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MEMORANDUM

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DATE: October 15, 2012

SUBJECT: COMMENTS ON THE DRAFT RISK CHARACTERIZATION DOCUMENT FOR CHLOROPICRIN

The attached enclosure contains comments from the Office of Environmental Health Hazard Assessment (OEHHA) on the draft risk characterization document (RCD) for chloropicrin, prepared by the Department of Pesticide Regulation (DPR) and dated September 2, 2011. OEHHA reviews risk assessments prepared by DPR under the authority of Food and Agricultural Code section 11454.1.

In general, OEHHA agrees with the risk assessment methodology and most of the conclusions in the draft RCD. Several specific comments and recommendations are contained in the attachment.

Thank you for providing this draft document for our review. If you have any questions regarding OEHHA's comments, please contact Dr. Charles Salocks at (916) 323-2605 or you can contact me at (510) 622-3200.

Enclosure

cc: next page

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COMMENTS ON THE 2011 DRAFT RISK CHARACTERIZATION DOCUMENT FOR CHLOROPICRIN

OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

OCTOBER 2012

I. SUMMARY

In general, the Office of Environmental Health Hazard Assessment (OEHHA) agrees with the risk assessment methodology and most of the conclusions in the draft chloropicrin Risk Characterization Document (RCD).

Specifically, OEHHA concurs that upper respiratory effects are the most sensitive endpoint following acute chloropicrin exposure, as evidenced by inflammatory markers and reduced nasal airflow rates. However, we recommend that the Department of Pesticide Regulation (DPR) conduct a more in-depth analysis of the decrements in nasal inspiratory flow rate that were observed in the critical study (Cain, 2004). Further, because chloropicrin is a potent acute respiratory irritant, we recommend incorporation of an additional three-fold pharmacodynamic uncertainty factor to account for differences in response to chloropicrin exposure in infants, children and those with pre-existing respiratory illnesses such as asthma. OEHHA also concurs with the selection of Cain (2004) and York (1993) as the experimental basis for the 1- and 24-hour reference concentrations (RfCs), respectively, but recommends use of Cain (2004) as a basis for establishing an 8-hour RfC.

OEHHA also concurs with the identification of rhinitis in rats, observed in the subchronic inhalation study of Chun and Kintigh (1993), as the experimental basis for the seasonal RfC, and identification of bronchiectasis in mice, reported in the chronic inhalation study conducted by Burleigh-Flayer et al. (1995), as the basis for the chronic RfC. However, OEHHA recommends that the seasonal and chronic RfCs for children incorporate the breathing rate for infants (0 to 2 years of age) from the document, *Air Toxics Hot Spots Program Risk Assessment Guidelines: Technical Support Document for Exposure Assessment and Stochastic Analysis* (OEHHA, 2012) rather than the breathing rate specified in DPR's 2000 joint policy memorandum. This change would reduce the seasonal and chronic RfC values for a child by about 12%.

OEHHA agrees with DPR's interpretation of the cancer bioassay data, and we agree that the weight of evidence is sufficient to conclude that chloropicrin is carcinogenic in rats and mice. We concur with DPR's identification of the 78-week mouse inhalation study conducted by Burleigh-Flayer et al. (1995) as the most appropriate basis for a cancer potency estimate, even though the less-than-lifetime exposure duration probably

reduced the sensitivity of this study. Using benchmark dose software, OEHHA also replicated DPR's cancer potency estimate [2.2 $(mg/kg\text{-}day)^{-1}$]. It is apparent that the genotoxicity data are sufficiently robust to conclude that chloropicrin is in all likelihood a genotoxic carcinogen. Therefore, alternative evaluations and potency estimates based on the supposition that chloropicrin may have a threshold for carcinogenicity are not supported by the experimental evidence.

II. BACKGROUND INFORMATION

In a memorandum dated March 23, 2009, OEHHA provided comments on the Chloropicrin Draft Exposure Assessment Document (EAD), Part A (dated November 14, 2008); and the Chloropicrin Draft RCD, Part B (dated December 2, 2008). The documents were prepared by DPR, and the analysis and conclusions in them were developed for the purpose of identifying chloropicrin as a toxic air contaminant (TAC). (Together, the 2008 EAD and RCD are referred to as "TAC documents" in the comments that follow). DPR's responses to OEHHA's comments were provided in two separate memoranda dated May 13, 2009, and May 21, 2009. In November, 2009, DPR issued revised versions of the two documents, titled *Evaluation of Chloropicrin as a Toxic Air Contaminant, Part A, Environmental Fate and Exposure Assessment* (Final Draft); and *Evaluation of Chloropicrin as a Toxic Air Contaminant, Part B, Human Health Assessment* (Draft). OEHHA subsequently reviewed these documents and summarized its findings on the health effects of chloropicrin in a memorandum dated November 24, 2009. DPR's November 2009 documents and OEHHA's findings were reviewed by the State's Scientific Review Panel (SRP) on Toxic Air Contaminants, and during a December 10, 2009 meeting the SRP determined that chloropicrin met the criteria to be a TAC and recommended to DPR that it be identified as such. Based on the findings of the SRP, chloropicrin has been identified as a pesticide TAC, listed in Title 3 CCR, section 6860(a).

The chloropicrin RCD reviewed in this attachment, dated September 2, 2011, as well as a December, 2011 EAD document (undergoing OEHHA review separately) update and expand the earlier documents that were used to identify chloropicrin as a TAC. The TAC documents addressed ambient air exposures that the general population might receive. These new documents address additional scenarios such as the exposure of bystanders as well as occupational exposures of workers who use, apply or otherwise might be exposed to chloropicrin.

III. ACUTE TOXICITY

The sections on Acute Toxicity (pp. 12-23), Risk Assessment for Acute Toxicity (pp. 46-50), Reference Concentration (pp. 60-61) and Risk Appraisal for Acute Toxicity (pp. 88-92) appear essentially unchanged from the chloropicrin TAC document. These sections are comprehensive and well written, and OEHHA is in general agreement with DPR's evaluation of the acute toxicity data.

However, the case for identifying respiratory irritation and inflammation as the critical acute effects could be strengthened by including discussion of the depressant effect of chloropicrin on nasal inspiratory flow rates. Further, since reduced respiratory flow has the potential to affect more severely the health of children and persons with asthma and other pre-existing respiratory conditions (OEHHA, 2008), we recommend inclusion of an additional three-fold uncertainty factor (UF) in the calculation for the 1-hour RfC. If this additional child-specific uncertainty factor were included, the 1-hour RfC would 1.5 ppb, which is significantly lower than DPR's proposed 8-hour RfCs for children and adults. Consequently, the value for the 8-hour RfC would default to OEHHA's recommended 1-hour value.

The RCD identifies two key studies as the basis to derive exposure values intended to prevent adverse human health effects from acute exposure to chloropicrin. Comments on each of these two key studies follow.

1. Cain (2004)

OEHHA concurs with the selection of this study as the basis for deriving the reference concentration (RfC) level for one-hour exposures. Cain (2004) evaluated the effects of chloropicrin exposure on healthy, young adult human volunteers and reported three significant endpoints: ocular irritation, increased nasal nitric oxide levels (an early sign of epithelial inflammation), and decreased nasal inspiratory flow. Tests were conducted in three phases, with Phase 2 and Phase 3 providing the majority of effects data.

The RCD identifies a NOEL for ocular irritation of 50 ppb at 20 minutes from Phase 2 of the Cain study. However, this NOEL was not used by DPR as a basis for an RfC or to evaluate margins of exposure (MOE). In this phase of the study, qualitative responses were reported on each participant's belief and confidence in whether chloropicrin could be detected. OEHHA concurs that this qualitative data, while indicating ocular detection is occurring, does not necessarily indicate the degree to which an adverse effect is occurring. Therefore, OEHHA concurs with DPR's use of Phase 3 data for risk assessment purposes. [However, OEHHA notes that Table 14 (p. 48) in the Risk Assessment section mistakenly indicates by asterisk that the 50 ppb is the $BMCL_{10}$ (that is, the concentration equivalent to the lower limit of the 95% confidence interval on the

estimated 10% response rate) because the 50 ppb level was not derived using benchmark dose calculations.]

Phase 3 of the Cain (2004) study reports three key endpoints: Ocular irritation, increased nasal nitric oxide levels and decreases in nasal inspiratory flow rates. Each of these endpoints is discussed below.

a. Ocular irritation

The RCD identifies ocular irritation in Phase 3 of Cain (2004) as a significant adverse effect with an estimated NOEL of 26 ppb based on a $BMCL_{10}$. Because ocular sensory irritation appears to involve a common physiological mechanism in humans, that of direct stimulation of the trigeminal nerve of the ocular mucosa, the intraspecies uncertainty factor (UF) in the RCD was reduced to 1 to account for similarities in pharmacodynamics and pharmacokinetics. OEHHA concurs that this may be the primary mode of action for ocular irritation, but also notes (as does the RCD and the original Cain study) that differential sensitivity is reported in the study. In fact, some participants felt no effects whatsoever even at the highest dose (150 ppb) tested after an hour of exposure, while others reported effects within minutes and continued to feel effects after exposure ceased. Cain (2004) notes that typically in chemosensory studies, "differences of twofold or threefold occur commonly" (p. 96). But given the range of responses in test subjects, even Cain (2004) concludes that there are people who "are less sensitive than others" (p. 96) to the irritant properties of chloropicrin. This range of sensitivity adds uncertainty to the derivation of a health protective value.

As such OEHHA considered the application of an uncertainty factor to account for this differential in reported effects. However, in calculating the estimated NOEL of 26 ppb, DPR did not convert the study data into quantal units, as did U.S. EPA (2009), which assigned a numeric value to the severity of irritancy. US EPA (2009) used this quantal methodology in its benchmark dose calculations, assigning an average score of 1.5 (mild irritation) as the cutoff for acceptability of ocular irritancy. DPR made no assumption about the severity of the ocular irritation. Instead DPR set the effect threshold by using "the standard deviation of the average scores" from the exposure group, as compared to those "with exposure to the blank air" (p. 77). This results in a more conservative (that is, lower) estimation of the threshold for ocular irritation.

OEHHA concurs with this health-protective approach and with DPR's finding that the $BMCL_{10}$ of 26 ppb is an appropriate benchmark dose for ocular irritation that, given the methodological approach used, partially accounts for variable human sensitivity. However, because data characterizing the response of children are unavailable, an additional UF of 3 appears to be warranted to protect infants and children.

b. First Upper Respiratory Endpoint: Increased Nitric Oxide (NO) Levels

Significant increases in exhaled nasal nitric oxide (NO), which is considered an early indication of mucosal inflammation, were also reported during Phase 3. This is the first of two upper respiratory effects reported by Cain (2004). The LOEL for this endpoint was 100 ppb. DPR considered exhaled nasal NO to be an adverse effect of greater significance than that of ocular irritation and derived a $BMCL_{05}$ of 44 ppb. To account for possible pharmacodynamic and pharmacokinetic differences among people, DPR applied an intraspecies UF of 10. DPR's resultant one-hour RfC for chloropicrin is 4.4 ppb based on increased nasal NO.

OEHHA concurs with DPR that exhaled NO represents a potentially more adverse human effect than ocular irritation. The study author in Cain (2004) noted that a 25% increase in this marker is considered a clinically significant level for respiratory inflammation. In populations with pre-existing respiratory conditions, like asthma, this level of inflammation could exacerbate those conditions and possibly necessitate medical attention. The test populations in this study were all healthy young adults without any history or symptoms of respiratory illnesses. Given this, OEHHA concurs with the adoption of an intraspecies UF of 10 and recommends an additional pharmacodynamics UF of 3 in keeping with OEHHA's methodology for acute respiratory irritants, like acrolein, which may exacerbate respiratory illnesses such as asthma in children (OEHHA, 2008). Thus, applying a cumulative UF of 30, the resultant one-hour RfC recommended by OEHHA would be 1.5 ppb based on increased nasal NO.

c. Second Upper Respiratory Endpoint: Decreased Nasal Inspiratory Flow Rates

Cain (2004) also reported decreases (>10%) in post-exposure nasal inspiratory flow rates in Phase 3 following one-hour exposures at 150 ppb. This reduction in the subjects' ability to inhale following chloropicrin exposure is the second upper respiratory effect that was observed. The decreased flow rates were attributed to mucosal swelling. However it appears that DPR did not analyze these data using benchmark dose concentration software as was done with the other two significant endpoints. This was due possibly to the non-monotonic nature of the data. However, OEHHA recommends that DPR re-evaluate this data to determine if a $BMCL_{05}$ can be ascertained for this endpoint. Decreased respiratory capability is potentially significant, especially to those populations with existing respiratory diseases and chronic airway obstructions. As such, the endpoint of decreased nasal inspiratory flow deserves to be investigated as a possible basis for an RfC.

If a $BMCL_{05}$ cannot be ascertained for this endpoint, we recommend the use of the traditional toxicological methodology as discussed in the RCD's Risk Appraisal section

(p. 89), where an uncertainty factor of 10 was applied to account for pharmacokinetic and pharmacodynamic uncertainties. To that, OEHHA recommends applying an additional intraspecies pharmacodynamic UF of 3, as we recommend above for exhaled NO and in keeping with public health guidelines (OEHHA, 2008). Thus, the resultant recommended RfC would be 3.3 ppb for mucosal swelling and decreased inspiratory flow rates. However, this value falls above the one-hour RfC of 1.5 ppb recommended by OEHHA.

OEHHA notes and concurs with the conclusion that mild eye irritation is an important property of chloropicrin when used as a *warning agent* in fumigation applications. At low levels of exposure eye irritation appears to be a reversible effect. As such, it is an uncomfortable but useful effect as a warning property. However, mucosal swelling which results in decreased nasal airflow serves no acceptable function. The fact that Cain's subject population was limited to healthy young adults with no history of chronic rhinitis, asthma or other respiratory illness only adds uncertainty to the question of what adverse effects similar exposures would have to those with pre-existing respiratory illnesses. If nasal swelling can occur in healthy young adults to the extent that it compromises normal inhalation, then persons with impaired status might be at greater risk of a more adverse response.

Due to their potentially significant public health implications, OEHHA recommends that these considerations be thoroughly discussed in the RCD. The reported significant decreases in inspiratory nasal flow rates in healthy young adults, coupled with significant increases in exhaled nasal NO (an indicator of epithelial inflammation) creates a concern that populations with pre-existing respiratory distress could be at higher risk from exposure to this potent irritant. Infants and children with developing respiratory systems, and infirmed people with decreased or obstructed respiratory capacity, could be significantly affected by chloropicrin exposures. For this reason, OEHHA also recommends the use of an additional UF of 3 to account for the uncertainties in response to chloropicrin exposure in vulnerable populations as illustrated above.

d. Summary Conclusions and Recommendations Based on the Cain (2004) Study

OEHHA concludes that respiratory effects occur at, and possibly below, those which cause mild ocular irritation, and that respiratory effects can carry greater health risks for bystanders who have obstructive respiratory disorders or other pre-existing respiratory diseases. OEHHA recommends that DPR give additional consideration to this endpoint in its development of health-protective strategies. To that end, OEHHA recommends a further analysis of the inspiratory flow rate data and recommends that DPR provide a more thorough discussion of this endpoint in the Acute Toxicity section of the RCD.

OEHHA further supports DPR's conclusion that there is insufficient data in the Cain (2004) study to predict severity of effects beyond the one-hour exposure duration. Given the acute upper respiratory effects following an hour of exposure – those of significantly reduced inspiratory flow and increased markers of mucosal inflammation – there is uncertainty over what effects might have occurred following more extended exposures. As such OEHHA concurs with the general principle of using longer duration studies to derive 8- and 24-hour exposure values, provided that they do not significantly exceed the 1-hour exposure value derived from Cain (2004).

Table 1 provides a comparison of RfCs derived by DPR and OEHHA based on the Cain (2004) study. While both agencies identify the same endpoints and doses, OEHHA's values differ due to the addition of an uncertainty factor to account for intraspecies pharmacodynamic differences, as discussed above.

Table 1. Comparison of Possible One-Hour RfCs for Chloropicrin Based on Cain (2004)

Possible RfCs (ppb)		Agency	Uncertainty Factors	Endpoint	Effect Level (ppb)
Child	Adult				
1.5	1.5	OEHHA	30	Increased nasal NO expiration	LOEL = 100
4.4	4.4	DPR	10		$BMCL_{05}$= 44
3.3	3.3	OEHHA	30	Decreased inspiratory flow rate	NOEL = 100 $BMCL_{05}$ not derived

2. York (1993)

As discussed in our memorandum to DPR dated November 24, 2009, OEHHA concurs with the conclusions reached by DPR on the York (1993) inhalation study which reported lung discoloration in rabbits exposed to 400 or 1,200 ppb for six hours per day for 14 days. The NOEL for this study was 400 ppb, from which DPR derived human equivalent concentrations (HECs) of 270 ppb and 580 ppb for children respectively, for 8-hour exposures. To these values DPR applied a UF of 100 account for interspecies and intraspecies variation in sensitivity, resulting in RfCs ppb and 5.8 ppb, respectively. As these values exceed OEHHA's RfC of 1.5 ppb derived from the Cain (2004) study, OEHHA recommends the use 1.5 ppb exposure value for 8-hour exposures as well. DPR also cited York (1993) as the basis for the 24-hour RfC values of 0.92 ppb for children and 1.9 ppb for adults, which do not significantly differ from the 1- and 8-hour RfCs of 1.5 ppb recommended by OEHHA.

Table 2 provides a comparison of the 8-hour RfCs derived by DPR and OEHHA based on studies conducted by Cain (2004) or York (1993). We differ in our conclusion regarding the most appropriate experimental basis for the 8-hour RfC.

Table 2. Comparison of Possible 8-Hour RfCs for Chloropicrin Based on Cain (2004) and York (1993)						
Exposure Duration	*Possible RfCs (ppb)* *Child*	*Adult*	*Agency*	*Endpoint*	*Effect Level (ppb)*	*Basis/UF*
8 hours	1.5	1.5	OEHHA	Increased nasal NO expiration	LOEL = 100 $BMCL_{05}$ = 44	Cain (2004) UF = 30
	2.7	5.8	DPR	Lung discoloration in pregnant rabbits	HEC_{child} = 270 HEC_{adult} = 580	York (1993) UF of 100

V. SUMMARY CONCLUSIONS AND RECOMMENDATIONS REGARDING THE ACUTE TOXICITY OF CHLOROPICRIN

The Acute Toxicology sections of the Chloropicrin RCD are well written, thoroughly researched and comprehensive. OEHHA concurs with the selection of the Cain (2004) study, and identification of adverse respiratory effects as critical endpoints, as the basis for the one-hour health-protective values. We also support the methodology that DPR used to derive estimated NOELs. For acute respiratory effects, OEHHA recommends application of a total 30-fold intraspecies UF to protect sensitive populations including children with asthma and people with respiratory obstructive diseases. OEHHA also recommends use of the resultant RfC, 1.5 ppb, for 1- and 8-hour exposures since it is significantly lower than the 1- and 8-hour RfCs derived by DPR.

DPR relied on data from a longer-duration study in rabbits (York, 1993) to derive a 24-hour health-protective value. The resultant RfCs for children and adults were 0.9 and 1.9 ppb, respectively. These values bracket OEHHA's proposed one- and eight-hour RfC, 1.5 ppb, which was based on human data from the Cain (2004) study. The fact that DPR's 24-hour RfCs were calculated on the basis of an entirely different data set supports the more general conclusion that a health-protective value for exposure durations of up to 24 hours is on the order of 1-2 ppb.

VI. SUBCHRONIC (SEASONAL) AND CHRONIC TOXICITY

Three subchronic inhalation toxicity studies of chloropicrin have been conducted in rodents. The lowest NOAEL was 300 ppb 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 was identified in a rat study where increased lung weights and lesions were observed (Chun and Kintigh, 1993). DPR conducted benchmark dose analysis of the adverse pulmonary effects reported in both studies (presented in Table 16 of the RCD) and concluded that rhinitis in female rats was the most sensitive endpoint.

Two chronic inhalation studies of chloropicrin have been conducted, one in rats (Burleigh-Flayer and Benson, 1995) and one in mice (Burleigh-Flayer et al., 1995). Similar adverse effects were observed in both studies, including reduced survival, reduced body weights and food consumption, increased lung weights and non-neoplastic and neoplastic changes in the respiratory tract. The NOAEL was 100 ppb in both studies. As was done with data from the subchronic studies, DPR conducted benchmark dose analysis of the pulmonary effects observed in these studies (Table 18 of the RCD). A default benchmark response (BMR) of 5% was used except for bronchiecstasis, where a BMR of 2.5% was derived due to greater concern about this irreversible pathological lesion. DPR concluded that bronchiectasis in male and female mice (combined because the incidence in both sexes was similar) was the most sensitive endpoint associated with chronic exposure, even when comparison was made at the 5% response level.

OEHHA concurs with these conclusions and the methodology that was used to identify the critical endpoints. However, for the purpose of estimating seasonal and chronic RfCs in children, DPR used a default breathing rate of 0.59 m^3/kg-day for all children. This value is similar to the age-weighted breathing rate of 0.56 m^3/kg-day for children up to 9 years of age that is specified in the *Technical Support Document for Exposure Assessment and Stochastic Analysis* (OEHHA, 2012). However, OEHHA's guidelines also specify a breathing rate of 0.66 m^3/kg-day for infants less than two years of age. Therefore, the seasonal and chronic RfCs that DPR developed for children do not fully consider the exposure of very young children. For this reason we recommend that these RfCs be modified to reflect the higher breathing rate of children less than two years of age.

VII. GENOTOXICITY AND CARCINOGENICITY

The Chronic Toxicity/Carcinogenicity (pp. 30-38) and Genotoxicity (pp. 38-41) sections are essentially unchanged from the chloropicrin TAC document. OEHHA concurs with DPR in the interpretation of the bioassay data, and that the weight of evidence is sufficient to conclude that chloropicrin is carcinogenic in rats and mice. We also concur with DPR's conclusion that the sensitivity of the mouse inhalation bioassay conducted by Burleigh-Flayer et al (1995) was reduced because the study duration was just 78 weeks.

Specific comments on page 92 of the Hazard Identification section and on the Conclusions are provided below.

On page 92, the RCD document states:

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).*

The clarification of the procedure that was used to calculate the alternative RfC is warranted because as written it is problematic. First, inclusion of an additional 10-fold uncertainty factor, applied after incorporating the conservative step of adopting the $BMCL_{01}$, would result in carcinogenicity RfC of 1.6 ppb, not 16 ppt. However, as discussed below, this would not ultimately be health-protective.

Second, the argument for a threshold is problematic. DNA damage is generally repaired fairly quickly. If it were not, the consequence of exposure to even low levels of genotoxins would be substantial increases in morbidity and mortality. However, DNA repair is neither completely efficient nor 100% error-free. For example, DNA damage which occurs in replicating cells may not be repaired, leading to gene mutations. DPR noted in the document that in the Comet assay performed by Liviac *et al.* (2009), "...the level of DNA damage caused by chloropicrin was higher than that seen with the positive controls in this study" (p. 56). The DNA repair kinetics in that study do not provide convincing evidence that chloropicrin should be considered to be functionally non-genotoxic.

Additionally, the chloropicrin *in vivo* genotoxicity data are quite limited, often inconclusive, and suffer from experimental deficiencies. The RCD stated that the sex-linked recessive lethal assay using *Drosophila melanogaster* Canton-S wild-type males reported by Valencia *et al.* (1985) found that "Chloropicrin was negative when administered by injection, but gave equivocal results when administered in the feed." The *Drosophila melanogaster* sex-linked recessive lethality data reported by Auerbach (1950) was negative, but the test males were only exposed for 2 – 9 minutes. García-Quispes *et al.* (2009) reported that chloropicrin was negative in the Drosophila wing-spot test. However, the data were the result of only one experiment. In the same study, the results for bromonitromethane were negative in one experiment, but essentially inconclusive in a second experiment, suggesting substantial experimental variability in

this assay system when testing halonitromethanes. Giller *et al.* (1995) reported negative results for the newt micronucleus test at exposure levels less than those reported to cause DNA damage in *E. coli* in the same study. Mehmood (2003) reported negative results for the rat hepatocyte unscheduled DNA synthesis test for chloropicrin. As DPR noted in the Carcinogenicity - Weight of Evidence section of the document, "The UDS assays were also not very meaningful since this assay has a reputation for not being very sensitive".

Given the substantial positive *in vitro* genotoxicity results, chloropicrin should not be considered to have a threshold for carcinogenicity despite the weak negative *in vivo* data. The weight of scientific evidence from these genotoxicity studies supports a non-threshold mode of carcinogenic action. A carcinogenicity RfC can be calculated from a $BMCL_{01}$ as a NOAEL equivalent for carcinogenicity for comparison purposes, but this would not be scientifically appropriate for use in conducting a human health risk assessment.

VIII. CONCLUSIONS REGARDING THE CARCINOGENICITY OF CHLOROPICRIN

The chloropicrin Toxic Air Contaminant (TAC) Human Health Assessment (DPR, 2009) states: "The off-site air concentrations of chloropicrin following enclosed space fumigation are of great concern since all of the MOEs were less than the target MOEs by 2-4 orders of magnitude. The lifetime exposure for bystanders following enclosed space fumigation with chloropicrin is also of great concern since the cancer risk estimates were several orders of magnitude higher than the negligible risk level." The 2011 RCD does not include a discussion of human health risks associated with the enclosed space fumigation exposure scenario in the Conclusions section. The document would be improved by the addition of such a discussion.

Additionally, the Conclusions section of the RCD did not provide a balanced assessment of the cancer risk for bystanders of chloropicrin soil fumigation compared to the Conclusions section in the TAC document: "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)" (page 104). One of DPR's primary conclusions regarding the mouse cancer bioassay conducted by Burleigh-Flayer et al. (1995) was that the sensitivity of the study was reduced because the exposure duration was just 78 weeks: "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" (page 58). The data from the genotoxicity studies were not entirely positive, but obtaining mixed results from various genotoxicity studies is typical of most carcinogens, particularly those that are volatile

like chloropicrin. The uncertainties in the chloropicrin cancer risk assessment may have caused either an overestimation or an underestimation of the true cancer risk. For this reason, the document would be strengthened if the statement on page 104 were eliminated.

As noted in our memo of November 24, 2009, OEHHA verified DPR's cancer potency estimate using BMDS 2.1.1 (Benchmark Dose Software, U.S. EPA) to calculate a cancer potency estimate of 2.2 $(mg/kg\text{-}day)^{-1}$, which results in a unit risk value of 6.4×10^{-4} $(\mu g/m^3)^{-1}$. The cancer potency estimate was based on data from the 78-week mouse inhalation study conducted by Burleigh-Flayer et al. (1995), and OEHHA concurs with the identification of this study as the most appropriate basis for a cancer potency estimate.

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Office of Environmental Health Hazard Assessment

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M E M O R A N D U M

TO: Gary T. Patterson, Ph.D., Chief
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FROM: Anna M. Fan, Ph.D., Chief *(Original Signed By Dr. Anna Fan)*
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DATE: December 17, 2012

SUBJECT: COMMENTS ON THE DRAFT EXPOSURE ASSESSMENT DOCUMENT FOR CHLOROPICRIN

The Office of Environmental Health Hazard Assessment (OEHHA) has reviewed the draft exposure assessment document (EAD) for chloropicrin, prepared by the Department of Pesticide Regulation (DPR), dated December 27, 2011. Our comments are provided n the attachment. Exposure estimates reported in this document were used to estimate risks to human health in the Risk Characterization Document, previously reviewed by OEHHA. OEHHA reviews risk assessments prepared by DPR under the authority of Food and Agriculture Code section 11454.1.

In general, OEHHA agrees with the exposure assessment methodology and conclusions of the draft EAD. Several specific comments and recommendations are contained in the attachment.

Thank you for providing this draft document for our review. If you have any questions regarding OEHHA's comments, please contact Dr. Charles Salocks at (916) 323-2605 or Dr. Anna Fan at (510) 622-3200.

Attachment

cc: George V. Alexeeff, Ph.D., D.A.B.T.
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Attachment

Comments on the 2011 Draft Exposure Assessment Document for Chloropicrin

Office of Environmental Health Hazard Assessment

December 2012

General Comments

In general, the Office of Environmental Health Hazard Assessment (OEHHA) agrees with the exposure assessment methodology and the conclusions in the draft chloropicrin Exposure Assessment Document (EAD).

The draft "Estimation of Exposure of Persons in California to Pesticide Products that Contain Chloropicrin" summarizes exposures related to the uses of chloropicrin in California. Exposure estimates are made for bystanders, persons who handle chloropicrin during fumigation, persons who breach tarps, and individuals involved with structural fumigation when chloropicrin is used as a warning agent. Comments on each major section of the document are provided below. Editorial suggestions are provided after the technical comments.

1. Abstract

In some instances, the percentage of chloropicrin as the Active Ingredient (AI) in the various studies used to estimate exposure is unclear. For example, on page 8 (lines 42-43), formulations that have chloropicrin as an AI are defined as "…products containing chloropicrin concentrations above 2%." For the purpose of obtaining "*screening level* estimates of exposure" (page 8, line 6), it would be reasonable to assume a default chloropicrin concentration of 100%. This assumption would be consistent with the summary of chloropicrin-containing products registered for use in California (Table 2, page 13), which indicates that eight products have chloropicrin as the sole AI and they range in concentration from 94 to 100%. For screening purposes, it appears that a more transparent and health protective approach would be to estimate exposure for products that contain 100% chloropicrin, knowing that use of products with a lower percentage AI would result in proportionally lower exposures.

OEHHA suggests that summarizing the exposure estimates presented in the top half of page 9 in a table rather than writing them out as text would improve readability and greatly facilitate comparison of these results.

The statement that exposures resulting from use of a methyl bromide formulation that contains 10.5% chloropicrin are "anticipated to be greater" than exposures resulting

from use of formulations that contain 2% chloropicrin as a warning agent (page 9, lines 5-6) appears to be more nuanced than it needs to be. Given the five-fold concentration difference, the exposure resulting from use of 10.5% chloropicrin would surely be greater than the exposure resulting from use of 2% chloropicrin.

2. Introduction

At the end of the introduction, the mode of action is discussed. OEHHA concurs that the mode of toxic action is not well characterized. OEHHA recognizes that Sparks et al., 2000 conclude that the reaction with sulfhydryl groups of hemoglobin (Hb) and decreased oxygen transport are potential pathways for toxicity. However, OEHHA recommends that the report also point out that acute pulmonary and ocular irritation do not occur via this mode of action (page 11, lines 1-5).

The report adequately covers the physiochemical properties, formulations, and pesticide use and sales. However, OEHHA recommends that, if possible, the information on number of registered products containing chloropicrin be updated. Are the data for chloropicrin use in California available for 2009-2011, and can this information be incorporated into the report?

3. Reported Illnesses

The EAD summary of reported illnesses associated with chloropicrin is clear and concise. The EAD summarizes the reported illnesses associated with chloropicrin when used alone and in combination with another fumigant as a warning agent. As reported, in the Kern County (2003) incident, nearby residents complained of eye and throat irritation after soil fumigation even though an 18 meter buffer zone had been established. In the 2005 Monterey incident, residents 2-3 miles away complained of odor and eye irritation following a tarped bed application.

OEHHA was not able to replicate all the percentage of illness types described in the text at the bottom of pages 18 and19. The discrepancies are relatively small but should be re-checked by the authors.

The systemic effects reported in Table 4 and footnote (b) (eye, respiratory, and systemic effects) associated with chloropicrin exposure and illness cases suggest that chloropicrin exposure may cause additional chronic effects (e.g., degeneration of the nasal epithelium) that are similar to those seen with other Toxic Air Contaminants (TACs) such as acrolein, acetaldehyde, and formaldehyde. The text at the bottom of page 9 indicates that systemic effects were reported in 32% of the cases where chloropicrin was used alone and in 44% of the cases where chloropicrin was used in combination with other fumigants.

OEHHA suggests that consideration be given to potential adverse effects in sensitive sub-populations that may be exposed to chloropicrin. Studies have shown that children and asthmatics are more sensitive to the irritating effects of chemicals that can adversely affect respiratory health. In addition, eye irritation can be increased in those wearing glasses or contact lenses or those with pre-existing eye conditions. OEHHA believes that an additional uncertainty factor is warranted to establish short-term risk-based exposure standards for chloropicrin.

Bystander exposure is also a concern for continuous (seasonal) exposure. The EAD cites a study where fourteen people experienced symptoms upon entering a structure after the application was concluded (page 18, lines 16-24). In another report (Teslaa et al., 1986), a family developed serious symptoms 3 to 4 weeks post fumigation (page 21, lines 4-13). In the latter study, the residual chloropicrin level was 30-48 parts per billion (ppb) [202-323 micrograms per cubic meter ($\mu g/m^3$)] six weeks after the application. In addition, Table 7 notes that the reported concentrations of chloropicrin in ambient air may underestimate actual short-term exposures (page 42, line 25). The EAD also points out that the public may be exposed in locations that are far from the sites of application (page 25, line 41).

OEHHA further recognizes that there are data gaps in the characterization of bystander exposure that need to be addressed. The effects of simultaneous exposure to chloropicrin and its photodegradation byproduct phosgene have not been characterized. Furthermore, the EAD notes that no phosgene monitoring has been conducted in conjunction with any chloropicrin application (page 105, line 32).

4. Label Precautions and California Requirements

It appears that the criteria for use of air-purifying respirators (APRs) were established without taking into consideration the results of the Cain (2004) study. The criteria are described on page 23, lines 28-31: "Handlers can resume work activities without air-purifying respirators, if two consecutive breathing zone samples taken at the handling site at least 15 minutes apart show levels of chloropicrin have decreased to less than 0.15 ppm (150 ppb), provided that handlers do not experience sensory irritation." However, the Cain (2004) study established that the threshold for acute (one-hour) sensory (ocular) irritation in humans is lower than 150 ppb. Benchmark dose analysis of the data indicated a $BMCL_{10}$ for ocular irritation of 26 ppb. [See Chloropicrin Risk Characterization Document (DPR 2011), page 49.] At concentrations of 100 and 150 ppb, eye irritation was clearly detectable in humans subjects after exposure durations of just 19 and 10 minutes, respectively (DPR 2011; page 21). These data demonstrate that persons exposed to 100-150 ppb *will* experience eye irritation after relatively short exposure durations. For this reason, it appears that the relevance of the 150 ppb analytical criterion for respirator use needs to be re-evaluated and perhaps lowered to

no more than 100 ppb. Furthermore, since APRs are assumed to confer 90% protection, it would be reasonable to restrict APR use to situations where the airborne concentration of chloropicrin is ≤ 1,000 ppb [1 part per million (ppm)]. Working in environments where the concentration is greater than 1 ppm should not be permitted, even when APRs are available.

5. Exposure Scenarios

The exposure scenarios presented in the EAD include occupational handlers exposed during chloropicrin applications (before aeration or tarp removal), occupational handlers conducting aeration activities (tarp punching, splitting and removal), reentry scenarios, airborne exposures of bystanders, and ambient air exposures. OEHHA concurs that the highest realistic exposures, based on available data, should be used for quantitative risk assessment purposes. OEHHA agrees with the parameter values used to estimate bystander exposure, including an 8-hour workday for occupational bystanders and a residential 24-hour/day scenario. This section provides a thorough review of the data on occupational handler scenarios and reentry scenarios.

The EAD states that exposures to the public are possible in areas that are far from application sites. OEHHA recommends that the California Air Resources Board continue to conduct air monitoring in counties with high use to improve the data available.

The field fumigation scenarios were based on typical application rates to calculate ambient air concentrations. OEHHA is concerned that the data used for these calculations may not adequately reflect the increased use of chloropicrin in California (see Table 3 and Figure 2). OEHHA recommends using more recent data from the Pesticide Use Report to update Appendix III and to address the possibility that maximum application rates have increased. In addition, it would be important to determine if greater statewide use might lead to higher cumulative (multiple source) exposures, particularly in those counties where use of the fumigant is high. As statewide chloropicrin use increases and use of methyl bromide declines, cumulative exposure to chloropicrin might be particularly critical for residential bystanders. DPR may want to consider a sensitivity analysis that assumes higher cumulative exposures.

6. Pharmacokinetics

One metabolic pathway briefly mentioned in the EAD is the formation of thiophosgene intermediates. This is a pathway of concern as these types of adducts may lead to chronic health effects. OEHHA notes that studies using the intraperitoneal route of exposure for determining the pharmacokinetics of chloropicrin are of questionable relevance for extrapolating to the inhalation route of exposure (page 29, lines 18-29). However, OEHHA recognizes that DPR must use the data available to them.

7. Environmental Fate

Persistence in Soil Environment

The potential for chloropicrin persistence in soil and groundwater is a concern and should be further evaluated as this can represent a potential exposure long after soil fumigation and may lead to long-term bystander exposure via infiltration into residential indoor air. The increased use of chloropicrin in California has potential to exacerbate this situation. On page 34, lines 21-26, Guo et al., 2003b noted that levels as high as 500 milligrams per kilogram (mg/kg) persisted in the soil 7 years after a manufacturing facility had ceased operations, and groundwater beneath the facility had chloropicrin concentrations ranging from 10-150 milligrams per liter (mg/l). Other studies were reviewed examining the half-lives of chloropicrin in different soil types and conditions. This section would benefit from a conclusion paragraph that summarizes the major findings on half-lives and soil types and conditions.

In a soil metabolism study, Olson and Lawrence (1990) added 250 ppm of radiolabeled chloropicrin to sandy loam under aerobic conditions. The EAD notes that "The estimated half-life "…was approximately 5 days; about 70% of the applied radiolabel was recovered by the 90th day of the study as CO_2, while most of the rest was volatilized chloropicrin" (page 31 lines 32-35). This suggests that the parent compound degrades quickly ($t_{½}$ = 5 days) but that ultimate degradation to CO_2 requires considerably longer time. Did the authors of this study analyze for the presence of any specific degradation by-products? This may be significant since reductive dechlorination by-products of chloropicrin appear to be mutagenic (Chloropicrin Risk Characterization Document, page 56). A more detailed explanation of these results would probably be helpful.

Persistence in Water Environment

While exposure to light may decrease persistence of chloropicrin in some water environments by photodegradation, ground water is not typically exposed to light prior to consumption and therefore would not be degraded by this mechanism. OEHHA recommends this distinction be made on page 35. OEHHA also recommends that the studies on hydrolysis and photohydrolysis (pages 35-37) be summarized through the use of a table, or some over-arching conclusions about the results of these studies be listed at the end of the section. The section on oxidation-reduction reactions adequately summarizes the limited existing data on this subject. The section on chloropicrin disinfection byproducts in drinking water states that chloropicrin is present in drinking water only at low concentrations (< 10 μg/L). Use of the word "low" may be misinterpreted to mean insignificant or of no concern. OEHHA recommends that the report simply state that "the concentrations were measured at <10 μg/L," rather than

characterizing or describing them as “low”. On page 38, lines 4-7, the EAD reviews a study by Wells et al. (2001) that found boiling tap water samples decreased chloropicrin concentrations to below the LOD. However, it should be noted in the report that very few people boil their tap water prior to use.

OEHHA concurs with the analysis and conclusion regarding bioconcentration in “Aquatic Organisms” section (page 38): the potential for chloropicrin to bioconcentrate in aquatic organisms is low.

Persistence in Air Environment

Photolysis

While chloropicrin is reactive with a short half-life in the presence of sunlight, tarping of fields during soil fumigation will probably limit the amount of sunlight reaching the soil. While OEHHA recognizes that field data on phosgene generation are not available, we also recommend a cautious approach in relying on laboratory experiments (e.g., Helas and Wilson, 1992; Carter et al., 1997) examining the rates of photodegradation in flasks or chambers, using incident light levels comparable to ground level measurements, to estimate production of phosgene as a photodegradation product (page 39, line 31-32). The estimated half-lives do not take into consideration tarping of the soil which will limit sunlight penetration and not be comparable to estimations based on full ambient sunlight (page 39-40, line 38, 1-3).

There is a concern for phosgene exposure in ambient air after soil fumigation with chloropicrin. In one laboratory study, phosgene was formed at almost a 1:1 ratio with the amount of chloropicrin added, which ranged from 500-2000 ppb (page 40 line 41-44). Chloropicrin and phosgene are both acute eye and respiratory irritants but their chemical and physical properties are different. As a result, they may have adverse impacts in different regions of the airways and/or lungs. Therefore, the effect of concurrent exposure to these compounds could be more severe than exposure to either chemical alone. OEHHA believes that the issue of phosgene production and concurrent exposure to chloropicrin and phosgene should be evaluated further.

8. Environmental Concentrations

Air

OEHHA recommends citing the actual TAC document with a reference at the beginning of this section (page 42, line 2).

Ambient Air

The EAD states that the concentrations shown in Table 7 (page 42, line 25) may underestimate actual ambient air concentrations for short-term exposures. The use of chloropicrin has increased since 2001, when the most recent studies cited in this table were conducted. Has ambient air monitoring been performed in counties where chloropicrin use is high since 2001?

Application Site Air – Soil Fumigation

OEHHA agrees with the statement that it is unlikely that the measurements from one particular study will capture the highest possible air concentrations for an application method (page 44, line 6-7).

OEHHA also concurs that direct flux estimation is an appropriate method for estimating chloropicrin flux in conjunction with an air dispersion model to estimate off-site concentrations associated with soil fumigation. The report provides a very clear explanation of the ISCST3 model (page 44, lines 20-45).

Off-Site Concentrations

The review of the ARB studies of off-site concentrations (pages 46-48) was clear and informative, and addressed known data limitations. The data from these studies are reported in Tables 8 and 9. OEHHA agrees with the use of both laboratory and field spikes to check on both the analytical procedure and the environmental conditions. The percent recoveries were provided and the results appropriately adjusted.

Field Volatility (flux)

OEHHA agrees with the methodology used in the field volatility studies, which included lab and field spikes, recovery rates, replications and validation for quality assurance, as well as calculation of coefficients of variation (CVs). OEHHA recommends that an explanation be added (page 51 lines 22-27) to further explain how and why flux values for different application methods vary between night and day (Table 10).

OEHHA concurs with the rationale for the selection of the highest concentration (230 $\mu g/m^3$) associated with bedded tarp applications for seasonal and bystander exposures (page 54, lines 17-26).

Application Site Air – Structural Fumigation

OEHHA recommends adding an additional column to include the corrected concentrations after field spike recoveries in Table 13 (35 $\mu g/m^3$, 54 $\mu g/m^3$, and 27 $\mu g/m^3$) (pages 56, line 23; page 57, line 11; page 57, line 23).

In the discussion of the study conducted by Barnekow and Byrne (2006), OEHHA recommends citing Table 15 ("Concentrations Used to Estimate Exposure of Bystanders to Chloropicrin from Structural Fumigation") on page 58 (lines 31 and 40), and page 59 (line 8).

Water

Considering the large increase in use of chloropicrin in California (as shown in Table 3 and Figure 2) and the statement that no ground water sampling has been performed since 1996, OEHHA recommends that further testing of well water samples in California be performed.

9. Exposure Assessment

Bystander Exposure

OEHHA concurs with the use of the 24 hour/day time period as the worst case assumption for residential bystander exposure (page 61). OEHHA also agrees with the use of the highest realistic exposures to bystanders in the exposure assessment.

Soil Fumigation

OEHHA concurs with the values used for the estimated exposure of bystanders to chloropicrin from soil fumigation (Table 16).

Were the data on applications of chloropicrin in Ventura County (Figure 6) used in calculating the seasonal, annual, and lifetime estimates reported in Table 16, or is this graph only being shown to represent the seasonal nature of chloropicrin's use in the county?

Structural Fumigation

While Table 17 partially replicates data that were already presented in Table 15, OEHHA recommends retaining Table 17 because it assists the reader in understanding the discussion in the "Structural Fumigation" section (page 63).

Residential Reentry

OEHHA concurs with the calculations for residential reentry exposure based on indoor air concentrations.

Ambient Air

OEHHA recommends referencing earlier sections in the report that discuss the ambient air monitoring in this section (page 65) for ease of cross-referencing information and understanding the details of the cited studies.

Occupational Exposure: Soil Fumigation

OEHHA recommends that earlier sections of the report that reviewed the studies discussed here should be cited here (page 66 line 3-4) for ease of cross-referencing information and understanding the details of the cited studies.

With limited data, OEHHA concurs that data from short-term studies are the best available for estimating mean daily exposures. However, most of the calculations are based solely on two key studies (Beard et al., 1996; Rotondaro, 2004). This suggests a significant data gap; there is a need for additional studies to be done in this area.

The following 1-hour exposure estimates for occupational handlers were taken from Tables 36 and 37 (pages 86 and 87) and Tables 21 and 23 (pages 70 and 72). They describe two exposure scenarios involving two chloropicrin formulations and two different application methods.

Concentration	Scenario (Application Method)	Handler Population	Exposure (ppb)	Ratio
100%	surface drip irrigation, tarped	tarp punchers	7.79	11.46
10.5%	surface drip irrigation, tarped	tarp punchers	0.68	
100%	broadcast shank, tarped	tarp removers	2310	7.52
10.5%	broadcast shank, tarped	tarp removers	307	

Intuitively, it seems logical to presume that – for any given exposure scenario – the airborne exposure concentration will be proportional to the concentration of chloropicrin in the formulation. However, this does not appear to be the case: for both exposure scenarios, the ratio of the exposure concentrations (11.46 and 7.52) is not equivalent to the ratio of the chloropicrin concentrations in the two formulas (9.52). While the discrepancies are not large, an explanation for the lack of direct proportionality should be provided.

Occupational Exposure: Structural Fumigation

OEHHA recommends that earlier sections of the report reviewing the studies mentioned here should be cited in this section (page 66 line 3-4) for ease of cross-referencing information and understanding the details of the cited studies.

10. Exposure Appraisal

Overall, OEHHA recognizes that there are very little data available for the exposure estimates. In general, OEHHA believes that DPR used the best data available for estimating exposures. However, OEHHA does recommend, wherever possible, updating the use data in the report. In addition, OEHHA recommends that DPR in conjunction with ARB consider further air monitoring studies. The uncertainties and

assumptions reviewed in this section, including application rates, likelihood of multiple applications and likelihood of adjacent applications should be taken into account when addressing overall exposure and consequent health risk.

OEHHA is also concerned about chloropicrin's degradation to phosgene and the potential for concurrent exposure to both chemicals. There is a lack of toxicity information on concurrent exposure to chloropicrin and phosgene. Both chemicals cause acute eye and pulmonary toxicity. This represents a serious data gap. OEHHA recommends concurrent monitoring of both chloropicrin and phosgene in all future field studies.

OEHHA is concerned with the systemic effects associated with chloropicrin exposure that may cause additional chronic effects (e.g., degeneration of the nasal epithelium). In addition, OEHHA suggests that consideration be given to potential adverse effects in sensitive sub-populations that may be exposed to chloropicrin. Therefore, OEHHA believes that an additional uncertainty factor is warranted to establish short-term risk-based exposure standards for chloropicrin.

Additional Editorial Comments

1. Summarizing Conclusions

The studies summarized throughout the report are well-reviewed. OEHHA recommends providing conclusions at the end of each section after a group of studies are reviewed, which would be helpful for the reader. The document contains a large amount of data that are reported for a wide variety of parameters. Conclusions at the end of these sections would be helpful in justifying the values that were selected for use in the exposure assessment section.

2. Table 4

Table 4 summarizes the types of illnesses and cases reported in California from 1992-2008. If available, updated information for 2009 to the present should be added.

3. Table 8

Table 8 contains a wealth of information and is accompanied by excellent summaries of the studies in the text. However, it is very difficult to match the studies with the table because the references are footnoted. It would be much easier to compare the summaries of the studies with the values summarized in the table if an additional column were created, and the citations were listed next to each description in the row rather than footnoted. Additional details and notes can remain as footnotes.

4. Use of the Adjective “Low”

OEHHA recommends that the term “relatively low concentrations” mentioned in the introduction be better defined with respect to both its use as a warning agent (page 9) and its ability to cause eye irritation (page 10). Perhaps a specific range of concentrations would be less vague.

The introduction states that chloropicrin has the potential to cause adverse health effects at low doses (page 10). OEHHA suggests that the term “low” not be used here. OEHHA suggests that a range of doses be provided at which adverse health effects were observed. Does the Cain (2004) study provide a scientifically valid basis for assessing whether a given exposure concentration is indeed “low” or is in fact sufficient to cause eye and airway irritation in humans?

dpr Department of Pesticide Regulation

Brian R. Leahy
Director

Edmund G. Brown Jr.
Governor

MEMORANDUM

TO: Anna M. Fan, Ph.D., Chief
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FROM: Gary T. Patterson, Ph.D., Chief
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Lisa Ross, Ph.D., Acting Chief
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DATE: February 6, 2013

SUBJECT: CHLOROPICRIN: TRANSMITTAL OF RESPONSES TO OEHHA'S COMMENTS ON DPR'S RISK CHARACTERIZATION DOCUMENT & EXPOSURE ASSESSMENT DOCUMENT

On December 29, 2011, the Department of Pesticide Regulation (DPR) transmitted its draft chloropicrin risk characterization document (RCD) and exposure assessment document (EAD) for OEHHA's review. DPR received OEHHA's comments on the draft RCD on October 15, 2012, and the draft EAD on December 17, 2012.

DPR's responses to OEHHA's comments are attached. If you have questions regarding DPR's responses to the comments pertaining to the draft RCD, please contact Dr. Jay Schreider at 916-445-4241. If you have questions regarding DPR's responses to the comments pertaining to the draft EAD, please contact Dr. Sheryl Beauvais at 916-445-4268.

DPR is in the process of finalizing both documents. Once the documents are finalized, they will be posted on DPR's external Web site at http://www.cdpr.ca.gov/docs/risk/rcd.htm.

Attachment

cc: Dr. David Ting, OEHHA (e-copy)
Dr. Jay Schreider (e-copy)
Dr. Sheryl Beauvais (e-copy)

Department of Pesticide Regulation

Brian R. Leahy
Director

Edmund G. Brown Jr.
Governor

TO: Gary Patterson
Supervising Toxicologist
Medical Toxicology Branch

VIA: Jay Schreider *[Original signed by J. Schreider]*
Senior Toxicologist
Medical Toxicology Branch

FROM: Carolyn Lewis *[Original signed by C. Lewis]*
Associate Toxicologist
Medical Toxicology Branch

DATE: November 14, 2012

SUBJECT: RESPONSE TO OEHHA'S COMMENTS ON THE CHLOROPICRIN RISK CHARACTERIZATION DOCUMENT

The following response is to comments the Office of Health Hazard Assessment provided on October 15, 2012, after review of the document "Chloropicrin Risk Characterization Document" date September 2, 2011.

I. Summary – See responses to the detailed comments under sections II-VIII.

II. Background Information - No comments in this section.

III. Acute Toxicity

1. Cain (2004)

Footnote in Table 14 (p. 48) on the NOEL for Phase 2 was in error. That only applied to the $BMCL_{10}$ for Phase 3. The number reported for Phase 2 is a NOEL, not a BMCL. This footnote was removed.

a. Ocular Irritation

In the Risk Appraisal Section of the Risk Characterization Document (RCD) dated Sept. 2, 2011 is a discussion of the uncertainty factor applied to the eye irritation on page 94. In that discussion, it was recommended the toxicokinetic component of the intraspecies uncertainty factor could be dropped for this endpoint since it involves the direct interaction of the chloropicrin with the trigeminal nerves so there would be no anticipated toxicokinetic variation. However, DPR's risk assessor recommended that the toxicodynamic component of 3 be retained for this endpoint because of a paper by Shusterman et al. (2003) that reported individuals with allergic rhinitis were more sensitive to sensory irritation. Furthermore, children have not been

tested for their sensitivity to sensory irritants, so it is unclear if they are more or less sensitive than young adults. This uncertainty factor of 3 for eye irritation was not changed based on OEHHA's comment.

b. First Upper Respiratory Endpoint: Increased Nitric Oxide (NO) Levels

The intraspecies uncertainty factor recommended in the RCD for increased nitric oxide in expired nasal air was the standard default uncertainty factor of 10. This includes both the toxicokinetic and toxicodynamic components that should cover the increased sensitivity in children and asthmatics. Because a BMD analysis was done and the $BMDL_{05}$ was used for the point of departure, some intraspecies variation was already taken into consideration. Furthermore, the need for an additional uncertainty factor beyond the default seems questionable given that the increase in nitric oxide is a subclinical sign. It also seems odd that an additional uncertainty factor should be applied to a mild effect in a human study (where there would be more certainty) than to the endpoints seen in the animal studies, which were more adverse and there was more uncertainty with the interspecies extrapolation. Therefore, no additional uncertainty factor beyond the default intraspecies uncertainty factor of 10 was applied to this endpoint.

c. Second Upper Respiratory Endpoint: Decreased Nasal Inspiratory Flow Rates

A BMD analysis of the reduced nasal air flow was not originally conducted for this study since the effect was only seen at the highest dose level and did not appear to be as sensitive an endpoint as either the eye irritation or the increased nitric oxide levels, which were seen at the lowest dose level. It seemed unlikely that a good fit could be obtained given that the response was only seen at one dose level, and there were only two treatment groups. Furthermore, even if one could obtain a BMDL with this data, it would presumably be higher than that obtained for increased nitric oxide or eye irritation, which were seen at the lowest dose level. Nonetheless, DPR attempted to do a BMD analysis of this data based on OEHHA's recommendation. The analysis was done on the differences in the pre- and post-exposure inspiratory and expiratory flow rates on Day 1, which showed the most dramatic differences. Not surprisingly, it was not possible to get a good fit with any model. The main problem did not appear to be due to the response being non-monotonic, but rather due to non-homogeneous variances, which reduced the degrees of freedom in the model. In fact, in looking at the means and standard deviation (SD) generated to use in the BMD analysis, it was surprising that any significant differences were seen, because the variation in the response was quite large. For example, on Day 1 the differences in inspiratory air flow were -3.15±197, 17.3±175, and -57.3±128 ml/sec at 0, 100 and 150 ppb, respectively. (Note: on the graphs on p. 81 and 82 of the study report, the error bars represent the standard error of the mean, not the standard deviation which understates the variation seen in this endpoint). Closer examination of the respective pre-exposure means and SD (440±177,403±153 and 496±121 ml/sec) and post-exposure means and SD (437±180,

420±166 and 439±125 ml/sec) shows that the biggest differences between groups were seen in the pre-exposure means, rather than the post-exposure means, suggesting that any differences between groups was not related to treatment. The study investigator reported a significant effect of treatment in their analysis of variance by level by order (pre-exposure vs. post-exposure), but our independent analysis using a non-parametric test [1] did not find any significant differences based on treatment. DPR concluded that while it is possible there was some marginal effect on air flow at the highest dose level, this endpoint is not very sensitive given the large variation in responses even to the blank air. Therefore, by designating the lowest dose level as a NOEL, DPR believes it was making a very cautious, health protective assumption. However, to use an additional uncertainty factor of 3 on top of the default intraspecies factor of 10 for this endpoint was not warranted, especially given that no additional uncertainty factors for children and asthmatics were used for more adverse effects seen in the animal studies. The discussion of this endpoint was modified slightly to indicate a BMD analysis was not possible.

d. Summary Conclusions and Recommendations Based on the Cain (2004) Study

DPR did not revise the endpoint (increased nitric oxide in expired nasal air) or the intraspecies uncertainty factor (10) applied to this endpoint to evaluate 1-hr exposures to chloropicrin after consideration of OEHHA's comments.

2. York (1993)

OEHHA recommends using the Cain (2004) study to evaluate 8-hr exposures despite stating in section III.1.d. that they support DPR's conclusion that there was insufficient data in the Cain study to predict severity of effects beyond on-hour exposure duration. OEHHA also states that they concur with the general principal of using longer duration studies to derive the 8-hr and 24-hr NOELs. OEHHA did not provide any additional justification in this section for using the Cain study for the 8-hr exposures. Therefore, DPR did not change the NOEL used for evaluating 8-hr exposures.

IV. (Section number skipped in OEHHA's memorandum)

V. Summary Conclusions and Recommendations Regarding the Acute Toxicity of Chloropicrin

DPR has not changed any of the endpoints or uncertainty factors applied to the acute NOELs used in this risk assessment based on OEHHA's comments. The endpoints used in this risk assessment have not changed from the risk assessment conducted for chloropicrin to evaluate its

[1] Shirley, E., 1977. A non-parametric equivalent of Williams' test for contrasting increasing dose levels of a treatment. Biometrics 33(2): 386-389.

potential as a toxic air contaminant. That risk assessment underwent a thorough review by the Scientific Review Panel and there are no new data to justify changing these values.

VI. Subchronic (Seasonal) and Chronic Toxicity

DPR default breathing rates for children and adults is being reevaluated and may be revised to reflect USEPA values from their Exposure Factors Handbook. In the meantime, the default values that were identified in an inter-branch scientific policy memorandum will remain in effect. Regardless, the differences in breathing rates that OEHHA is proposing are small and would not make a significant difference in the conclusions given the extremely small MOEs calculated.

VII. Genotoxicity and Carcinogenicity

First, as stated in the RCD if one calculated a $BMCL_{01}$ for lung tumors in female mice, it would be 14 ppb. The corresponding HEC would be 16 ppb. The HEC was divided by an uncertainty factor of 1,000 rather than the default of 100 because of the uncertainty regarding its carcinogenic potential, which resulted in a RfC of 16 ppt, not 1.6 ppb as OEHHA suggested. Regardless, this approach was not used, but was included in the Risk Appraisal section for comparison if one assumed a threshold.

Second, the argument for a threshold is not considered strong otherwise a threshold would have been assumed. It was not. DPR concluded in the Weight of Evidence section in Hazard Identification that "a genotoxic mode of action for tumor formation was more likely than not". This discussion in the Risk Appraisal section is merely to present some of the uncertainty in the risk assessment and alternate interpretations of the genotoxicity data.

Third, DPR agrees that some of the *in vivo* genotoxicity tests were of questionable relevance and these were mentioned in the Weight of Evidence in the Hazard Identification section. However, there was one *in vivo* mouse micronuclei assay that was negative and met FIFRA guidelines. Mortalities and clinical signs were seen at the highest dose level in this study. These results cannot easily be dismissed, but by themselves do not negate the overwhelming positive results in the *in vitro* studies.

Therefore, the discussion of the carcinogenic potential in the Risk Appraisal section has not been changed.

VIII. Conclusions Regarding the Carcinogenicity of Chloropicrin

Enclosed space fumigation is no longer a registered use for 100% chloropicrin; therefore, this use was removed from the exposure scenarios evaluated for chloropicrin.

OEHHA suggests that there are no uncertainties in the cancer risk for chloropicrin, yet they also state that mixed results for genotoxicity studies are typical for most carcinogens. These mixed genotoxicity results means there is uncertainty about the mode of action for carcinogenicity and about the best approach for evaluating it. DPR has taken a health protective approach in assuming there are no thresholds, but to not discuss the uncertainty in this assumption is not balanced in our view. Consequently, the statement on page 104 about the uncertainties in cancer potency is considered entirely appropriate in the Risk Appraisal section and will not be changed.

Department of Pesticide Regulation

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M E M O R A N D U M

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FROM: Sheryl Beauvais, Ph.D., Senior Toxicologist *(original signed by S. Beauvais)*
Worker Health and Safety Branch
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DATE: January 28, 2013

SUBJECT: RESPONSES TO OEHHA COMMENTS ON CHLOROPICRIN EXPOSURE ASSESSMENT DOCUMENT (HS-1880)

The Office of Environmental Health Hazard Assessment (OEHHA) sent comments, dated December 17, 2012, on the Department of Pesticide Regulation's (DPR's) final draft Exposure Assessment Document (EAD) for chloropicrin, dated December 27, 2011. The EAD was sent to OEHHA on December 29, 2011. During the 11½ months the EAD spent in review at OEHHA, the summaries of registered products, uses, and illnesses became outdated. Furthermore, scenarios and exposure estimates in the EAD were based on product labels current in December 2011. Recently, new product labels were registered with mitigation measures including buffer zones for chloropicrin. As a result of the extended time in review, the EAD contains many exposure estimates that do not reflect current uses.

DPR will not update the EAD, however. None of the suggestions made by OEHHA would result in substantial change to health risk estimates. Rather than delay mitigation further, the EAD will be finalized without additional revision. New data and product labels will be used in determining appropriate mitigation, including the extent to which additional mitigation may be needed.

Responses to specific comments are given below. Each paraphrased comment is italicized and followed by DPR's response.

1. Abstract

Screening level estimates should be only on products containing 100% chloropicrin; all other concentrations result in lower estimates.

Response: Chloropicrin is used as a warning agent and as a pesticidal active ingredient; the EAD considers both types of uses. Risk managers may consider these uses differently, as for example, irritation is a key component of the warning agent use. Furthermore, the use patterns differ, and a product containing 2% chloropicrin is not necessarily applied at a proportionately lower rate because the rate must be efficacious for the non-chloropicrin active ingredient (AI). Differences in use rates also cause some products containing chloropicrin and either methyl bromide or 1,3-dichloropropene to yield higher exposures than products containing 100% chloropicrin. Products

containing less than 100% chloropicrin are included in the EAD when appropriate.

Summarize exposure estimates in a table in the abstract for better readability.

Response: DPR agrees that a table would allow readers to quickly find specific estimates, if the EAD were to be revised.

State without qualification that exposures associated with use of products containing 10.5% chloropicrin are greater than those associated with 2% chloropicrin.

Response: The qualifying phrase that OEHHA asks be excluded merely indicates an assumption made in the exposure assessment. In the absence of exposure data collected during use of these specific products, DPR's default is to assume that greater amounts of active ingredient correlate linearly with greater exposure. This assumption leads to DPR's practice of adjusting concentrations in air linearly based on maximum application rate, when calculating exposure estimates at the maximum rate.

2. Introduction

Update information on number of chloropicrin products.

Response: The products currently registered are summarized below in Table 1. Several mixtures containing methyl bromide were inactivated, as well as all products containing methyl iodide.

Table 1. Chloropicrin-Containing Products in California as of January 2013

Active Ingredient [a]	Number of Products [b]	Chloropicrin Concentration Range (%)	Fumigation Type [c]	Number of Products with Greenhouse Uses [d]
Methyl Bromide	19	0.5 – 55	Soil	19
Chloropicrin 2.0% [e]	(5)	0.5 – 2.0	Soil/Structural	(5)
Chloropicrin 10.5% [e]	(1)	10.5	Soil	(1)
Chloropicrin 19.8 – 67%	(13)	19.8 – 67	Soil	(13)
1,3-Dichloropropene	13	15 – 60	Soil	1
Chloropicrin as sole AI	8	94 – 100	Soil/Structural [f]	7
Total	40			

[a] Active ingredient (AI) in addition to chloropicrin.
[b] Seven products intended for manufacture use only (i.e., no pesticidal uses) were omitted.
[c] Soil may be fumigated outdoors (e.g., pre-plant fields or replant tree holes), or indoors in greenhouses unless specifically prohibited.
[d] Includes products where greenhouse use is not specifically prohibited by product label. In most cases, specific instructions are provided for soil fumigation in greenhouses.
[e] In these products, chloropicrin is considered a warning agent, and is listed on the label as an "other ingredient" or an "inert ingredient." Chloropicrin at higher concentrations is listed as an active ingredient.
[f] Sulfuryl fluoride product labels provide instructions for using chloropicrin as a warning agent, which is required for sulfuryl fluoride structural fumigations. Four of the nine chloropicrin product labels contain a statement referring to sulfuryl fluoride labels for warning agent directions in structural fumigations.

Update chloropicrin use data.

Response: Pounds chloropicrin applied statewide between 2006 and 2010 are summarized below in Table 2. Data for 2011 and 2012 have not yet been released.

Table 2. Chloropicrin Use in California, 2006 – 2010

Use Site	Pounds Applied [a]				
	2006	2007	2008	2009	2010
Soil fumigation, pre-plant [b]	5,017,305	5,488,746	5,537,727	5,685,770	5,824,800
• Strawberries	3,236,844	3,408,331	3,643,946	3,950,176	4,610,400
• (Strawberry % of soil) [c]	(64.5%)	(62.0%)	(65.7%)	(69.5%)	(79.2%)
• Tree crops [d]	23,342	68,762	74,481	88,310	67,932
Commodity fumigation [e]	359	734	2,058	1,164	2,694
• Non-research commodity [f]	0	0	921	818	1,956
Turf/Sod	4,913	15,911	2,196	7,789	1,118
Structural Pest Control	1,126	4,316	1,260	3,808	1,665
Total Pounds Used	5,018,831	5,494,541	5,543,140	5,687,600	5,824,800
Soil fumigation % of total [g]	100%	99.9%	99.9%	99.9%	99.9%

[a] From DPR (2007; 2008; 2009; 2010; 2011). Multiply values by 0.455 to get use in kg applied. Average use during 5-year interval: 5,211,366 lbs (2,368,803 kg).
[b] Includes all use listed under specific crops, as well as non-specific pre-plant fumigations. Totals include applications to strawberries and tree crops, which are also listed separately for the reasons given below.
[c] Percent of chloropicrin use for pre-plant soil fumigation reported in strawberry beds or fields. Pre-plant soil fumigation for strawberries is the greatest single use of chloropicrin.
[d] Tree crops can be fumigated by handwand as well as by other soil fumigation methods.
[e] Includes commodity fumigation done for research purposes.
[f] Use reported for commodity fumigation, but not reported as research.
[g] Percent of total reported chloropicrin use that was due to pre-plant soil fumigation.

3. Reported Illnesses

Update chloropicrin illness summary.

Response: Reported illnesses associated with chloropicrin in California between 1992 and 2009 are summarized below in Table 3. Data for 2010 through 2012 have not yet been released. The slight discrepancies in percentages noted by OEHHA are due to DPR's use of the "ROUND" function in Excel to calculate the percentages. These differences do not impact risk management decisions.

Systemic effects were reported for some illnesses associated with chloropicrin alone as well as in combination with other pesticides, suggesting potential for additional chronic health effects.

Response: The purpose of this comment is unclear. Seasonal, annual, and even lifetime exposures were estimated, which allow DPR to address chronic health effects identified for chloropicrin in the RCD. Summaries and speculation about toxicity are outside the scope of the EAD.

Table 3. Types of Illness Cases Reported in California (1992 – 2009) [a]

Illness Type [b]	Alone [c]	In Combination [d]	As Warning Agent [e]	Total
Eye only	246	52	25	323
Eye & Respiratory	128	49	28	205
Eye, Respiratory & Systemic	95	34	39	168
Eye & Systemic	75	25	19	119
Systemic	10	17	52	79
Respiratory & Systemic	4	19	40	63
Respiratory	10	16	17	43
Skin	0	4	25	29
Other combinations of types [f]	6	13	33	52
Total	574	229	278	1,081

[a] Illness cases that were potentially associated with chloropicrin exposure or that were associated with or indirectly related to fumigants with chloropicrin as a warning agent. "Definite" means that both physical and medical evidence document exposure and consequent health effects, "probable" means that limited or circumstantial evidence supports a relationship to pesticide exposure, and "possible" means that evidence neither supports nor contradicts a relationship (Holland, 2012).

[b] Eye effects include irritation, burning, itching and watery eyes. Respiratory illnesses include irritation of nose, throat, and lungs; coughing; wheezing; lung congestion; asthma and other breathing difficulties. Systemic illnesses include symptoms such as nausea, dizziness, headache, numbness. Skin effects include itching, rashes, and burns.

[c] Chloropicrin was applied as a sole active ingredient.

[d] Chloropicrin formulated in a product with 1,3-dichloropropene or methyl bromide in which the chloropicrin concentration is above 2%. Includes thirteen cases involving Methyl Bromide 89.5%, which contains chloropicrin 10.5% as a warning agent. Of these thirteen cases, seven reported effects to eyes along with respiratory illness, four reported only eye effects, one reported only skin effects, and one reported eye effects and systemic illness (see footnote *b* for explanation of illness types).

[e] Chloropicrin used in conjunction with sulfuryl fluoride, or formulated with methyl bromide in a product with chloropicrin concentration less than or equal to 2%.

[f] Includes seven less commonly reported combinations of eye, skin, respiratory, and systemic effects.

"OEHHA suggests that consideration be given to potential adverse effects in sensitive sub-populations that may be exposed to chloropicrin...OEHHA believes that an additional uncertainty factor is warranted to establish short-term risk-based exposure standards for chloropicrin."

Response: Both adverse effects (beyond summarizing reported illnesses) and uncertainty factors are outside the scope of the EAD.

Illness reports suggest that seasonal exposures should be estimated for bystanders to structural fumigation.

Response: DPR has requested data from registrants to help address potential health concerns with chloropicrin concentrations following structural fumigation. However, seasonal exposures are not anticipated for bystanders to structural fumigation.

Teslaa *et al.* (1986) reported on symptoms following an illegal release of chloropicrin into a basement, in contrast to structural fumigations conducted according to requirements in California. For example, Teslaa *et al.* (1986) did not mention the legally required aeration; from their description chloropicrin was released and no additional action taken to clear fumigant from the house. Furthermore, the elevated concentrations measured 6 weeks post-application suggest the initial concentrations were far higher than would be encountered following a structural fumigation in which chloropicrin is a warning agent. Available data suggest that elevated chloropicrin concentrations do not occur for more than a few days following a properly conducted fumigation (Barnekow and Byrne, 2006). The account published by Teslaa *et al.* (1986) was included solely for its description of reported symptoms, not as a prediction of conditions accompanying structural fumigation.

Address data gaps in characterization of bystander exposure, such as simultaneous exposure to chloropicrin and phosgene.

Response: Several key data gaps, including lack of data for phosgene concentrations associated with chloropicrin fumigation, were discussed in the Exposure Appraisal section of the EAD. DPR has initiated a pilot project to determine whether measurable phosgene concentrations occur during soil fumigations with chloropicrin.

4. Label Precautions and California Requirements

Instructions for use of respiratory protection given on product labels should be reevaluated in light of human sensory irritation data.

Response: Recommending changes to content of pesticide product labels is outside the scope of the EAD. Product label content is discussed in the EAD to the extent that it impacts assumptions used in calculating exposure estimates.

5. Exposure Scenarios

"OEHHA recommends that the California Air Resources Board continue to conduct air monitoring in counties with high use to improve the data available."

Response: Recommending future actions by the California Air Resources Board is outside the scope of this EAD. DPR has ongoing projects to monitor concentrations of several pesticides including chloropicrin in multiple communities.

Ambient air exposure estimates should assume higher application rates, because of increasing use.

Response: As explained in the EAD, ambient air concentrations, which would reflect increasing and decreasing use of chloropicrin, were not used to estimate public airborne exposures. Instead, the EAD used bystander exposures estimated from application site monitoring and adjusted for the maximum allowed application rates. As maximum allowed application rates have not increased, exposures are not underestimated in the EAD by changes in applications over time.

6. Pharmacokinetics

The pharmacokinetic data reported in the EAD involved intraperitoneal injection, which is not a relevant exposure route.

Response: DPR recognizes that pharmacokinetics might vary by exposure route, and that inhalation is the major route of chloropicrin exposure. DPR agrees with OEHHA that as the reported studies were the only ones available, it was appropriate to discuss them.

7. Environmental Fate

The EAD should include a conclusion paragraph summarizing major findings on chloropicrin persistence in soil.

Response: DPR agrees that a paragraph summarizing conclusions would be helpful to readers, if the EAD were to be revised.

If Olson and Lawrence (1990) analyze specific degradation byproducts in their soil metabolism study, the EAD should discuss these results in detail, especially if reductive dechlorination byproducts were identified.

Response: Olson and Lawrence (1990) followed metabolism using radiolabeled chloropicrin, and did not identify intermediate metabolites.

As groundwater is not exposed to sunlight, degradation of chloropicrin by photohydrolysis is not relevant in groundwater; the EAD should state this fact. A table should be added to summarize studies on hydrolysis or photohydrolysis.

Response: DPR agrees that water is exposed to sunlight upon reaching the surface, and that photodegradation is not relevant for chloropicrin in groundwater. DPR agrees that a table would allow readers to quickly understand available data on reactions in groundwater, if the EAD were to be revised.

Use of tarps decreases the amount of sunlight reaching chloropicrin on soil surface, and may increase half-life.

Response: While little photolysis may occur under opaque tarps, monitoring of air concentrations during soil fumigation suggests that chloropicrin can volatilize and reach air outside the tarps. Exposure estimates and half-lives are based on chloropicrin concentrations measured outside of tarps.

"OEHHA believes that the issue of phosgene production and concurrent exposure to chloropicrin should be evaluated further."

Response: Several key data gaps, including lack of data for phosgene concentrations associated with chloropicrin fumigation, were discussed in the Exposure Appraisal section of the EAD. At the present time DPR lacks data to evaluate potential concurrent exposure to chloropicrin and phosgene. DPR has the authority to require submission of needed data, if pilot studies conducted by DPR suggest that substantial concurrent exposure occurs.

8. Environmental Concentrations

"Has ambient air monitoring been performed in counties where chloropicrin use is high since 2001?"

Response: DPR has conducted community-based air monitoring studies since 2001, including an ongoing air monitoring network in three communities. The three communities are Ripon in San Joaquin County, Salinas in Monterey County, and Shafter in Kern County. Chloropicrin is one of the pesticides monitored in DPR's community-based air monitoring projects. Monterey County is consistently one of the top two counties for chloropicrin use.

"OEHHA recommends that an explanation be added to further explain how and why flux values for different application methods vary between night and day."

Response: DPR agrees that an explanation would be helpful to readers, if the EAD were to be revised.

"OEHHA recommends adding an additional column to include the corrected concentrations after field spike recoveries in Table 13."

Response: DPR agrees that the additional column would be helpful to readers, if the EAD were to be revised.

"OEHHA recommends that further testing of well water samples in California be performed."

Response: Recommending future monitoring activity is outside the scope of this EAD.

9. Exposure Assessment

"Were the data on applications of chloropicrin in Ventura County (Figure 6) used in calculating the seasonal, annual, and lifetime estimates reported in Table 16?"

Response: Yes; as explained in the text between Table 16 and Figure 6, exposure was considered likely during the months in which chloropicrin use was at least 5% of the annual total use.

As soil fumigation bystander exposure estimates are based on two studies, additional data are needed.

Response: Recommending additional studies is outside the scope of this EAD.

Explain why exposure estimates for tarp punchers and tarp removers associated with soil fumigation using 100% chloropicrin and 10.5% chloropicrin are not proportionate to the differences in chloropicrin concentrations in the products.

Response: Estimated 1-hour exposures are proportionate to maximum application rates. The maximum application rate for broadcast shank application of any 100% chloropicrin product is 350 lbs chloropicrin/acre, and the maximum rate allowed for tarped surface drip is 300 lbs chloropicrin/acre. The corresponding maximum rates for Methyl Bromide 89.5%, which contains 10.5% chloropicrin, are equivalent to 46.7 lbs chloropicrin/acre and 26.4 lbs chloropicrin/acre for broadcast shank and surface tarp drip, respectively. The ratios in application rates are similar to the ratios in exposures, with some rounding error (350/46.7 = 7.49 and 300/26.4 = 11.4).

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