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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 $BMCL_{05}$= 44
4.4	4.4	DPR	10		
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 and adults, respectively, for 8-hour exposures. To these values DPR applied a UF of 100 to account for interspecies and intraspecies variation in sensitivity, resulting in RfCs of 2.7 ppb and 5.8 ppb, respectively. As these values exceed OEHHA's recommended 1-hour RfC of 1.5 ppb derived from the Cain (2004) study, OEHHA recommends the use of the 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)*		*Agency*	*Endpoint*	*Effect Level (ppb)*	*Basis/UF*
	Child	*Adult*				
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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