2003) suggest that, under some conditions, chloropicrin has the potential to contaminate soil and ground water. Additionally, chloropicrin may migrate laterally in soil gas and ground water, and subsequently move upwards into residential structures and buildings surrounding the site of application. If this were the case, populations living and/or working in structures near agricultural fields where chloropicrin is applied could be exposed via inhalation of indoor air. For these reasons, additional investigation of the persistence of chloropicrin in soil, its potential for subsurface migration away from field application sites, and its potential for infiltration into indoor air appears to be warranted.

Mechanism of Toxicity

7. The primary effects observed with short- and long-term chloropicrin exposure are sensory and respiratory irritation, although the mechanism of action is not well understood. Sparks et al. (2000) observed that chloropicrin was a moderately potent inhibitor of the enzymes, pyruvate and succinate dehydrogenase (PDH and SDH), and proposed that they were possible targets for the lacrimatory effects of chloropicrin

because of thiol groups in their active sites. Sparks et al. (2000) also correlated the inhibition of PDH and SDH with the lethality of various halonitromethanes, quinones, fungicides and other thiol-reactive chemicals.

8. Increased lung tumors following inhalation exposure and mammary tumors following oral exposure to chloropicrin have been observed. Due to positive results in numerous genotoxicity assays, most notably all eight reverse mutation assays with *Salmonella typhimurium*, a genotoxic mode of action for tumor formation is possible.

Pharmacokinetics

9. Forty-three to 47% of ^{14}C-chloropicrin administered to male Swiss Webster mice intraperitoneally at 1-3 mg/kg were excreted in the urine in the first 24 hours, followed by another 8-8.5% excreted in the urine between 24 and 48 hours. The metabolites appeared to be polar and volatile although none was identified. The other major route of excretion was expired air, with 6.5-15% detected as CO_2 in 48 hours. Only 2.5-9% of the administered dose was excreted in the feces 48 hours after dosing. At 1 hour and 48 hours after dosing, the liver had the highest level of radioactivity, followed by the kidney, lung, blood, fat and skin (Sparks et al., 1997).

10. Following intraperitoneal administration of 5 mg/kg chloropicrin to male Swiss Webster mice, Sparks et al. (2000) identified raphanusamic acid (2-thioxothiazolidine-4-carboxylic acid, TTCA) in the urine that was equivalent to approximately 1% of the administered dose. 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 dichloro and monochloro metabolites, or react with cysteine and then be cleaved by cysteine β-lyase to form raphanusamic acid via thiophosgene.

Inhalation Exposure: General Considerations

11. In evaluating whether chloropicrin meets the criteria to be listed as a TAC, the exposure assessment conducted by DPR considered airborne exposures to bystanders adjacent to pesticide application, in ambient air, and in indoor air. Bystanders consist of individuals who are not directly involved with chloropicrin application but who may be exposed during or after the application by drift. Bystanders are assumed to wear no protective clothing or equipment. Occupational bystanders include field workers on location for an 8-hour workday. Residential bystanders are assumed to be in the vicinity of chloropicrin application for 24-hour days. The ambient air is defined as the air further away from the vicinity of chloropicrin application. Ambient air exposure to chloropicrin is likely to be less than bystander exposure because dispersion further dilutes the chloropicrin concentration from the source. Because the public may encounter chloropicrin upon re-entry into the house following structural fumigation, indoor air exposures were also estimated for this scenario.

12. In its calculations of human equivalent concentrations, default breathing rates were used in accordance with the joint policy memorandum issued by the Worker Health and Safety

and Medical Toxicology branches (Andrews and Patterson, 2000). The values listed in this memorandum were based on the method of Layton (1993), which utilized food-energy intake values from the 1977-1978 Nationwide Food Consumption Survey (NFCS). For children, OEHHA recommends use of the inhalation rates published in the *Child-Specific Exposure Factors Handbook* (U.S. EPA, 2008), because they are based on four studies published in 2006 and 2007, and represent more current exposure conditions and improvements upon the approach used by Layton (1993). OEHHA believes that these inhalation rates are the most health-protective for young children. For example, the DPR policy memorandum recommends, "For children, when duration of activity and activity pattern are not specified, use the default value of 0.59 m^3/kg-day for infants since infants have the highest value among all children groups when body weight is considered." This value is based on an infant inhalation rate of 4.5 m^3/day and a mean body weight of 7.6 kg. The *Child-Specific Exposure Factors Handbook* (Table 6-1) recommends a long-term exposure mean inhalation rate of 5.4 m^3/day for the age group 6 to <12 months, which is significantly higher than the 4.5 m^3/day provided by Layton (1993). Using the same mean body weight of 7.6 kg, the daily inhalation rate for infants derived from the values in the 2008 Handbook (using the age group 6 to <12 months as the highest among infants) would be 0.71 m^3/kg-day. This is significantly higher than the default value provided by the DPR policy memorandum.

Ambient Air Exposure

13. A summary of available ambient monitoring studies for chloropicrin was provided by DPR in Table 5 (Part A). Chloropicrin concentrations reported in these studies are much lower than those reported in offsite (vicinity) monitoring during various types of field fumigation. OEHHA agrees with DPR's decision to exclude ambient air monitoring results from the exposure assessment because of shortcomings in the quantity and quality of available data.

Bystander Exposure following Soil Fumigation

14. Bystander exposures were evaluated by DPR following use of chloropicrin as a soil fumigant, as an enclosed space fumigant for crop storages or grain bins, and as a warning agent in structural fumigation. In the soil fumigation scenario, both offsite monitoring data collected 1.5-55 meters from the fumigated fields and emission (flux) estimates were presented. Since offsite air concentrations are proportional to chloropicrin application rates, the monitoring data were adjusted based on the maximum application rate allowed in California. The adjusted data are presented in Table 7 (Part A). Air dispersion using estimated emission rates (flux) as inputs was modeled to estimate bystander exposure at three meters from the soil fumigation site. The estimated exposure concentrations are presented in Table 14 (Part A). In reviewing the offsite monitoring data and modeling results, DPR elected to use the modeling results in the health risk assessment. OEHHA notes that this appears to be reasonable and health-protective.

Bystander Exposure following Structural Fumigation

15. Air Resources Board (ARB) offsite monitoring data collected during three structural fumigations and data published by Barnekow and Byrne (2006) during eight structural fumigations were used to estimate bystander exposures from structural fumigation. In these situations, chloropicrin was used as a warning agent in sulfuryl fluoride fumigation. Since ARB reported lower chloropicrin concentrations than Barnekow and Byrne, the latter were used to estimate bystander exposure from structural fumigation. Exposure concentration estimates are provided in Table 13 (Part A). DPR defined a range of offsite chloropicrin concentrations encountered during structural fumigation in California. OEHHA agrees that selecting the high-end of the range in estimating exposures is consistent with protection of public health.

Bystander Exposure following Enclosed Space Fumigation

16. In the absence of data for enclosed space fumigation, DPR estimated bystander exposures based on data from Barnekow and Byrne (2006), with adjustments indicated in footnote "a" of Table 16 (Part A). OEHHA agrees that the assumptions used to estimate bystander exposures from enclosed space fumigation are appropriate and reasonable.

Indoor Air Exposure following Structural Fumigation

17. Offsite monitoring of structural fumigations conducted by ARB, and Barnekow and Byrne (2006) also included indoor air measurements. DPR presents indoor air exposures based on the highest concentrations measured in the post-aeration period following structural fumigation in Table 17 (Part A). OEHHA agrees that using the highest concentrations is appropriate in a screening risk analysis such as this.

Acute Toxicity

18. Based on ocular irritation data from phase 3 of the Cain (2004) study, DPR estimated an acute NOEL of 26 ppb based on a $BMDL_{10}$. While a $BMDL_{05}$ has been cited as an approximation of the NOEL, DPR justified adoption of the $BMDL_{10}$ on the basis that noticeable eye irritation "...was a mild and reversible endpoint" (Part B, page 47). An RfC of 8.7 ppb was derived using an intraspecies uncertainty factor of three to account for pharmacodynamic variation in response ($UF_{H\text{-}d}$). Since the mechanism of sensory irritation appears to involve direct irritation of trigeminal nerve endings in the respiratory and ocular mucosa, the intraspecies uncertainty factor for pharmacokinetic variation ($UF_{H\text{-}k}$) was reduced from the default value of three to one. OEHHA concurs with this approach.

19. Regarding protection of potentially sensitive subpopulations, including children and individuals with asthma, OEHHA's *Technical Support Document for the Derivation of Noncancer Reference Exposure Levels* (2008, p. 76) noted that "...there is no evidence that infants and children have different or more irritation receptors than adults. Therefore, OEHHA has not assumed that children are more sensitive than adults to the sensory effects of eye, nasal or respiratory irritants. However, it must be considered that

many irritants, especially those that are chemically reactive, have the potential to exacerbate or induce asthma, which is a special concern for children's health."

20. The following points are relevant to an evaluation of chloropicrin's potential to exacerbate or induce asthma:
    - Respiratory irritation was also evaluated in phase 3 of the Cain (2004) study. The findings indicate that that chloropicrin-induced nose and throat irritation is not as sensitive an indicator of toxicity as eye irritation.
    - DPR presented an alternative analysis of the Cain (2004) data in the Risk Appraisal section of the TAC document. As shown in Table 29 (Part B), an acute one-hour NOEL was calculated based on elevated levels of exhaled nitric oxide (NO; regarded as an early sign of inflammation of the nasal epithelium) reported in the same study. In contrast to the analysis of ocular irritation, a response of 5% was identified as an estimated NOEL due to the greater toxicologic significance of nasal inflammation. The $BMDL_{05}$ for this endpoint was 44 ppb. When this value is used to estimate one-hour MOEs for bystander exposure following soil fumigation, the MOEs range from 0.027 to 0.0027, as shown in Table 29 (Part B).
    - If a default intraspecies uncertainty factor (UF_H) of 10 is applied to the estimated NOEL to account for pharmacokinetic ($UF_{H\text{-}k} = \sqrt{10}$) and pharmacodynamic ($UF_{H\text{-}d} = \sqrt{10}$) differences across the human population, the one-hour RfC would be 4.4 ppb. If this RfC is used to estimate one-hour "Percentage of RfC Concentration" values for bystander exposure following soil fumigation, the estimates range from 36,400 to 364,000. These values are essentially the same as those shown in Table 29 (Part B).

21. OEHHA recommends adoption of an intraspecies toxicodynamic uncertainty factor ($UF_{H\text{-}d}$) of 10 to estimate a one-hour RfC for chloropicrin. In support of this recommendation, we note important similarities in the toxicity profiles of chloropicrin and acrolein:
    - Both compounds are acute respiratory irritants and lachrymators, and have similar irritancy thresholds (<250 ppb).
    - Both are highly reactive, particularly with sulfhydryl groups (protein cysteine residues and glutathione), and their toxic effects are generally limited to the site of contact.
    - Exposure to acrolein at levels > 1 ppm causes mucous hypersecretion and exacerbation of allergic airway response in animal models. It is reasonable to predict that similar effects would be observed following exposure to irritating concentrations of chloropicrin.
    - The acute reference exposure level (REL) for acrolein was based on two studies of subjective ocular irritation in humans, and incorporated an intraspecies toxicodynamic uncertainty factor ($UF_{H\text{-}d}$) of 10 due to concern that acrolein could exacerbate asthma in children. The one-hour REL for acrolein is 1.1 ppb (OEHHA, 2008).

22. In keeping with the approach used to derive a one-hour REL for acrolein, OEHHA believes an additional intraspecies toxicodynamic uncertainty factor of 3 is warranted for the one-hour RfC for chloropicrin. Applying a cumulative intraspecies uncertainty factor of 30 (i.e., a $UF_{H\text{-}k}$ of 3 and a $UF_{H\text{-}d}$ of 10) to the estimated NOEL for chloropicrin-induced inflammation of the nasal epithelium (indicated by an increase in NO in expired

nasal air), a one-hour RfC for chloropicrin would be 1.5 ppb (44 ppb/30). This is approximately one-sixth the one-hour RfC derived by DPR in the chloropicrin TAC document. When this value is used to estimate one-hour "percentage of RfC" values for bystander exposure following soil fumigation, the estimates range from 107,000 to 1,070,000, or three-fold higher than the values shown in Table 29 (Part B). Since MOEs are based on the estimated NOEL, the MOE values shown in this table would remain unchanged.

23. DPR assessed potential adverse effects of eight-hour exposures based on data from a developmental toxicity study in rabbits (York, 1993). The experimental NOEL identified by DPR in this study was 400 ppb, and the eight-hour human equivalent concentrations (HECs) were 270 and 580 ppb for children and adults, respectively. In the TAC document, DPR applied a cumulative uncertainty factor of 100 to account for interspecies and intraspecies variation in sensitivity, and the corresponding RfCs were 2.7 and 5.8 ppb (Table 19, Part B). These values significantly exceed OEHHA's recommended one-hour RfC of 1.5 ppb, derived in paragraph 22. Therefore, OEHHA believes it would be appropriate to adopt the one-hour RfC as an eight-hour RfC. Using 1.5 ppb as the eight-hour RfC, the eight-hour "percentage of RfC" values for bystander exposure following soil fumigation range from 46,700 to 433,000 for children and adults.

24. While OEHHA's recommended one- and eight-hour NOELs and RfCs reduce the MOEs and increase the "percentage of RfC" values by a significant margin, they do not materially change the primary conclusion of DPR's analysis, namely, that chloropicrin clearly meets the criteria for listing as a toxic air contaminant.

25. DPR assessed the potential health effects of twenty-four-hour exposures based on data from the same rabbit developmental toxicity study (York, 1993). The 24-hour RfCs were 0.92 and 1.9 ppb for children and adults, respectively (Part B, Table 19). These values do not differ significantly from the recommended one-hour RfC of 1.5 ppb, derived above. Therefore, we do not recommend any changes to the assessment of 24-hour exposures.

Subchronic Toxicity

26. Five subchronic toxicity studies of chloropicrin have been conducted, including two oral studies in rats, two inhalation studies in rats, and one inhalation study in mice. In the oral studies, observed adverse effects included reduced body weights, reduced thymus weights, and histopathological changes in the forestomach. The lowest NOAEL for the oral route was 8 mg/kg-day in rats based on reduced body weights and histopathological changes in the forestomach (Condie et al, 1994). In the inhalation studies, observed adverse effects included reduced body weights, reduced food consumption, blepharospasm (an abnormal, involuntary blinking or spasm of the eyelids), increased lung weights, rhinitis, and histopathological lesions in the nasal cavity and lungs such as respiratory epithelial hyperplasia/dysplasia. The lowest NOAEL for the inhalation route was 300 ppb (2,000 $\mu g/m^3$) in mice based on reduced food consumption and body weights, increased lung weights and lesions in the respiratory tract (Chun and Kintigh, 1993). The same NOAEL of 300 ppb (2,000 $\mu g/m^3$) was also observed in a rat study based on increased lung weights and lesions in the lung (Chun and Kintigh, 1993). A benchmark dose analysis was used to evaluate data from the Chun and Kintigh (1993)

inhalation study in rats and Chun and Kintigh (1993) inhalation study in mice. Rhinitis in female rats was identified as the most sensitive endpoint for inhalation exposure. A $BMCL_{05}$ of 120 ppb (807 $\mu g/m^3$) based on rhinitis in female rats was therefore used to calculate HECs in children and adults, taking into consideration differences in breathing rates. The subchronic HECs were 73 ppb (490 $\mu g/m^3$) and 35 ppb (230 $\mu g/m^3$) for adults and children, respectively (Part B, Table 19). DPR calculated the reference concentrations (RfCs) by dividing the respective HECs by an uncertainty factor of 100 (10 for intra-species variation and 10 for interspecies variation). The RfCs for subchronic exposure were 0.73 ppb (4.9 $\mu g/m^3$) and 0.35 ppb (2.3 $\mu g/m^3$) for adults and children, respectively (Part B, Table 19).

27. In evaluating the subchronic RfCs for children and adults, OEHHA notes that the two-fold difference was based solely on the difference in breathing rates. As noted in paragraph 12, the respiratory rate assumed in the HEC calculation for children may not be sufficient to protect the very young (6-12 months of age).

Developmental and Reproductive Toxicity

28. Two inhalation studies of reproductive toxicity in rats have been conducted. The only adverse effect observed was reduced litter size due to reduced number of implantation sites. The reproductive NOAEL was 1.0 ppm based on the reduced litter size (Denny, 1996). The parental NOAEL was 0.5 ppm based on reduced body weights and pathological lesions in the lung (Schardein, 1994).

29. For developmental toxicity, one inhalation study in rats and one inhalation study in rabbits have been conducted. Adverse developmental effects included reduced fetal body weights, increased late-term abortions, skeletal variations in fetuses, and increased pre- and post-implantation losses. The lowest developmental NOAEL was 0.4 ppm in rats based on skeletal variations (Schardein, 1993). The lowest maternal NOAEL was 0.4 ppm in both rats and rabbits based on clinical signs and changes in body weights and food consumption (Schardein, 1993; York, 1993).

30. While available developmental and reproductive toxicity studies did not show evidence of differential susceptibility in developing animals, a data gap exists due to the lack of early life (neonatal and postnatal) studies. The differences between young children and adults are not limited to breathing rate; there are structural and physiological differences in the respiratory system as well. The respiratory defense is also immature in children compared to adults. Since potent respiratory irritants such as chloropicrin may trigger bronchoconstriction and excessive mucus secretion characteristic of asthma, children with their greater prevalence of asthma may have greater susceptibility compared to adults. Therefore, OEHHA recommends an intraspecies toxicodynamic uncertainty factor ($UF_{H\text{-}d}$) of 10 to evaluate potential adverse effects of subchronic chloropicrin exposure in children. This would reduce the RfC for sub-chronic exposure in children by a factor of three.

Chronic Toxicity

31. Six chronic studies have been conducted, including two oral studies in rats, one oral study in mice, one oral study in dogs, one inhalation study in rats, and one inhalation study in mice. In the oral studies, observed adverse effects included increased mortality rate, reduced body weights, changes in clinical chemistry values, neoplastic and non-neoplastic lesions in the stomach, liver, and mammary gland, and clinical signs such as urogenital stains, reddened eyes, and reddened ears. The lowest NOAEL observed for the oral route was 0.1 mg/kg-day in rats based on reduced body weights and lesions in the liver (Slauter, 1995). For the inhalation studies, the effects observed included reduced body weights, reduced food consumption, reduced survival rate, increased lung weights, and lesions in the nasal cavity and lungs. The lowest NOAEL of 100 ppb (670 $\mu g/m^3$) was observed in rats based on reduced body weights and increased mortalities (Burleigh-Flayer and Benson, 1995). The same NOAEL of 100 ppb (670 $\mu g/m^3$) was also observed in mice based on reduced food consumption and body weights, increased lung weights and lesions in the respiratory tract (Burleigh-Flayer et al, 1995). A benchmark dose analysis of data from the rat inhalation study (Burleigh-Flayer and Benson, 1995) and the mouse inhalation study (Burleigh-Flayer et al., 1995) was conducted. Bronchiectasis in female mice was identified as the most sensitive endpoint via the inhalation route. DPR used a $BMCL_{2.5}$ of 43 ppb (289 $\mu g/m^3$) based on bronchiectasis in female mice to derive the HECs after taking into consideration the differences in breathing rates. The HECs were 49 ppb (332 $\mu g/m^3$) and 23 ppb (157 $\mu g/m^3$) for adults and children, respectively. The HECs derived using $BMCL_{2.5}$ are 30% lower than those derived using the default $BMCL_{05}$ and are more health protective. DPR derived chronic RfCs of 0.49 ppb (3.3 $\mu g/m^3$) and 0.23 ppb (1.6 $\mu g/m^3$) for adults and children by applying an aggregate uncertainty factor of 100 (10 for interspecies variation and 10 for intraspecies variation) to the respective HECs.

32. Based on the rationale presented in paragraph 29, OEHHA recommends an intraspecies toxicodynamic uncertainty factor (UF_{H-d}) of 10 to evaluate potential adverse effects of chronic chloropicrin exposure in children. This would reduce the RfC for chronic exposure in children by a factor of three.

Genotoxicity

33. Chloropicrin was negative in the L5178Y TK+/- mouse lymphoma forward mutation assay, but was found to induce gene mutations in Salmonella typhimurium strains with and without metabolic activation in several studies. Chloropicrin also induced gene mutations in Escherichia coli WP2 hcr with and without metabolic activation. Chloropicrin did not elicit unscheduled DNA synthesis (UDS) in primary rat hepatocytes, but did cause DNA damage in E. coli (SOS chromotest assay) and in human-derived TK6 cells (Comet assay, oxidized base assay) (Liviac et al., 2009). Chromosomal damage data for chloropicrin are mixed. Chloropicrin induced chromosomal aberrations in Chinese hamster ovary (CHO) cells without metabolic activation (rat liver S-9) but not in human lymphocytes with or without S-9 using a nonstandard protocol. However, an increased sister chromatid exchange incidence was observed in human lymphocytes with and without S-9. No increase in micronuclei was seen in the peripheral blood erythrocytes of newt larvae exposed to chloropicrin for 12 days. Sex-linked recessive

lethality data for chloropicrin were negative or equivocal and wing-spot test data (somatic mutation and recombination assay) (Garcia-Quispes, 2009) were negative in Drosophila melanogaster. These data indicate that chloropicrin is a weak or equivocal inducer of chromosomal damage, causes DNA damage and gene mutations, and therefore should be considered to be genotoxic. OEHHA agrees with DPR's assessment that chloropicrin is genotoxic.

Carcinogenicity

34. 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.

35. The tumor data for the one year chloropicrin oral dog study (Wisler, 1994) was generally negative. However, the study duration was less than 10% of the animal lifetime, and only four animals/sex/dose were used in the study. Tumor data for the mouse oral study (NCI, 1978) were also negative. It should be noted that this study also used less than lifetime exposure (78 weeks), which would reduce study sensitivity.

36. In the mouse chloropicrin inhalation study (Burleigh-Flayer et al., 1995), fifty CD-1 mice/sex/dose were exposed (whole body) to chloropicrin vapors at 0, 0.1, 0.5 or 1.0 ppm for 6 hours/day, 5 days/week for at least 78 weeks. Surviving animals were sacrificed at week 82. A significant dose-response ($p < 0.01$) was observed for lung adenoma and carcinoma combined incidence in female mice exposed to chloropicrin. Additionally, lung adenoma and carcinoma combined incidence in high dose (1.0 ppm) female mice was significantly increased compared to controls by Fisher exact test ($p = 0.053$ unadjusted; $p = 0.038$ using a Poly-3 mortality incidence correction). This study used a less than lifetime exposure duration, which would tend to reduce the study sensitivity.

37. The NCI (1978) rat oral (gavage) exposure study was generally negative. However, the study used a less than lifetime exposure (78 weeks), a small control group (20 animals/sex) and suffered from high mortality in the treated groups. An unusual dosing protocol was also employed. 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.

38. In contrast, the rat chloropicrin oral gavage study by Slauter (1995) used a 2 year (approximately lifetime) exposure. There was no treatment-related effect on survival. A significant dose-response relationship was noted in the female rats for mammary fibroadenoma incidence ($p < 0.001$). Increased mammary fibroadenoma incidence was also significantly increased in the high dose group (10 mg/kg-day) compared to controls as determined by Fisher's exact test ($p < 0.05$).

39. The rat chloropicrin inhalation study (Burleigh-Flayer and Benson, 1995) also observed an increase in mammary fibroadenomas in high dose (1 ppm) female rats. This increase

did not reach statistical significance ($p = 0.1$), but it should be noted that this study used a less than lifetime exposure (78 weeks), which would tend to reduce the study sensitivity.

Cancer Risk Assessment

40. Chloropicrin has been observed to significantly induce lung adenomas and carcinomas in female mice exposed to chloropicrin for 78 weeks and sacrificed at 82 weeks (a less than lifetime exposure). A significant dose-response ($p < 0.01$) was observed for lung adenoma and carcinoma combined incidence in female mice exposed to chloropicrin. Additionally, lung adenoma and carcinoma combined incidence in high dose (1.0 ppm) female mice was significantly increased compared to controls by Fisher exact test ($p = 0.053$ unadjusted; $p = 0.038$ using a Poly-3 mortality incidence correction).

41. Additional support for chloropicrin carcinogenicity comes from the positive chloropicrin genotoxicity data, and a female rat oral cancer study which indicated that chloropicrin induced a significantly greater incidence of mammary fibroadenomas (10 mg/kg-day, $p < 0.05$, positive trend test) compared to controls. Mammary fibroadenomas are not malignant, but they are believed to have the capacity to progress to malignant tumor types. A cancer potency factor cannot be derived from this data set, but the data clearly support the finding that chloropicrin can induce tumors in animals.

42. The female mouse lung adenoma and carcinoma incidence data set described above can be used to calculate a cancer potency factor. Study chloropicrin air concentrations are converted to pharmacological dose (mg/kg-day), and then converted to human equivalent dose by multiplying by an interspecies scaling factor of body weight to the 3/4 power [(0.030 kg/70 kg)0.25 = 0.144]. OEHHA verified DPR's cancer potency estimate using BMDS 2.1.1 (Benchmark Dose Software, U.S. EPA) to calculate a cancer potency factor of 2.2 $(\text{mg/kg-day})^{-1}$, which results in a unit risk of 6.3×10^{-4} $(\mu g/m^3)^{-1}$.

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[1] Only those references that were not cited in the Chloropicrin TAC documents (DPR, 2009) are listed here.