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MEMORANDUM

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DATE: March 23, 2009

SUBJECT: COMMENTS ON DRAFT EXPOSURE ASSESSMENT DOCUMENT AND DRAFT RISK CHARACTERIZATION DOCUMENT FOR THE PESTICIDE ACTIVE INGREDIENT, CHLOROPICRIN

Enclosed please find a copy of the Office of Environmental Health Hazard Assessment's (OEHHA) comments for the active ingredient chloropicrin. These comments were prepared in response to the Chloropicrin Draft Exposure Assessment Document (EAD), Part A (dated November 14, 2008); and Chloropicrin Draft Risk Characterization Document, Part B (dated December 2, 2008) prepared by the Department of Pesticide Regulation (DPR). The information contained in these documents serves to identify chloropicrin as a candidate toxic air contaminant (TAC).

OEHHA reviews risk assessments prepared by DPR under the general authority of the Health and Safety Code, Section 59004, and also under the Food and Agricultural Code (FAC), Section 13129, in which OEHHA has the authority to provide advice, consultation, and recommendations to DPR concerning the risks to human health associated with exposure to pesticides. Pursuant to Food and Agricultural Code sections 14022 and 14023, OEHHA also provides review, consultation, and comments to DPR on the evaluation of the health effects of candidate TAC.

Should you have any questions regarding OEHHA's comments on cancer evaluation, please contact Dr. John Budroe at (510) 622-3145. For comments on noncancer evaluation, please contact Dr. Dan Qiao at (916) 327-8345. For comments on exposure assessment, please contact Dr. David Chan at (916) 327-0606. For other questions, please contact Dr. David Ting, Dr. Anna M. Fan or Dr. Melanie Marty at (510) 622-3200.

Enclosure

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Office of Environmental Health Hazard Assessment's Comments on the Draft Exposure Assessment Document and Draft Risk Characterization Document for the Pesticide Active Ingredient, Chloropicrin

The Office of Environmental Health Hazard Assessment (OEHHA) is responding to the request of the Department of Pesticide Regulation (DPR) to comment on the draft Exposure Assessment Document (EAD) and draft Risk Characterization Document (RCD) for chloropicrin (trichloronitromethane).

OEHHA reviews risk assessments prepared by DPR under the general authority of Health and Safety Code Section 59004, and also under Food and Agricultural Code Section 13129, in which OEHHA has the authority to provide advice, consultation, and recommendations to DPR concerning the risks to human health associated with exposure to pesticides. Pursuant to Food and Agricultural Code sections 14022 and 14023, OEHHA also provides review, consultation, and comments to DPR on the evaluation of the health effects of candidate Toxic Air Contaminant (TAC).

Based on OEHHA's comments, DPR will issue a revised document for comments by the public and the Pesticide Registration and Evaluation Committee. The final draft will then be submitted to the Scientific Review Panel (SRP) on Toxic Air Contaminants. OEHHA will also prepare findings regarding chloropicrin (Food and Agricultural Code Section 14023).

Review of the Draft Exposure Assessment Document

Exposure Scenarios

The scope of the EAD is limited to potential atmospheric exposures of chloropicrin to bystanders. Other scenarios such as occupational exposures are not included in the assessment.

Chloropicrin is a soil fumigant that is used alone or as a warning agent for other fumigants due to its strong lachrymatory effects and low odor threshold. Chloropicrin is also used in structural fumigation. Based on these uses, DPR outlined two scenarios in which bystanders can be exposed to chloropicrin from soil or structural fumigations. In the first scenario, exposure was estimated for individuals next to the field where chloropicrin has been used as an active ingredient in soil fumigation. In the second scenario, exposure was estimated for individuals next to fumigated structures where chloropicrin has been used as a warning agent.

During a briefing session, DPR further clarified that it is not legal to use chloropicrin as an active ingredient in structural fumigation in California and that it is also not legal to use chloropicrin (as an active ingredient or a warning agent) to fumigate cargo ship containers even though methyl bromide's use is permitted. Accordingly, DPR has not included structural fumigation with

chloropicrin as an active ingredient or cargo container fumigation as scenarios in the exposure assessment.

For the public to better comprehend the selection of exposure scenarios, OEHHA recommends that DPR provide an overview of the exposure scenarios considered, and the rationale for selecting or rejecting scenarios for further consideration.

Soil Fumigation

DPR used the "typical" chloropicrin application rates cited by U.S. EPA in computing ambient air concentrations and estimating long-term exposure from soil fumigation. DPR in reviewing soil fumigation data indicated that California's average chloropicrin application rates do not exceed those "typical" application rates. Because this screening analysis is intended to be conservative, a 90+ percentile value should be used instead of the typical application rates. In doing so, DPR would be consistent with the approach it used to estimate the exposure duration of four months. In that instance, DPR provided a statistical analysis to show that 92 percent of the annual use occurred in a 4-month period to support the use of this duration as a conservative estimate for seasonal and annual exposures.

Structural Fumigation

DPR compared and contrasted monitoring and modeling data in rationalizing the application of modeling data in assessing exposures from soil fumigation. In assessing exposure from structural fumigation, DPR felt that modeling is unlikely to yield much higher estimates than values from the monitoring data and opted to use monitoring data only. OEHHA noted that DPR's analysis was based on limited monitoring data (collected from three structural fumigations) and on sulfuryl fluoride fumigation only. This small (and perhaps under-representative) sample size would suggest a further review of the need for modeling to increase the confidence that the monitoring data are representative and applicable. If modeling is deemed unnecessary, the reasons for that finding should be discussed in the report. If modeling is desirable, it is recommended that a conservative application rate of chloropicrin based on warning agent use data be selected as a modeling input.

Review of the Draft Risk Characterization Document

Acute Toxicity

Reference concentrations (RfCs) were calculated by DPR for three exposure scenarios: 1-hour, 8-hour, and 24-hour exposures. Reference concentrations are the concentration level at or below which no adverse health effects are anticipated for specified exposure duration to a specific chemical. The acute 1-hour RfC listed in the DPR document is 17 micrograms per cubic meter

($\mu g/m^3$) (2.5 parts per billion [ppb]) for children and adults, and is based on ocular irritation in a human exposure study. DPR conducted a benchmark concentration (BMC) analysis and the 1-hour RfC is derived from a $BMCL_{10}$ of 170 $\mu g/m^3$ (25 ppb) and an intraspecies uncertainty factor (UF) of 10 to account for variability in the reactions of individuals to chloropicrin. The $BMCL_{10}$ is defined as the 95 percent lower confidence limit of the concentration expected to produce responses in ten of every 100 subjects exposed at this dose. DPR's 1-hour RfC is comparatively more health-protective than U.S. EPA's acute RfC of 491 $\mu g/m^3$ (73 ppb), which is also derived from the $BMCL_{10}$ using the same human study. The difference in the outcomes is mainly due to U.S. EPA's use of an intraspecies factor of one and re-adjustment of the eye irritation threshold in the data analysis. DPR decided to use $BMCL_{10}$ instead of $BMCL_{05}$ (the 95 percent lower confidence limit of the concentration expected to produce responses in five of every 100 subjects exposed at this dose) as the point of departure because the health endpoint, eye irritation, is considered a relatively mild effect. OEHHA has used a 5 percent response rate in deriving several Reference Exposure Levels (RELs) for air contaminants, and shown that the $BMCL_{05}$ appears to be equivalent to a No Observed Adverse Effect Level (NOAEL). DPR should provide additional justification that the $BMCL_{10}$ used in this case is a NOAEL.

Comparing DPR's 1-hour RfC of 17 $\mu g/m^3$ (2.5 ppb), 8-hour RfC of 18 $\mu g/m^3$ (2.7 ppb) for children or 39 $\mu g/m^3$ (5.8 ppb) for adults, and 24-hour RfC of 6.1 $\mu g/m^3$ (1 ppb) for children or 13 $\mu g/m^3$ (2 ppb) for adults, it is counterintuitive to have an 8-hour acute RfC that is greater than the 1-hour acute RfC, and based on animal rather than human data. DPR states, "If Haber's Law does not apply to the eye irritation, then the 8-hour RfC...should be the same as the 1-hour RfC." DPR also noted that the severity of the irritation appeared to plateau over time. Ocular irritation is generally considered to be concentration-dependent rather than time-dependent, and therefore Haber's Law would not apply to this endpoint. DPR's 1-hour RfC value should be adopted as the 8-hour acute RfC value for both adults and children.

Subchronic (Seasonal) Toxicity

Seasonal RfCs of 5.9 $\mu g/m^3$ (0.88 ppb) and 12 $\mu g/m^3$ (1.8 ppb) for children and adults, respectively, are listed in the DPR document. These values are based on a NOAEL of 2000 $\mu g/m^3$ based on increased lung weight and respiratory tract histopathological lesions in rats exposed to chloropicrin by inhalation. This was a 13-week (6 hours/day, 5 days/week) inhalation study. DPR developed a Human Equivalent Concentration (HEC) using only a respiratory rate adjustment, rather than employing a Regional Gas Dosimetry Ratio (RGDR) adjustment, and an uncertainty factor of 100 (10 for intraspecies differences and 10 for interspecies differences). This data set may lend itself to a benchmark dose procedure. Also, a RGDR adjustment should be used to calculate the HEC. DPR stated in this document that "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." However, the RGDR adjustment has been in use by US EPA since 1994, and is used

by several regulatory agencies, including OEHHA. In the absence of a specific deposition model for chloropicrin, OEHHA recommends that DPR use an RGDR adjustment in calculating HECs.

DPR indicated that the effect of not adjusting for RGDR is about a three-fold difference; that is, its subchronic RfC (0.88 ppb) was 3-fold higher than U.S. EPA's subchronic RfC (0.27 ppb). However, that was a comparison between a child RfC and an adult RfC. This difference is about seven times if an adult RfC comparison is made (DPR's subchronic RfC (1.8 ppb) for adults to U.S. EPA's subchronic RfC (0.27 ppb) for adults).

Chronic Toxicity

DPR developed chronic RfC values of 1.9 $\mu g/m^3$ (0.29 ppb) and 4.1 $\mu g/m^3$ (0.62 ppb) for children and adults, respectively. These values were based on the application of an UF of 100 (10 for intraspecies and 10 for interspecies) to a NOAEL (670 $\mu g/m^3$) based on reduced survival and body weight gain in rats exposed to chloropicrin by inhalation for 107 weeks (6 hours/day, 5 days/week) (Burleigh-Flayer and Benson, 1995). In contrast, OEHHA developed a chronic REL of 0.4 $\mu g/m^3$ for chloropicrin based on a similar study in mice also conducted by Burleigh-Flayer *et al.* (1995). The NOAEL from this study was the same as the NOAEL from the rat chloropicrin inhalation study. OEHHA applied a benchmark dose (BMD) procedure to nasal rhinitis and bronchiectasis data and derived a HEC by applying an RGDR adjustment for extrathoracic effects and an overall UF of 30. The interspecies UF was reduced from 10 to 3 since an RGDR adjustment was made. The resulting REL is approximately 5-fold and 10-fold less than the DPR RfC values for children and adults, respectively, and is more health protective to exposed populations. These OEHHA procedures have become preferred methodologies for use by California air quality agencies in noncancer risk assessment. Additionally, the toxic endpoints in the mouse chloropicrin inhalation study (nasal rhinitis and bronchiectasis) are more specific to chloropicrin exposure than the more general toxicity endpoints (decreased survival, body weight gain) in the rat chloropicrin inhalation study. It would be preferable if DPR would adopt the chronic REL for chloropicrin as its chronic RfC value for both adults and children. However, children may be more sensitive than adults. DPR should consider an additional toxicokinetic uncertainty factor and discuss how toxicodynamic uncertainties might be addressed (see discussion under Developmental Toxicity).

Genotoxicity

OEHHA believes that chloropicrin should be considered genotoxic. DPR stated that the available genotoxicity studies for chloropicrin showed mixed results, with positive results observed in some studies while negative results have been shown in other studies. DPR reported that chloropicrin induced gene mutations in *Salmonella* in several studies, and induced DNA damage in *E. coli*. Kawai *et al.* (1987) and Sariasiani and Stahl (1990) also described the induction of gene mutations by chloropicrin in *Salmonella* (not included in the DPR document). One mammalian gene mutation study using L5178 $TK^{+/-}$ mouse lymphoma cells was negative, and sex-linked recessive lethal data (measuring germ cell genotoxicity) in *Drosophila*

melanogaster were mixed. Chloropicrin was observed to induce chromosomal aberrations in Chinese hamster ovary (CHO) cells and sister chromatid exchanges, but not chromosomal aberrations in human lymphocytes. It was noted that in the human lymphocyte chromosomal aberration assay, the cells were exposed to chloropicrin before mitogenic stimulation, rather than after mitogenic stimulation, which is the usual experimental procedure for this assay. This change in protocol may have caused the assay to return false negative results. In summary, chloropicrin has been observed to induce both gene mutations and chromosomal damage, and should be considered genotoxic.

Carcinogenicity

Chloropicrin has been observed to induce lung adenomas and carcinomas in female CD-1 mice exposed to chloropicrin via inhalation for 78 weeks and sacrificed at 82 weeks (a less than lifetime exposure) (Burleigh-Flayer *et al.*, 1995). DPR correctly states that the tumor dose-response was statistically significant ($p < 0.01$) based on the Armitage-Cochran trend test. However, DPR states that none of the tumor incidences at any of the doses were significantly greater than those of the control animals when evaluated using the Fisher exact test. It is not clear if this statement was based on a statistical analysis by DPR or was the conclusion of the study authors. Based on a one-tailed Fisher exact test, the lung adenoma and carcinoma incidence in the high dose group (1 part per million [ppm]) is significantly greater ($p < 0.05$) than that of controls.

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 (NCI, 1978). 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.

Using the female mouse lung adenoma and carcinoma incidence data set, the cancer risk assessment model TOXRISK (Crump *et al.*, 1991) calculates a cancer potency factor of 4.4 $(\text{mg/kg-day})^{-1}$, which results in a unit risk of 1.2×10^{-3} $(\mu g/m^3)^{-1}$. Individuals exposed to the proposed DPR child chronic RfC (1.9 $\mu g/m^3$) would have a 70-year cancer risk of 2 in 1000 or 1 in 1000 if a 4-month per year exposure is assumed.

The fact that chloropicrin is known to interact with thiols also makes it necessary to consider the carcinogenic risk of this chemical. Such interaction with thiols has been implicated in processes of mutagenesis and carcinogenesis.

Developmental Toxicity

DPR indicated that developmental and reproductive toxicity studies did not show evidence of differential susceptibility in developing animals, and neither endocrine disruption nor neurotoxicity been observed in animal inhalation studies. In developing acute 8-hour, acute 24-hour, sub-chronic and chronic RfCs, DPR addressed the issue of increased sensitivity of children solely on the basis of breathing rate difference between children and adult—a two-fold difference. OEHHA is concerned that adjusting this exposure parameter alone may not adequately protect fetuses, neonates, and children.

Toxicokinetic and toxicodynamic differences should also be addressed. Children and particularly neonates can be quite different both toxicodynamically and toxicokinetically from adults. Data from the two developmental studies cited by DPR suggested that the inhaled chloropicrin impacts the fetus. Absence of ossification and reduced ossification in fetal bone development were observed. Octanol/water partition coefficient (K_{ow}) is an indicator of lipophilicity. It has been used to evaluate the potential ability of a given chemical to cross membranes or accumulate in fat tissues. An (K_{ow}) comparison further suggests that chloropicrin is likely to cross the placenta to impact fetuses and be present in breast milk to affect infants. Methylene chloride and 1,2 dichloroethane, which have lower octanol/water partition coefficients (log K_{ow} of 1.3 and 1.48) than chloropicrin (log K_{ow} of 2.43), have been shown to penetrate the placenta and distribute to breast milk. OEHHA ran a number of toxicokinetic modeling analyses and concluded that a toxicokinetic safety factor of 10 (3-fold on top of the traditional intraspecies toxicokinetic subfactor) may not be adequate for all chemicals, routes of elimination, or for the entire population, in particular the subpopulation of infants. A toxicokinetic subfactor of 10 is therefore recommended to protect infants, unless data are available to indicate that this subpopulation is not at higher risk due to differences in toxicokinetics. The Air Toxics Hot Spots Risk Assessment Guidelines, recently approved by the Scientific Review Panel on Toxic Air Contaminants, recommend an additional uncertainty factor for toxicokinetics in the absence of adequate data demonstrating no need for the factor. DPR should review the toxicokinetic issue and discuss the appropriateness of applying a toxicokinetic safety factor for protection of fetuses, infants, and children.

The chloropicrin risk assessment was based on overt toxicity endpoints. From the toxicodynamic point of view, DPR should elaborate on the uncertainties associated with other possible adverse effects, including functional deficits. DPR, in reviewing the mode of action of chloropicrin, indicated that the chemical preferentially reacts with sulfhydryl groups of peptides. Chloropicrin's metabolic pathways also suggest its potential for generating oxidative stress. Because of the potential for chloropicrin to adversely affect various enzyme systems via the mechanism of sulfhydryl group interactions, OEHHA is especially concerned about low-dose, early-life exposure and the possibility of functional deficits occurring later in life. These deficits may pertain to the functioning of the nervous, immune, reproductive, pulmonary, or metabolic system. While OEHHA has not found studies in the literature that investigated enzyme inactivation, oxidative stress, epigenetic dysregulation, or health effects associated with early-life chloropicrin exposure, this concern remains because other chemicals having a similar sulfhydryl

mechanism of action, such as arsenic, methylene chloride, 1,2 dichloroethane, and 1,2 dibromoethane, are known to produce some or all of these effects. The potential ramification is that chloropicrin may affect enzyme systems during critical periods in development, resulting in irreversible health effects, some of which may not be detectable until much later in life.

For example, methylene chloride can inactivate a cytochrome P450 isoenzyme (Foster et al., 1992) and erythrocyte glutathione S-transferase (Ansari et al., 1987), and dibromoethane can inhibit the catalytic activity of glyceraldehyde 3-phosphate dehydrogenase (Loecken and Guengerich, 2008). Moreover, Dichloroethane and dibromoethane have been shown to cause oxidative stress (Albano et al., 1984; Ianits'ka et al., 2005).

Clearly the aforementioned effects will impact fetuses, infants, and children more than adults because organ systems undergoing cell proliferation, differentiation, migration, and maturation are more susceptible. When evaluating chemicals under the air toxics program, OEHHA sometimes invokes an additional uncertainty factor for toxicodynamic differences by lifestage.

In summary, OEHHA recommends that DPR: (1) articulate in both the developmental toxicity and risk characterization sections that the assessment is based on available data on overt toxicities and discuss other possible health effects (given chloropicrin's mechanism of toxicity) as a source of uncertainty, and (2) consider how these toxicodynamic uncertainties might be addressed for adequate protection of fetuses, infants, and children.

Risk Characterization

DPR indicated in the RCD that bystander exposure to chloropicrin used in soil fumigation poses a health concern. As shown in Table 20 of the RCD, all margin of exposures (MOEs) estimated for 1-hour acute exposures for children and adults are less than 1. Many of them are orders of magnitude lower than what would be considered adequate based on a human study NOAEL (i.e., 10). Most MOEs estimated for seasonal and chronic exposures for children and adults are between 1 and 10; all of them are less than 100.

DPR indicated in the RCD that bystander exposure to chloropicrin used in structural fumigation poses a health concern. As shown in Table 21, MOEs estimated for 1-hour acute exposures for children and adults are less than 10.

Based on the MOEs estimated for soil and structural fumigations, chloropicrin would meet the criteria for listing as a toxic air contaminant.

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