

Chloropicrin Mitigation Proposal

Control of Resident and Bystander Acute Exposure
From Soil Fumigation Applications

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Background

The Department of Pesticide Regulation (DPR) is proposing mitigation measures designed to protect bystanders (persons near an application site but not directly involved with the application) and residents from off-site exposure to chloropicrin. The purpose of this document is to obtain input from stakeholders who may be impacted by these mitigation measures, including growers and licensed applicators who use chloropicrin, and people who live or work near field fumigations. DPR also welcomes alternative ideas that are not included in this document. After reviewing and considering all comments and suggestions, DPR will prepare a final document for use in the mitigation of off-site exposures.

Chloropicrin is widely used as a field fumigant injected into the soil or applied through drip irrigation. The treated field is generally covered with a tarp at or before application. For broadcast applications, the tarp is removed several days later after the fumigant has dissipated. For drip and bedded applications, the tarp is left on the field during the entire growing season. Holes are punched in the tarp for planting after the fumigant has dissipated. Chloropicrin is used either alone or in combination with other fumigants. In addition to its fumigant pesticidal properties, chloropicrin is also added (about two percent by weight) as a warning agent to odorless products that contain methyl bromide, and as a warning agent to structures just prior to the application of sulfuryl fluoride. This mitigation proposal does not address chloropicrin use as a warning agent either in soil fumigants or in structural fumigations.

Following field fumigations, chloropicrin rapidly diffuses through the soil in all directions, then dissipates quickly, with half-lives ranging from approximately an hour to several days. Dissipation is faster at higher temperatures, and slower in oxygen-depleted conditions. Volatilization is the major pathway through which chloropicrin dissipates from soil, although tarps can significantly reduce volatilization. In water, chloropicrin can persist for several days in the absence of light, but it degrades rapidly when subjected to light of suitable wavelengths, with half-lives ranging from 6 hours to 3 days. In air, chloropicrin is reactive, primarily undergoing photolytic reactions. Laboratory photolysis studies suggest that chloropicrin degrades rapidly in sunlight, with an estimated half-life in the range of 3 – 18 hours under constant illumination, and results in photo-degradation products including phosgene and ozone.

DPR completed a Risk Characterization Document (RCD) for chloropicrin as a toxic air contaminant (TAC) in February 2010. Focusing on residents and bystander exposure, the RCD assessed the health risk of chloropicrin based on evaluations of toxicology studies, and exposure estimates from air monitoring, computer modeling, and other data. In December 2010, DPR issued a Risk Management Directive directing staff to develop use restrictions. After chloropicrin was designated as a TAC effective January 8, 2011, DPR staff initiated development of use restrictions following the TAC procedures specified in state law.

Currently, chloropicrin is subject to several sets of regulatory requirements to control exposures and other potential hazards. As with all pesticides, people who apply chloropicrin must comply with all requirements on product labels. In addition, chloropicrin is classified as a Restricted Use Pesticide under federal law, and designated a restricted material under state law. As such, applications must be supervised by a certified applicator and a restricted materials permit must

be obtained from the county agricultural commissioner (CAC) prior to purchase and use. For each restricted material, CACs are required to evaluate the proposed application of the restricted material and surrounding sensitive sites and determine if a substantial adverse health or environmental impact will result from its use. Based on the evaluation, the CAC can issue the permit, condition the permit to require site-specific use practices to mitigate potential adverse effects, or deny the permit. CACs have implemented additional conditions for chloropicrin permits, but the conditions vary from county to county due to local conditions. Applicators must follow all requirements on product labeling, state law and regulations, and permit conditions. Where there are differences between federal, state, or county requirements, the most restrictive requirement must be followed.

Scientific and Regulatory Basis

United States Environmental Protection Agency (U.S. EPA) Reregistration Eligibility Decision

In July 2008, U.S. EPA published the document, “Reregistration Eligibility Decision (RED) for Chloropicrin, opening a public comment period on the implementation aspects of the risk mitigation measures they were requiring as conditions of reregistration.

After reviewing the comments and new data, U.S. EPA determined that the main risk of concern for handlers, workers, and bystanders associated with the soil uses of chloropicrin is from acute inhalation exposure as a result of volatilization of the fumigant. In May 2009, after consulting with stakeholders and obtaining extensive public input, U.S. EPA issued an [Amended RED](#) for the soil fumigant pesticides, including chloropicrin. The Amended RED incorporated final new safety measures to increase protections for agricultural workers and bystanders. These measures establish a baseline for safe use of the soil fumigants throughout the United States, reducing fumigant exposures and significantly improving safety. Measures added to labels in the first phase, Phase 1 of implementation, included Fumigant Management Plans, good agricultural practice requirements, and new worker protection measures among other things. Phase 1 labels took effect in January 2011.

As of December 1, 2012, a final set of soil fumigant product label changes went into effect, implementing new protections primarily for bystanders and residents. The amended product labels incorporate the second and final phase of mitigation measures required by the EPA’s 2009 RED for the soil fumigants, including chloropicrin. The new measures appearing on soil fumigant Phase 2 labels include buffer zones and posting, emergency preparedness and response measures, training for certified applicators supervising applications, Fumigant Management Plans, and notice to State Lead Agencies who wish to be informed of applications in their states. A summary of these requirements are described in Appendix 1.

DPR Determinations

In determining the appropriate target level for mitigation purposes, DPR reviewed the RCD, U. S. EPA’s risk assessment and RED, chloropicrin pesticide use reports, and illnesses related to chloropicrin use. DPR also evaluated the human studies conducted by Cain in 2004.

Chloropicrin can cause eye, nose, throat, and upper respiratory irritation. Results from a chloropicrin human sensory irritation study (Cain, 2004) indicate that eye irritation is the most sensitive effect. Most of the study participants detected chloropicrin within 20-30 minutes at 150 parts per billion (ppb). Twenty percent of the individuals reported some eye discomfort at 100 ppb, and 40 percent of the individuals reported increasing discomfort at 150 ppb. U.S. EPA selected a reversible acute endpoint from this human study, and determined a bench mark concentration level of 73 ppb. At this level U.S. EPA does not expect eye or nose irritation, or upper respiratory changes. The studies concluded that the acute effects of chloropicrin seen at the 100 ppb level are mild and reversible, and that acute effects of eye irritation are not expected at 73 ppb. DPR agrees with U.S. EPA that the primary effect observed with acute exposure to chloropicrin is sensory irritation, and has determined that the appropriate regulatory target level to restrict acute exposure to chloropicrin is 73 ppb averaged over an eight-hour period. This target level is below the National Institute of Occupational Safety and Health's reference exposure level of 100 ppb averaged over an eight hour period.

In December 2010, DPR issued a RMD (Appendix 2), directing staff to develop use restrictions on pesticide products containing the active ingredient chloropicrin to mitigate unacceptable acute exposures to residents and bystanders. Although acute effects of eye irritation are to be expected, reversible, and necessary when used at the levels of a warning agent, protection of residents and bystanders against those effects could be attained when chloropicrin is used as an active ingredient in soil fumigations. In April 2013, DPR provided further explanation of the conclusion that the carcinogenic potential of chloropicrin is equivocal (Appendix 3).

Scope of DPR Mitigation Strategy

The mitigation measures discussed in this document are designed to protect bystanders and residents from off-site exposures to chloropicrin, both as the sole active ingredient and when used in conjunction with methyl bromide or 1,3-D as an active ingredient in soil fumigations. This mitigation proposal does not address chloropicrin use as a warning agent either in soil fumigants or in structural fumigations. As stated in the December 31, 2010 Risk Management Directive, the target level for this mitigation effort is 73 ppb averaged over an eight-hour period.

Proposed Mitigation Measures

This draft mitigation proposal document was developed using U.S. EPA label changes (Appendix 1) as the foundation for mitigating off-site exposures. The new U.S. EPA safety measures went into effect after DPR completed its RCD and therefore were not considered when estimating bystander's exposure to chloropicrin. In addition to U.S. EPA's action, DPR is generally proposing the following: longer buffer zones, extended time period between applications with overlapping buffer zones, and eliminating some buffer zone credits based on a more protective approach for estimating flux (off-site air concentrations) for different application methods. DPR also considered applicable California regulations, application methods, use patterns, CAC permit conditions, and incident cases to justify the additional restrictions, such as reduced maximum acreage treated within a 24-hour period. DPR evaluated additional data on totally impermeable film or TIF tarps that U.S. EPA did not include in its evaluation during their

mitigation development. These data showed significant reductions in flux during and after applications, resulting in the justification for smaller buffer zones. DPR met with Office of Environmental Health Hazard Assessment, the California Department of Food and Agriculture, the Air Resources Board, the Air Pollution Control Districts, and the County Agricultural Commissioners (CAC), worker advocate groups and registrants to discuss early mitigation concepts. DPR is proposing the following additional restrictions beyond labeling and regulation to protect residents and bystanders.

1. **Buffer zone distances:** The methods used to determine buffer zone distances and related requirements are described in detail in DPR's buffer zone development document (Appendix 4: memorandum from Terrell Barry to Randy Segawa, dated March 26, 2013), and summarized here. As with other fumigants, DPR used air monitoring data and computer modeling to determine the buffer zones. Data from air monitoring of specific application sites was used to estimate chloropicrin emissions (flux) during and following fumigations. The flux values were input into a computer model to estimate air concentrations under a variety of conditions. Buffer zones were determined by calculating the distance from the fumigated area to the 73 ppb target concentration for different combinations of application rates, acreage, and weather conditions.

Tables 1 and 2 show the proposed buffer zone distances, based on the type of tarp used for the application:

- Tarps assigned a 60% buffer credit by current labels (also known as totally impermeable film or TIF tarp): All buffer zone distances (all percentiles, all application rates, and all acreages) are the proposed minimum distance of 25 feet
- Tarps assigned a buffer credit of less than 60% by current labels (referred to in this document as non-TIF tarp) (Table 1).
- Untarped (Table 2).

DPR proposes to assign all fumigation methods allowed by labeling to one of these groups for buffer zone purposes, except tree hole, greenhouse, and some other specialty fumigations. Buffer zone development was based on chloropicrin application studies that were used to estimate flux profiles of the three application method types (15 tarp with no buffer credit, 9 tarp with 60% buffer credit, and 4 untarped). With the available data, DPR could not identify statistically significant differences in flux for other application parameters, such as bed vs. broadcast application. There was also insufficient data to determine if the fluxes for applications using tarps assigned 20% or 40% buffer credit were significantly different from other tarps. U.S. EPA used different methods to estimate flux and specified additional application methods for the label buffer zones.

Five years of weather data from Ventura was used to determine buffer zone distances for each of the three application method types (untarped, non-TIF tarp, and TIF tarp). For an application with particular combination of acreage and application rate the buffer zone distance actually needed will vary depending on weather conditions. Shorter buffer zones are required to mitigate off-site air concentrations when weather conditions are breezy or there is a high degree of vertical mixing of air such as during warm summer days. DPR used the

computer model to estimate the maximum downwind distance at which 73 ppb occurred for several thousand hypothetical applications, accounting for a wide range of weather conditions and flux. The model showed that the buffer zone distance (distance to 73 ppb) varied greatly. For example, DPR made approximately 27,000 estimates of the buffer zone distance for a non-TIF application to a 40-acre field at 350 pounds per acre. The maximum downwind distance to 73 ppb (buffer zone) for this scenario ranged from 0 to 4,700+ feet, with 50% of the hypothetical applications having a distance of less than 240 feet, and 95% of the applications having a distance of less than 2,842 feet. Appendix 2 shows proposed buffer zone distances at a range of percentiles of protection. The percentiles represent the level of protection, based on the frequency or probability of exceeding the 73 ppb target concentration beyond the perimeter of the buffer zone. For example, the 95th percentile would result in the maximum air concentration beyond the perimeter of the buffer zone being no greater than the 73 ppb target concentration on average for 95 percent of all applications.

Once DPR selects the modeled percentile of protection, the proposed buffer zone distances will vary with three factors: application method (untarped, non-TIF tarp, TIF tarp), application rate, and number of acres fumigated. (Buffer zone credits are addressed in the next issue.) The application rate is adjusted if only portions of a field are fumigated. Usually an entire field is fumigated prior to planting (flat or broadcast fumigation). In some cases, such as certain orchards, only the planting rows are fumigated (strip fumigation). Similarly, sometimes a field is fumigated after forming the planting beds, and only the bedded portions of the field are fumigated (bed fumigation). For strip, bed, and drip fumigations, the application rate is adjusted to account for the fumigated and unfumigated areas. For example, a flat field of 40 acres could be entirely fumigated at a broadcast rate of 150 pounds per acre, resulting in a total amount of $40 \times 150 = 6,000$ pounds of chloropicrin applied. The same 40 acre field could be fumigated after forming beds. If the bed width is 32 inches, and the row spacing is 48 inches, the beds comprise $32 \div 48 = 67$ percent of the 40-acre field. An application rate of 150 pounds per acre to the beds is a “broadcast-equivalent” rate of $150 \times 0.67 = 100$ pounds per acre, resulting in a total amount of $100 \times 40 = 4,000$ pounds of chloropicrin applied. A comparison of the buffer zone distances for this example is shown in the tables below.

Example: Comparison of Buffer Zone Distances for Untarped Fumigation Methods⁴

DPR protection level: 95th percentile

Field area (application block): 40 acres

Application rate for treated area: 150 pounds per acre

Bed area: 67% of field area (32 inch bed width, 48 inch row spacing)

Application Method	Treated Area App Rate (lbs/ac)	Broadcast-Equivalent App Rate (lbs/ac)*	DPR Buffer Distance (ft)	Label Buffer Distance (ft)
Untarped-Broadcast	150	150	1402	1038
Untarped-Bed	150	100	755	350
Untarped-Deep (broadcast)	150	150	1402	760
Untarped-Drip	150	100	755	997

*The broadcast-equivalent application rate is used to determine the buffer zone.

Example: Comparison of Buffer Zone Distances for Tarped Fumigation Methods

DPR protection level: 95th percentile

Field area (application block): 40 acres

Application rate for treated area: 150 pounds per acre

Bed area: 67% of field area (32 inch bed width, 48 inch row spacing)

Application Method	Treated Area App Rate (lbs/ac)	Broadcast-Equivalent App Rate (lbs/ac)*	DPR Buffer Distance (ft)	Label Buffer Distance (ft)
Non-TIF Tarp-Broadcast	150	150	941	179
Non-TIF Tarp-Bed	150	100	412	25
Non-TIF Tarp-Strip	150	100	412	136
Non-TIF Tarp-Drip	150	100	412	40
TIF Tarp-Broadcast	150	150	25**	25
TIF Tarp-Bed	150	100	25**	25
TIF Tarp-Strip	150	100	25**	54
TIF Tarp-Drip	150	100	25**	25

*The broadcast-equivalent application rate is used to determine the buffer zone.

**All DPR buffer zones for applications with TIF tarps are the proposed minimum distance.

The 95th percentile is the highest level of protection proposed by DPR, so the distances listed above are the largest proposed buffers for these scenarios. In two circumstances at the 95th percentile, the label buffer zones are larger and more stringent than DPR’s proposed buffer zones: for untarped-drip applications and applications using TIF tarps. Other label buffer

zones may be larger than DPR's proposed buffers depending on the percentile of protection selected.

DPR is considering a range from the 80th to the 95th modeled percentile of protection for determining buffer zones. DPR is reviewing various factors that assist in determining the need for appropriate buffer zones to protect bystanders and residents. These factors include the distances of proposed buffer zones, current use practices and existing buffer zones, the number of applications where no reported incidents occurred, and the number of reported incidents. According to the data from DPR's Pesticide Use Reports from 2008-2011, a total of 10,284 applications of chloropicrin as an active ingredient were made during the 4-year period. A total of approximately 23.6 M pounds of active ingredient were applied to 210,800 acres. DPR's Pesticide Illness Surveillance Program data indicate that 13 episodes occurred during the same time period. The illness symptoms for those episodes were consistent with the acute effects of eye and nasal irritation. This represents 0.13% of episodes relative to the number of applications of chloropicrin in the 4-year period. Additionally, investigations revealed that the air concentrations in the majority of these illness events were related to a rare combination of conditions. To address these rare conditions, DPR believes additional mitigation measures can be implemented by County Agricultural Commissioners through restricted material permits to address local conditions at chloropicrin fumigation sites. This information will be considered when choosing from the range of 80th to 95th modeled percentile level of protection.

2. **Buffer zone credits:** DPR's initial evaluation of the buffer zone credits specified by labels indicates the following:

- Tarps with 60% credit: data supports greater credit (see table above)
- Tarps with 40% credit: insufficient data to support a buffer credit
- Tarps with 20% credit: insufficient data to support a buffer credit
- "Symmetry" application rig credit: insufficient data to support a buffer credit
- Potassium thiosulfate credit: insufficient data to support a buffer credit
- Water treatment credit: additional DPR evaluation in progress
- Organic content credit: additional DPR evaluation in progress
- Soil temperature credit: additional DPR evaluation in progress
- Clay content credit: additional DPR evaluation in progress

As discussed in DPR's buffer zone development document (Appendix4) there is an insufficient number of field studies to statistically evaluate the difference in flux for the 40% credit tarp, as well as the 20% credit tarp, "Symmetry" application rig, and potassium thiosulfate amendment. However, DPR is conducting additional research to evaluate the effectiveness and assessing enforceability of the other credits, including the credits for water treatment, organic content, soil temperature, and clay content.

3. **Minimum buffer zones:** For field fumigations of chloropicrin-only and in combination with 1,3-D, the proposed minimum buffer zone is proposed in the range of 60 to 100 feet when non-TIF tarps or no tarps are used. When TIF tarps are used, the minimum buffer zone is 25

feet. For fumigations of chloropicrin in combination with methyl bromide, the minimum methyl bromide buffer zones apply as required in regulation.

4. **Additional DPR restrictions for emergency preparedness and response measures:**

Conditions which trigger emergency preparedness are identified on the product labeling. The certified applicator can choose to either conduct fumigant site monitoring, or to provide response information for neighbors. In addition to what is required by the labeling, DPR has proposed the following additional restrictions for these options.

- **“Response information for neighbors” option:** Response information must be provided in both English and Spanish.
- **“Fumigant site monitoring” option:** In addition to the requirements specified on the labeling, DPR proposes to limit sensory irritation monitoring to persons with full olfactory capabilities (e.g. not impaired by allergies or colds). Monitoring must be done at the outer edge of the buffer zone. At the start of each monitoring period, wind direction must be determined and recorded on the Post-Application Summary. Monitoring must be done in the direction of bystanders, residences and businesses, and in the direction that the wind is blowing (if this is a different direction from the residences and businesses and potential areas where bystanders may be present). Calm days would require monitoring in all directions.

5. **Notice of intent requirements:** The operator of the property to be treated must submit a notice of intent (NOI) to the CAC at least 48 hours before the fumigation begins. Besides including the date of application, the NOI must also include the time the fumigation is scheduled to begin. The fumigation cannot begin sooner than the time listed on the NOI, and must begin within 12 hours of the scheduled time. If fumigation does not begin within the 12 hour window, a new NOI must be submitted. The CAC can determine if another 48 hour waiting period is needed.

6. **Maximum acreage and field separation:**

- The maximum acres to be treated at one location (a single application block) within a 24 hour period must not exceed 40 acres.
- The combined acreage for two or more application blocks with overlapping chloropicrin buffer zones must also not exceed 40 acres.
- Labels prohibit overlapping buffer zones unless a minimum of 12 hours elapses from the time the first application block is complete until the start of a second application block.
- DPR proposes that if at least 12 hours, but less than 36 hours elapse from the time the first application block is complete until the start of the last application block (total of all blocks must not exceed 40 acres), the buffer zones must be recalculated based on the combined acreage of the chloropicrin application blocks with overlapping buffer zones.
- Exception: if all applications with overlapping buffer zones use TIF tarps, the acreage does not need to be combined to calculate the buffer zones, but the combined acreage cannot exceed 40 acres.
- NOTE: Labels require a buffer zone from the start of application until 48 hours after the application is complete. Buffer zones could overlap between 36 and 48 hours after

application and the buffer zones would be calculated based on the individual block size (acreage not combined) and the combined acreage could exceed 40 acres.

7. **Tarp cutting**: Any application using tarps that qualify for a reduction in buffer zone distance must wait a minimum of 9 days after application before tarp cutting is initiated. All tarps (whether they qualify for a buffer reduction credit or not) cannot be removed sooner than 24 hours after tarp cutting or perforation.

8. **Tree hole fumigations**: DPR proposes additional restrictions for tree hole fumigations, restricting the number of injection sites per acre, and determining a maximum number of sites that can be treated per day. The table below shows the estimated maximum number of tree holes that can be fumigated in one acre, with a buffer zone of 25 feet, at different protection level probabilities:

Protection Level	Max Tree Holes
80%	230
85%	220
90%	190
95%	160

Table 1 – DPR Proposed buffer zone distances (feet) for applications using non-TIF tarps

80th percentile

App Rate (lb/ac)	App Size (AC)				
	5	10	20	30	40
100	0	16	16	16	16
150	16	16	16	39	93
200	16	28	152	227	291
250	41	156	289	394	489
300	128	251	425	576	693
350	198	342	557	733	893

85th percentile

App Rate (lb/ac)	App Size (AC)				
	5	10	20	30	40
100	0	16	16	16	16
150	16	16	79	156	216
200	16	119	266	370	468
250	118	254	441	598	738
300	212	373	621	838	1005
350	293	491	793	1043	1269

90th percentile

App Rate (lb/ac)	App Size (AC)				
	5	10	20	30	40
100	16	16	16	16	96
150	16	104	249	355	446
200	145	271	479	644	794
250	249	430	706	929	1136
300	348	575	924	1220	1471
350	444	716	1139	1490	1808

95th percentile

App Rate (lb/ac)	App Size (AC)				
	5	10	20	30	40
100	16	16	216	322	412
150	171	338	571	765	941
200	352	560	903	1185	1441
250	475	769	1212	1576	1916
300	607	960	1504	1957	2371
350	731	1141	1777	2325	2842

Table 2 – DPR Proposed buffer zone distances (feet) for untarped applications

80th percentile

App Rate (lb/ac)	App Size (AC)					
	1	5	10	20	30	40
100	0	16	16	115	176	228
150	16	103	209	359	482	597
200	16	225	378	616	813	993
250	62	336	544	864	1133	1375
300	117	443	704	1106	1435	1733
350	165	545	860	1339	1727	2084

85th percentile

App Rate (lb/ac)	App Size (AC)					
	1	5	10	20	30	40
100	0	16	61	170	253	322
150	16	145	272	461	615	755
200	16	281	467	756	987	1195
250	88	405	651	1027	1334	1623
300	145	523	825	1295	1682	2048
350	201	637	1004	1562	2031	2478

90th percentile

App Rate (lb/ac)	App Size (AC)					
	1	5	10	20	30	40
100	16	16	134	274	383	481
150	16	214	375	620	825	1010
200	38	368	602	961	1252	1521
250	123	514	814	1275	1651	2005
300	195	645	1013	1588	2052	2515
350	256	773	1207	1888	2468	3025

95th percentile

App Rate (lb/ac)	App Size (AC)					
	1	5	10	20	30	40
100	16	100	258	454	613	755
150	16	323	540	873	1148	1402
200	88	509	819	1291	1690	2066
250	197	687	1084	1686	2188	2683
300	278	848	1321	2059	2686	3290
350	345	1001	1543	2426	3209	3922

Appendix 1

U.S. EPA Mitigation

U.S. EPA developed mitigation measures for products containing the active ingredient chloropicrin. These measures are intended to mitigate unacceptable exposures to workers and residents and bystanders. The measures have been implemented in two phases.

Phase 1 Changes that Went Into Effect December 31, 2010:

- **Restricted Use Pesticide Classification:** U.S. EPA reclassified all of the soil fumigants undergoing reregistration as restricted use pesticides.
- **Agricultural Worker Protection:** Persons engaged in activities that are part of the fumigation process are considered “handlers”, with specific requirements and restrictions in place on the label.
- **Handler Training Information:** U.S. EPA required fumigant registrants to develop training information and materials for fumigant handlers working under the supervision of the certified applicator in charge of fumigation. The certified applicator must provide this information to each handler, or confirm that the handler has received the information within the past 12 months.
- **Handler respiratory protection:** In general, if handlers experience sensory irritation they must either stop work and leave the area or use air-purifying respirators to protect them from unsafe levels. Air monitoring (using a direct read detection device) is required while handlers use respirators to ensure concentrations do not exceed the upper working limit of respirators. All handlers who will wear a respirator must be fit-tested, trained, and medically examined to ensure they do not have health problems that could make use of a respirator dangerous. An air purifying respirator with the appropriate cartridges must be available for each handler who will wear a respirator.
- **Tarp handling:** There are specific time limitations on when tarps can be perforated and removed, with a minimum of 5 days from completion of the application to protect workers from unsafe levels (if a weather condition exists that necessitates early removal, persons removing the tarp must wear the PPE required for handlers on that label).
- **Entry-restricted period (ERP):** The ERP is similar to the restricted entry interval (REI), but is intended to restrict inhalation exposure, whereas the REI is intended to restrict dermal exposure. Entry into treated fields (including early entry that would otherwise be permitted under the WPS) by any person other than a trained and equipped handler is prohibited from the start of the application until the ERP has expired.
- **Good Agricultural Practices:** Many good agricultural practices recommended on older fumigant labels became mandatory on the new labels, such as proper soil preparation/tilling and soil moisture and temperature restrictions. These practices reduce off-site movement of the fumigant.
- **Application Method and Rate Restrictions:** Labels restricted certain fumigant application methods that lead to risks that are difficult to address, such as untarped applications for some fumigants. The labels also lowered the maximum application rates to reduce exposures to handlers and bystanders.

- **Site-Specific Fumigant Management Plans:** Labels required fumigant users to prepare a written, site-specific fumigant management plan (FMP) before fumigations begin. Only Phase 1 requirements are addressed. A post-fumigation application summary (PAS) is required within 30 days of completing the application. The certified applicator supervising the application must complete the PAS, which describes any deviations from the FMP that have occurred, measurements taken to comply with GAPs, monitoring results taken as because of handler sensory irritation, as well as any complaints and/or incidents that have been reported to him/her. Documentation of this information assists CACs in compliance activities and investigating episodes.

Phase 2 Changes that Went into Effect December 1, 2012:

- **Compliance Assistance and Assurance Measures:** In states that require notification of fumigant applications, applicators must notify State and Tribal Lead Agencies for pesticide enforcement about fumigant applications they plan to conduct. In California, applicators are not required to notify DPR. Under California's restricted materials requirements, applicators must notify the agricultural commissioner of the county in which the application occurs.
- **Site-Specific Fumigant Management Plans:** All label requirements must be addressed in the FMP.
- **Soil Fumigant Training for Certified Applicators:** New labels require certified applicators to successfully complete a U.S. EPA- approved training program. U.S. EPA- approved soil fumigant training programs are found at http://www.epa.gov/opp00001/reregistration/soil_fumigants/. In California, commercial applicators who meet state certification and licensing requirements in Sub-Category O meet the label requirement for applicator training and renewal. Private applicators must successfully complete a registrant-developed training program every 36 months. Additional training enhances the certified applicator's knowledge of fumigant requirements.
- **Community Outreach and Education Programs:** U.S. EPA is requiring fumigant registrants to develop and implement outreach programs to ensure that information about fumigants is available within communities where soil fumigation occurs. Outreach programs will address the risk of bystander exposure, buffer zones, how to recognize early signs of fumigant exposure, and how to respond appropriately in case of an incident. These programs are still under development.
- **Information for First Responders:** Fumigant registrants are required to develop information for first responders in high fumigant use areas to help them recognize incidents related to soil fumigant exposure, how to recognize early signs and symptoms of exposure, and how to treat persons who have been exposed. This information was sent directly to a designated emergency response person in each state. In California, this information was sent to the State Fire Marshal's Office <http://osfm.fire.ca.gov/training/pdf/US%20EPA/EmergencyResponderCoverNote.pdf>.
- **Buffer zones:** New labels require fumigant users to establish a buffer zone around treated fields to reduce risks from acute inhalation exposure to bystanders. The buffer zone extends outward from the edge of the fumigated area (application block) equally in all directions. All non-handlers, including field workers, residents, pedestrians, and other

bystanders, must be excluded from the buffer zone during the buffer zone period except for transit. The buffer zone period begins at the start of the application and lasts for a minimum of 48 hours after the application is complete. Buffer zone distances are included as tables on product labels. Buffer zone distances vary depending on application rate, number of acres fumigated, and the fumigation method. Labels also specify “credits” that reduce buffer distances, in order to encourage users to employ practices that reduce emissions, such as high-barrier tarps or post-application water seals. Some credits are available for site conditions that may reduce emissions (e.g., high organic or clay content of soils). Credits can be added, but cannot total more than an 80% reduction. The minimum buffer zone distance is 25 feet, and the maximum distance is 2,640 feet (1/2 mile).

- **Posting requirements:** New labels require buffer zones to be posted at usual points of entry and along likely routes of approach to the buffer unless a physical barrier prevents access to the buffer. The signs must include a “do not walk” symbol, fumigant product name, and contact information for the certified applicator in charge of the fumigation. Posting of buffer zones notifies workers to stay out of a hazardous area.
- **Emergency Preparedness and Response Requirements:** To reduce risks to people who live or work near a fumigated field, fumigant labels require the certified applicator to perform emergency preparedness and response measures. These measures are required when the buffer zone is greater than 25 feet, and residents or businesses are within certain distances from the outer edge of the buffer zone:

If the buffer zone is:	AND there are residences and businesses within:
>25 feet but ≤100 feet	50 feet from the edge of the buffer zone
>100 feet but ≤200 feet	100 feet from the edge of the buffer zone
>200 feet but ≤300 feet	200 feet from the edge of the buffer zone
>300 feet	300 feet from the edge of the buffer zone or the buffer zones overlap

When one of the conditions listed above are met, the certified applicator can choose to **either** conduct fumigant site monitoring, or to provide information for neighbors. Requirements of each option are included on the labels, and are summarized below:

Response information for neighbors – If the certified applicator chooses to provide response information, the label requires that he must ensure that the required information be provided to residences and businesses that triggered the response at least 1 week before the application begins. The information may include application dates that are within 4 weeks of the date that the notice is delivered to the residences or businesses. If the application does not occur during the specified timeframe, the information must be delivered again. The information can be delivered as a mailing, door hanger, or other methods that will inform the residences and businesses. The provided information must include:

- Location of the application block
- Fumigant(s) applied, including the active ingredient, name of the fumigant product(s), and the EPA registration number
- Contact information for the applicator and property owner
- Time period when the application is planned to take place
- Early signs and symptoms of exposure to the fumigant(s) applied, what to do, and who to call if they believe they are being exposed (911 in most cases)
- How to find additional information about fumigants.

Fumigant site monitoring – If the certified applicator chooses to conduct fumigant site monitoring, he or the handler(s) under his supervision is required to:

- Monitor for sensory irritation in areas between the buffer zone outer perimeter and residences and businesses that trigger this requirement; and
- Monitor for sensory irritation, beginning the evening on the day of application and continuing until the buffer zone period expires. The monitoring must be done a minimum of 8 times during the buffer zone period, including:
 - 1 hour before sunset
 - During the night
 - 1 hour after sunrise, and
 - During daylight hours.

If the handler conducting the monitoring experiences sensory irritation, the emergency response plan must be implemented immediately.

- **Restrictions for difficult to evacuate sites:** Difficult to evacuate sites are listed on labels as pre-K to grade 12 schools, state licensed daycare centers, nursing homes, assisted living facilities, hospitals, in-patient clinics, and prisons. Applications are restricted within specified distances of these sites.
 - No fumigant application with a buffer zone greater than 300 feet is permitted within ¼ mile of difficult to evacuate sites unless the site is not occupied by children from state-licensed day care centers, students (pre-K to grade 12), patients, or prisoners during the application and the 36 hour period following the end of the application
 - No fumigant application with a buffer zone of 300 feet or less is permitted within 1/8 mile of difficult to evacuate sites unless the site is not occupied by children from state-licensed day care centers, students (pre-K to grade 12), patients, or prisoners during the application and the 36 hour period following the end of the application.
- **Emergency response plan requirements:** The certified applicator must include a written emergency response plan in the FMP that identifies:
 - Evacuation routes
 - Locations of telephones
 - Contact information for first responders and local/state/federal/tribal personnel, and
 - Emergency procedures/responsibilities (e.g. adding water to the field, repairing tarps, fixing equipment, evacuating upwind) if:

- There is an incident
- sensory irritation is experienced outside of the buffer zone
- there are equipment/tarp/seal failures or complaints, or other emergencies.



Mary-Ann Warmerdam
Director

Arnold Schwarzenegger
Governor

Appendix 2

Risk Management Directive Documents

December 31, 2010

TO: Interested Parties

SUBJECT: RISK MANAGEMENT DIRECTIVE

This letter outlines the Department of Pesticide Regulation's (DPR's) risk management decision related to the development of use restrictions on pesticides containing the active ingredient chloropicrin as it relates to exposures to residents and bystanders. This risk management decision was made after consultation with the Office of Environmental Health Hazard Assessment, the Air Resources Board, and the California Air Pollution Control Officers Association, as required by Food and Agricultural Code section 14023(e). A subsequent risk management directive will be developed to address occupational exposures after completion of the comprehensive risk characterization document (RCD).

Chloropicrin has been used as an agricultural pre-plant soil fumigant for decades, either alone or in combination with other fumigants. DPR placed chloropicrin into reevaluation in 2001 on the basis of air monitoring data received from the Chloropicrin Manufacturers Task Force. The data indicated that air concentrations at some distances from treated greenhouses exceeded the National Institute of Occupational Safety and Health's reference exposure levels of 0.1 parts per million (ppm). In addition to its fumigant pesticidal properties, chloropicrin is also added (about 2 percent by weight) as a warning agent to odorless products that contain methyl bromide and methyl iodide. Chloropicrin is also added as a warning agent to structures just prior to the application of sulfuryl fluoride. Using the information from the reevaluation and other data, DPR completed an RCD for chloropicrin as a toxic air contaminant (TAC) in February 2010. Based on the RCD and the recommendation of the TAC Scientific Review Panel, DPR will designate chloropicrin as a TAC effective January 8, 2011.

In 2006, the U.S. Environmental Protection Agency (U.S. EPA) finalized its risk assessment of chloropicrin. Following that, U.S. EPA published its Reregistration Eligibility Decision (RED) for chloropicrin in July 2008. The RED specified certain required mitigation measures and identified data gaps that chloropicrin registrants must address to be eligible for reregistration. U.S. EPA is currently using a two-year, phased-in approach to ensure the required mitigation



measures are incorporated in the labels beginning in 2011. DPR is collaborating with U.S. EPA on this endeavor.

Acute Effects: Methodology and Target Levels

After evaluating information available (including DPR's RCD), U.S. EPA's risk assessment and RED, chloropicrin pesticide use reports, and pesticide illness reports, U.S. EPA-approved labels, and California county permit conditions for counties with high uses of chloropicrin, DPR will develop mitigation measures for agricultural soil fumigation applications that will address the acute effects of chloropicrin for residents and bystanders. Although acute effects of eye irritation are to be expected, reversible, and necessary when used at the levels of a warning agent, protection of residents and bystanders against those effects could be attained.

DPR has determined that the appropriate regulatory target level to restrict acute exposure to chloropicrin is 73 parts per billion (ppb) or 0.073 ppm averaged over an eight-hour period. This level is based on the evaluation of human studies by Cain in 2004, literature review, U.S. EPA's risk assessment, and DPR's RCD. Based on the human study by Cain, acute effects of eye irritation will not be expected at 73 ppb. According to the same study, 20 percent of the individuals reported some eye discomfort at 100 ppb, and 40 percent of the individuals reported increasing discomfort at 150 ppb. Since the level of discomfort was reported subjectively by individual scoring instead of direct clinical observation, it is difficult to ascertain the dose levels at which the individuals experienced those effects. Additionally, a published study by Prentiss in 1973 noted that lacrimation or tearing was observed at 300 ppb, although no data supporting that statement was presented. Therefore, DPR will develop mitigation measures to restrict chloropicrin exposures to a regulatory target level of 73 ppb or 0.073 ppm averaged over an eight-hour period. This target level is also below the National Institute of Occupational Safety and Health's reference exposure level of 100 ppb. Additionally, since no nasal or throat irritation was reported at the 100 ppb up to the 150 ppb level in the study, protection of the eye irritation effect most likely protects against upper respiratory effects. DPR will use analytical modeling tools to develop mitigation measures using an eight-hour exposure. In order to minimize the likelihood of short-term peak concentrations, DPR will consider other information and tools when developing restrictions.

Since mild ocular effects were first experienced at the 100 ppb level in the study, eye irritation is deemed as a more sensitive endpoint than nasal effects. This is the conclusion reached in DPR's RCD. The RCD also notes an endpoint of increased nitric oxide in expired air at a reference concentration of 4.4 ppb. Increased nitric oxide in expired air is a precursor to the nasal effects of chloropicrin. Although this level is much lower than the regulatory target level, it was reached based on statistical calculations instead of considering both the toxicologically sensitive endpoint and statistical considerations.

According to the study, the acute effects of chloropicrin seen at the 100 ppb level are mild and reversible. Those effects are also consistent with the lowest level (level 1) of exposures identified by the acute exposure guidelines developed by the National Research Council for airborne concentrations of substances. Because of the permeability of chloropicrin's vapors and the accessibility of ocular nerve endings, and eye effects resulting from those exposures, individuals may experience discomfort, irritation, or certain asymptomatic nonsensory effects, but they are also transient and reversible. These effects are consistent with the acute exposure guidelines level 1, although the small number of subjects inherently limits the human study and the group may not adequately represent the most sensitive individuals. However, not even these effects are expected to occur at the regulatory target level.

Seasonal and Chronic Effects

Since the chemical effects of chloropicrin make it very permeable to the mucous membranes, especially the ocular membranes, its ocular effects are much more of a concern in mitigation development than its nasal effects. According to DPR's RCD, submitted studies, reviewed literature, and other studies, eye irritation is the most sensitive endpoint for chloropicrin. This was also evident in the human exposure studies by Cain. Therefore, in developing mitigation measures, we believe that addressing the ocular effects during acute exposures will address the seasonal and chronic effects from inhalation exposures to chloropicrin.

Lifetime Exposure Effects

Carcinogenicity was discussed in DPR's RCD as one of the possible outcomes for lifetime exposures to chloropicrin. DPR scientists concluded this endpoint based on a weight-of-evidence approach using animal data that showed some tumor formation only in female mice and inconsistent in-vitro and in-vivo genotoxicity tests. From that determination, cancer potency factors were calculated from statistical tests based on a small set of animal data using multiple uncertainty factors to extrapolate to human exposures. Although instinctively conservative and health protective, the confidence in this approach is ambivalent. Additionally, U.S. EPA does not classify chloropicrin as a carcinogen, and a review of data presented by the National Toxicology Program also concludes that the results of the animal studies are inconclusive. After evaluating all available information on the carcinogenic potential of chloropicrin and the differing scientific opinions on this subject, the issue appears to be equivocal at this time.

Conclusion

Since DPR's comprehensive RCD, which includes occupational exposure scenarios, is undergoing internal review and has not been completed, DPR will determine which occupational exposures require risk mitigation through another risk management directive after completion of the comprehensive RCD. In the meantime, DPR will develop mitigation measures in consultation with the Air Resources Board, the air pollution districts, and the county agricultural commissioners, as required by Food and Agricultural Code section 14024(a) to protect public health concerns for residents and bystanders.

Interested Parties
December 31, 2010
Page 4

If you have any questions, please contact Dr. Marylou Verder-Carlos, DPR Assistant Director, at 916-445-3984 or mverdercarlos@cdpr.ca.gov.

Sincerely,

A handwritten signature in black ink, appearing to read "Chris Reardon". The signature is fluid and cursive, with the first name "Chris" being more prominent than the last name "Reardon".

Chris Reardon
Chief Deputy Director
916-445-4000

cc: Dr. Marylou Verder-Carlos



Brian R. Leahy
Director

MEMORANDUM APPENDIX 3

Edmund G. Brown Jr.
Governor

TO: Christopher Reardon
Chief Deputy Director

Original Signed by:

FROM: Marylou Verder-Carlos, D.V.M., M.P.V.M.
Assistant Director
916-445-3984

DATE: April 23, 2013

SUBJECT: THE RISK MANAGEMENT DIRECTIVE (RMD): RECONSIDERATION OF
THE CARCINOGENICITY OF CHLOROPICRIN

Summary

In February 2010, Department of Pesticide Regulation (DPR) scientists issued the final version of the “Evaluation of Chloropicrin as a Toxic Air Contaminant, Part B Human Health Assessment” (TACHHA)¹. Based upon peer review recommendations of the Office of Environmental Health Hazard Assessment (OEHHA) and Scientific Review Panel (SRP), this revised final document included an analysis justifying the treatment of chloropicrin as a carcinogen and the quantification of its carcinogenic potency. Subsequently, in July 2010, the U.S. EPA Carcinogen Assessment Review Committee² concluded that chloropicrin is not likely to be carcinogenic to humans.

In light of these developments, and in preparation for the issuance of risk management directive (RMD) for the development of mitigation measures, DPR reviewed the evidence and analysis of the carcinogenic effects of lifetime exposure to chloropicrin. After the review, DPR determined that the conclusion of the TACHHA was not adequately supported and that the evidence on the carcinogenicity of chloropicrin was *equivocal*. In the comprehensive risk characterization document (CRCD)³ finalized in November 2012, the probability of carcinogenicity was stated with caveats and uncertainties. Further support for this conclusion was provided by the analysis of DPR’s biostatistician⁴ who reviewed the data and found that the application of the particular statistical test used to quantify cancer potency in support of the TACHHA’s conclusion may not be appropriate. Additionally, in October 2011, the Carcinogen Identification Committee of the Office of Environmental Health Hazard Assessment (OEHHA) assigned chloropicrin in the lowest priority possible for cancer assessment.

¹ DPR, Evaluation of Chloropicrin as a Toxic Air Contaminant, Part B Human Health Assessment, February 2010

² U.S. EPA, 2010. Chloropicrin: Report of the Cancer Assessment Review Committee. Office of Pesticide Programs, U.S. Environmental Protection Agency. June 30, 2010.

³ DPR, Chloropicrin Risk xCharacterization Document, November 2012.

⁴ [Jessop, H. 2013. Memorandum to Sheryl Beauvais](#): Relevance of the Bieler-Williams poly-3 trend test in the analysis of carcinogenicity of chloropicrin. April 3, 2013.



The purpose of this memorandum is to explain the rationale for the equivocal conclusion and what it means in the context of assessing the need for mitigation.

Background

In 1995 and 1997, DPR reviewed rat and mouse oncogenicity studies and concluded that chloropicrin was not carcinogenic. In 2008, DPR conducted a human health assessment using the same data and submitted the draft “Evaluation of Chloropicrin as a Toxic Air Contaminant, Part B Human Health Assessment” (TACHHA) to OEHHA for peer review to fulfill the requirements for the Toxic Air Contaminant risk assessment process. Once again, DPR did not conclude that chloropicrin was a carcinogen. However, OEHHA’s review stated that DPR should consider the carcinogenicity of chloropicrin based on the positive results of the female mice and apply an additional statistical analysis (poly-3 trend test) to justify the quantification of carcinogenicity. In 2009, the Scientific Review Panel (SRP) endorsed the quantification of carcinogenicity as well.⁵ To obtain concurrence on the TACHHA, DPR scientists revised the document based on OEHHA and SRP’s recommendation and finalized the document in February 2010.

The TACHHA cites certain facts and relies on a statistical analysis of one female mice study as support for the quantitative assessment of carcinogenicity and the calculation of a cancer potency factor for chloropicrin. Below, is a critical review of the significance of the facts cited to support the TACHHA assessment and the statistical method used to analyze the one underlying study. Based on that review, bolstered by assessments done by two other governmental entities subsequent to the finalization of the TACHHA document that reached a contrary conclusion on carcinogenicity, DPR finds that the carcinogenic potential of chloropicrin appears *equivocal*.

Meaning of Equivocal

Multi-disciplined cancer assessment agencies like the International Agency for Research on Cancer (IARC), and the U.S. National Toxicology Program (NTP) have developed a hierarchy of terms they use to describe the strength of the data they review and ultimately base their conclusions about the carcinogenicity of a chemical. IARC stratifies degrees of certainty with terms (categories) like “known” or “probable” or “possible” or “probably not” (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, 2012). NTP uses different terms to categorize interpretative conclusions such as “clear evidence of carcinogenicity”, “some evidence of carcinogenicity”, “equivocal evidence of carcinogenicity”, “no evidence of carcinogenicity” and “inadequate study of carcinogenicity.” In a document published by NTP regarding the carcinogenicity of sodium fluoride, it states “equivocal evidence is a category for

⁵ Scientific Review Panel, 2010. “Findings of the Scientific Panel on the Evaluation of Chloropicrin as a Toxic Air Contaminant as adopted in the panel’s February 24, 2010 meeting.”
http://www.cdpr.ca.gov/docs/emon/pubs/tac/tacpdfs/chloropicrin/letter_0410.pdf.

uncertain findings demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that *may* be chemically related” (National Toxicology Program Technical Report Series, 1990). The term “*equivocal* evidence of carcinogenicity” generally denotes that there is not enough evidence to establish a clear manifestation of a carcinogenic hazard.

Basis for TACHHA’s Conclusion and Counter Points

The TACHHA presented data evaluations to support a conclusion of carcinogenicity based on various *in-vitro* tests (tests performed in an artificial environment, outside the living organism), *in-vivo* tests (tests performed or made to occur within a living organism or natural setting), a 78-week mouse inhalation study and 2-year rat oral and inhalation studies. The following points summarize the information cited in the TACHHA⁶ (page 58) to identify the carcinogenic potential which served as the basis for the quantitative assessment of carcinogenicity of chloropicrin:

1. Chloropicrin is a strong electrophile
2. Chloropicrin tested positive in three in-vitro tests for DNA damage
 - a. SOS chromotest with *E. coli*
 - b. SCGE assay with Chinese hamster ovary (CHO) cells
 - c. Comet assay with TK6 cells
3. Chloropicrin was positive in all 8 reverse mutation assays with *Salmonella*
 - a. In 6 of 8 studies, the positive responses were seen with TA100 strain with activation
4. Two *in-vitro* tests for clastogenicity were positive
 - a. Chromosomal aberrations assay with CHO cells
 - b. Sister chromatid exchange assay with human lymphocytes
5. Female mice exposed to chloropicrin vapors for 78 weeks had an increase in pulmonary adenomas and carcinomas
 - a. Combined incidence was significant by trend analysis ($p < 0.01$) and by pairwise comparison at the high-dose ($p < 0.05$), when adjusted for survival [*by the poly-3 trend test*]
 - b. Incidence of adenomas at the high dose (37%) was clearly outside the historical control range reported by the supplier (0-27%) during a similar time period
 - c. Increase in the multiplicity of these tumors was significant by trend analysis
 - d. There was a slight reduction in time to tumors at the high dose
 - e. Tumor incidence might have been higher if:
 - 1) Study duration were 104 weeks rather than 78 weeks
 - 2) Dose levels were higher
 - 3) Body weights and caloric intake were not reduced

⁶ DPR, Op. cit.

6. Female rats administered chloropicrin daily for 2 years by oral gavage had an increase mammary fibroadenomas
 - a. Increase was significant by trend analysis ($p < 0.05$) and by pair-wise comparison at the high dose ($p < 0.05$)

The following counter each summarized points on the list above:

- 1) Chloropicrin is a strong electrophile (*An electrophile is defined as a chemical electron deficient atom which can readily react with nucleophilic areas in the DNA or RNA. These reactions can then cause alterations that may lead to carcinogenesis*).
 - *Electrophilic compounds are present intracellularly at all times and their presence does NOT automatically result in genetic mutation or cancer. In fact, electrophilic species from dietary constituents are necessary for normal cell signaling.*⁷
- 2) Chloropicrin tested positive in three in-vitro tests for DNA damage.
 - *Among those three in-vitro tests, one of the assays demonstrated that the level of DNA damage was reported to be higher than that seen with positive controls. However the damage appears to be easily repaired based on the repair kinetics that were analyzed with the assay.*⁸
 - *In an unscheduled DNA synthesis (UDS) assay, chloropicrin was not genotoxic in rat hepatocytes over a concentration range that included moderately toxic levels. Chloropicrin showed no evidence of UDS.*⁹
 - *According to Dr. Errol Zeiger, current consultant for the NTP and former Head of the Mutagenesis Group in the Environmental Mutagenesis and Cancer Branch of the National Institute of Environmental Health Sciences (NIEHS), in-vivo tests are done to determine if genetic effects produced in-vitro can be translated to the in-vivo situation. The two negative in-vivo tests show that the chromosome damaging effects seen in-vitro are not present in-vivo.*¹⁰
 - *None of the in-vivo assays for chloropicrin were positive.*¹¹
- 3) Chloropicrin was positive in all 8 reverse mutation assays with Salmonella.

⁷ Schopfer, F., et al., Formation and Signaling Actions of Electrophilic Lipids. Chem. Rev. 111(10), 5997-6021, October 2011.

⁸ DPR, 2010, page 56, op.cit.

⁹ U.S. EPA, 2010, op. cit.

¹⁰ Zeiger, Errol. Chloropicrin Manufacturers Task Force letter to DPR, November 2009.

¹¹ DPR, 2010, page 57, op. cit.

- *The results for these tests were either not dose-dependent or not reproducible. This was attributed to the inconsistencies in the reported mutagenicity data to compound volatility. However, the overall data indicate that the mutagenicity of chloropicrin in Salmonella appears to be confined to the bacteria since the mammalian cell assays for gene mutations and chromosomal aberrations were clearly negative up to cytotoxicity concentrations.*¹²
- 4) Two in-vitro tests for clastogenicity were positive (*clastogenic is defined as the ability of a chemical to cause breaks in chromosomes, leading to the sections being deleted, added or rearranged. This is a form of mutagenesis and may then lead to carcinogenesis.*)
 - *The positive results from these assays were revisited and found to occur only at concentrations causing severe cytotoxicity. It is likely that the response is not indicative of a clastogenic response.*¹³
 - *Chloropicrin was weakly mutagenic in the Ames and in-vitro chromosome damage tests. These weak responses suggest that factors, other than direct mutagenicity, are responsible for the effects in the in-vitro assays. Since the two in-vivo tests are negative, it is most likely because the doses needed to induce the damage in chromosomes cannot be realized at the target cells in-vivo, even at doses that produce clinical signs of toxicity.*¹⁴
- 5) Female mice exposed to chloropicrin vapors for 78 weeks had an increase in pulmonary adenomas and carcinomas.
 - *There was a slight increase in adenomas of the lung in females by trend analysis but not by Fisher's exact test (Burleigh-Flayer et al, 1995¹⁵) Increase in lung tumors in males was not significant by either trend analysis or Fisher's test.*¹⁶
 - *According to an external pathology peer reviewer of the chloropicrin study, Dr. Robert M. Kovatch, "Neoplastic findings – Incidences of pulmonary adenomas were slightly increased but not significant statistically, in male and female mice of the mid and high exposure groups. Lesions were morphologically similar in control and chloropicrin exposed mice. The slightly elevated indices... were attributed to random variation rather than being test article related."*¹⁷

¹² U.S. EPA, 2010, op. cit.

¹³ Ibid.

¹⁴ Zeiger, op. cit

¹⁵ Chloropicrin: Vapor Inhalation Oncogenicity Study in CD-1 mice". BRRC Project 92-N1105, H.D. Burleigh Flayer, W.J. Kintigh and C.L. Benson, Bushy Run Research Center, Export, PA. April 25, 1995. Unpublished.

¹⁶ DPR, 2010, page 57, op. cit.

¹⁷ Kovatch R, Pathology Peer Review of Chloropicrin: Vapor Inhalation Oncogenicity Study in CD-1 (R) Mice. Study No. 92N1105. Pathology Associates International Corporation, Frederick, MD. January 1996. Unpublished.

- *Female mice had statistically significant trends for lung adenomas and combined lung adenomas and carcinomas. However, there were no significant pair-wise comparisons of the dosed groups with the controls. In addition the control females had 0/47 carcinomas, which is low based on historical control data from the literature. The lack of carcinomas in the concurrent control females resulted in a lower combined adenoma/carcinoma value for control females which contributed to the trend in the combined tumor rates.*¹⁸
- *A review of the NTP database on lung carcinogens found that 88% (15/17 studies) of the mouse lung tumor effects showed carcinogenic effects in both sexes. For the 12% (2/17 studies) that showed positive results on only one affected sex, the lung tumor effects were more pronounced.*¹⁹
- *The use of the poly-3 trend test may not be appropriate for the chloropicrin data set for a number of reasons: 1) the study showed no significant survival differences among dosed and control groups, possibly negating the need for a survival-adjusted statistical approach such as the poly-3 test; 2) the poly-3 test has not been validated for CD-1 mice, and may be biased by differences in the life spans of CD-1 mice (as compared to the B6C3F1 strain of mice used to validate the test); 3) for the case of low-incidence tumors, there is some evidence that the poly-3 test could yield results that are biased toward a Type I error (i.e. toward an overestimate of lifetime tumor incidence rates in the higher dose groups).*^{20, 21, 22}
- *Several agencies and experts arrived at the same conclusion, that the study does not justify a conclusion of carcinogenicity in humans for chloropicrin.*^{23, 24, 25, 26, 27, 28, 29}

¹⁸ U.S. EPA, 2010 op. cit.

¹⁹ Haseman, J.K. 2011. Letter to the Carcinogen Identification Committee, September 2011.

²⁰ Ibid.

²¹ Beiler, G.S. and Williams, R.L. 1993. Ratio estimates, the Delta Method, and Quantal Response Tests for Increased Carcinogenicity. *Biometrics* 49,793-801.

²² [Jessop, H. 2013. Memorandum to Sheryl Beauvais](#): Relevance of the Bieler-Williams poly-3 trend test in the analysis of carcinogenicity of chloropicrin. April 3, 2013.

²³ Chloropicrin: Vapor Inhalation Oncogenicity Study in CD-1 mice". BRRRC Project 92-N11076, H.D. Burleigh Flayer, W.J. Kintigh and C.L. Benson, Bushy Run Research Center, Export, PA. December 20, 1994.

²⁴ Kovatch, op. cit.

²⁵ <http://www.cdpr.ca.gov/docs/risk/toxsums/pdfs/136.pdf>.

²⁶ U.S. EPA, 1996. Chloropicrin: Mouse oncogenicity (MRID 43632201) and rat oncogenicity (MRID 437553301) studies. Memorandum from Stanley Gross to Paula Deschamp.

²⁷ Italy, 2010. Additional Report to the Draft Assessment Report on the active substance chloropicrin prepared by the rapporteur Member State Italy in the framework of Commission Regulation (EC) No 33/2008, March 2010.

²⁸ European Food Safety Authority; Conclusion on the peer review of the pesticide risk assessment of the active substance chloropicrin. *EFSA Journal* 2011;9(3):2084.[58 pp.].doi:10.2903/jefsa2011.available online:www.efsa.europa.eu/efsajournal.htm

²⁹ U.S. EPA, 2010 op. cit.

Toxicity Endpoint	Data Interpretation Made By	Interpretation
Mouse pulmonary adenoma (Chloropicrin: Vapor Inhalation Oncogenicity Study in CD-1 mice". BRRC Project 92-N1105, H.D. Burleigh Flayer, W.J. Kintigh and C.L. Benson, Bushy Run Research Center, Export, PA. April 25, 1995) Unpublished	Study Director	Not carcinogenic
	Independent Pathology Peer Reviewer	Not carcinogenic
	DPR 1995	Not carcinogenic
	DPR 1998	Not carcinogenic
	US EPA 1996	Not likely to be carcinogenic
	Italian Ministry of Health 2010 for the European Union EFSA Peer Review 2011	Not likely to be carcinogenic
	OEHHA 2001**	Not assessed
	OEHHA 2009	Likely to be carcinogenic
	DPR 2010	Likely to be carcinogenic
	US EPA Cancer Assessment Review Committee 2010	Not likely to be carcinogenic
	Carcinogen Identification Committee, OEHHA, October 2011	Lowest priority for conducting a review for carcinogenicity

** OEHHA conducted a non-cancer assessment of chloropicrin in 2001 using the same study.

- 6) Female rats administered chloropicrin daily for 2 years by oral gavage had an increase in mammary fibroadenomas.
- *The increase was significant by trend analysis and pair-wise comparison with controls at the high dose. However, the increase at the high dose was within the historical control range for the laboratory where the study was done so there is some uncertainty about the toxicological significance of the increase with these tumors.*³⁰
 - *A rat inhalation oncogenicity study³¹ was also done. The study showed that there was a slight increase in fibroadenomas in female rats but it was not statistically significant and it was within the historical control range for the laboratory. The*

³⁰ DPR, 2010, page 57, op. cit.

³¹ Chloropicrin: Vapor Inhalation Oncogenicity Study in CD rats. BRRC Project 92-N11076, H.D. Burleigh Flayer, and C.L. Benson, Bushy Run Research Center, Export, PA. July 29, 1995. Unpublished.

- conclusion for that study was that, administration of chloropicrin did not result in any treatment-related increases in tumors in male or female rats since the statistics showed no significant trend or pair-wise comparison for the tumors.*^{32,33}
- *An external peer reviewer also provided a review of the oral gavage study and the two-year inhalation carcinogenicity in rats. He stated that there was no statistical difference between the positive female rats and the controls and there was no evidence of a dose-response relationship. Therefore, he concluded that chloropicrin did not induce a carcinogenic response.*³⁴

Further Analysis

Since DPR scientists concluded based on limited evidence that “carcinogenicity could not be dismissed,” a cancer potency factor was calculated using the combined incidence of lung adenomas and carcinomas in female mice in the carcinogenicity study by Burleigh-Flayer, 1995. The adjusted incidence from the Poly-3 trend test was used to estimate potency with the Multistage Cancer model in the BMDS (BenchMark Dose Software). The calculations were based only on the positive results on the female mice and this resulted in a very high cancer potency factor, indicating that chloropicrin is a very potent carcinogen. The conclusion is based on the use of the poly-3 trend test, a statistical test which may not be the most appropriate test to use with this dataset for several reasons as stated in the appendix of this memorandum. Additionally, the comprehensive risk characterization document (CRCD)³⁵ that includes occupational, bystander and residential exposures, stated the following on page 58:

“Although the increase in tumors was not dramatic in either carcinogenicity study and all the in-vivo tests were negative, a “health protective” assumption was made that a genotoxic mode of action was involved based on the electrophilic structure and the positive in-vitro genotoxicity tests.

Logically, if chloropicrin was a very potent carcinogen, then the animal carcinogenicity studies should have been overwhelmingly positive in both mice and rats. Further, in the risk appraisal section of the CRCD on page 95:

“The carcinogenic risk estimates for residential and occupational bystanders for soil fumigation were significantly greater (10^{-3} to 10^{-2}) than the negligible risk level.

³² U.S. EPA, 2010, op cit.

³³ Brennecke, L, 1996. Memorandum to Stanley Gross, Chloropicrin: Pathology consult for rat oncogenicity study. October 25, 1996.

³⁴ Swenberg, J.A.;The Chloropicrin Manufacturers Task Force, Niklor Chemical Co., Long Beach, CA; IRDC, Mattawan, MI; 6/27/95; Rebuttal Document: 5/6/98

³⁵ DPR, 2012, op cit.

However, it should be noted that if there is a threshold for the carcinogenicity, the cancer risk estimates derived in this risk assessment could be overestimated by several orders of magnitude. Given the widespread use of chloropicrin, one would expect an association between exposure to chloropicrin and lung cancer would have been noticed by now if the cancer potency is as high as estimated.”

These statements reflect the uncertainty of the conclusion that chloropicrin is a carcinogen and these uncertainties are further emphasized by the differing scientific opinions on this issue.

Conclusions

- 1) The carcinogenicity data set for chloropicrin has not changed since it was completed in 1995. It consists of five long-term bioassays completed in rodents and one long-term (one bioassay) in dogs. That data set has been reviewed by DPR in 1995 and again in 1997, by U.S. EPA in 2009, by U.S. EPA Carcinogen Assessment Review Committee³⁶ (CARC) in 2010, by the Italian Ministry of Health in 2010 for the European Union EFSA Peer Review in 2011 and by the former Chief of Chemical Pathology and Director of the NIEHS Division of Toxicology and Research and Testing Program. Without exception each of these reviews of chloropicrin carcinogenicity found a non-cancer classification to be appropriate.
- 2) The previous six scientific arguments demonstrate the uncertainties on the carcinogenicity of chloropicrin. Moreover, after the TACHHA document was finalized in February 2010, the CARC also conducted a risk assessment on the carcinogenicity of chloropicrin in July 2010 and concluded that it is not likely a human carcinogen and therefore did not justify the quantification of a cancer potency factor.
- 3) In October 2011, the Carcinogen Identification Committee of the Office of Environmental Health Hazard Assessment (OEHHA) assigned chloropicrin in the lowest priority possible for cancer assessment.³⁷
- 4) Several authoritative bodies and toxicology experts have reviewed the chloropicrin toxicology database and do not consider the compound to be a carcinogen. Accordingly, there is no recognition of need to generate a cancer potency factor for chloropicrin or to perform a cancer risk assessment, quantitative or otherwise. The U.S. EPA and elsewhere, the World Health Organization (WHO), and the Italian Ministry of Health for the European Union have all concluded that a non-cancer classification for chloropicrin is appropriate. Additionally, organizations like the IARC or the International Programme of Chemical Society, who specialize in assessment of chemical carcinogenicity, have not shown interest in chloropicrin even though they are very likely aware of the data available on this compound.

³⁶ U.S. EPA, 2010. Op cit.

³⁷ Proceedings of the Prop 65 Carcinogen Identification Committee Meeting, October 12, 2011. OEHHA.

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Finally, to reiterate, the RMD issued by DPR in 2010 concluded that "...After evaluating all available information on the carcinogenic potential of chloropicrin and all the differing scientific opinions on this subject, the issue appears to be equivocal at this time." The information in this memorandum justifies the same conclusion: there is not enough evidence to establish that chloropicrin is a carcinogenic hazard requiring mitigation.

Attachment

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