

# Office of Environmental Health Hazard Assessment

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## MEMORANDUM

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**DATE:** May 4, 2004

**SUBJECT:** COMMENTS ON THE DEPARTMENT OF PESTICIDES REGULATION'S  
SULFURYL FLUORIDE RISK CHARACTERIZATION AND EXPOSURE  
ASSESSMENT DOCUMENTS

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Thank you for the opportunity to review the Risk Characterization and Exposure Assessment documents prepared by the Department of Pesticide Regulation (DPR) for the active ingredient, sulfuryl fluoride. The Office of Environmental Health Hazard Assessment (OEHHA) reviews risk assessments prepared by DPR under the general authority of the Health and Safety Code (HSC), Section 59004, and also under the Food and Agricultural Code (FAC), Section 13129, in which OEHHA has the authority to provide advice, consultation, and recommendations to DPR concerning the risks to human health associated with exposure to pesticide active ingredients.

In addition, pursuant to Food and Agricultural Code sections 14022 and 14023, OEHHA provides consultation to DPR on the evaluation of the health effects of candidate toxic air

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contaminants included in the TAC documents. As part of its statutory responsibility, OEHHA also prepares findings on the health effects of the candidate toxic air contaminants, which will be developed after DPR considers OEHHA's comments.

Currently, only one product is registered in California that contains sulfuryl fluoride as the active ingredient. This product, Vicane, is used for structural and non-food commodity fumigation. It controls a variety of pests such as dry wood termites, powder post beetles, old house borers, bedbugs, clothes moths, rodents, and cockroaches in dwellings, buildings, construction materials, furnishings, and vehicles. Vicane contains chloropicrin as a warning agent. In California, sulfuryl fluoride is a candidate for consideration as a toxic air contaminant under AB 1807, the Toxic Air Contaminant Act. Sulfuryl fluoride is not listed under Proposition 65, the Safe Drinking Water Act because it is not considered a developmental/reproductive toxicant or carcinogen.

The documents that were submitted to us provide an excellent overview of the available studies and scientific literature relevant to the toxicology of sulfuryl fluoride. Sulfuryl fluoride is a toxic gas that acts as a central nervous system depressant. Symptoms of poisoning include depression, slowed gait, slurred speech, nausea, vomiting, stomach pain, drunkenness, itching, numbness, twitching, and seizures. Inhalation may be fatal due to respiratory failure. Inhalation of high concentrations may cause respiratory tract irritation. Individuals with a history of chronic respiratory disease are at increased risk from exposure to sulfuryl fluoride. Skin contact with sulfuryl fluoride normally poses no hazard, but contact with liquid sulfuryl fluoride can cause pain and frostbite due to rapid vaporization.

In animal studies, neurotoxicity was observed in rats, mice, rabbits and dogs as a result of acute, subchronic, and chronic exposures. The primary target for sulfuryl fluoride toxicity in all species studied (rats, mice, rabbits, and dogs) was brain. The most common lesion found both in subchronic and chronic studies was vacuoles in the cerebrum.

For the most part, we agree with the presentation and discussion of the toxicology and risk assessment issues in these documents. However, we have several concerns and a number of observations and recommendations that we believe can improve the documents in achieving our mutual goals of protecting public health interests. While the current versions of the documents are comprehensive, they would benefit from clarifying and expanding specific issues that we have identified. We acknowledge and especially appreciate broad and thorough discussions of exposure related issues in the Exposure Assessment Document. The key recommendation of this review is that the quantitative risk assessment be revised by applying an additional ten-fold uncertainty factor, as suggested by U.S. EPA to account for toxicological data gaps and the potential additional sensitivity of infants and children to sulfuryl fluoride exposures.

A summary of our comments on the Risk Characterization and Exposure Assessment documents for sulfuryl fluoride is presented below. For more details please refer to the attachment.

1. OEHHA recommends revision of the quantitative risk assessment of sulfuryl fluoride by applying an additional ten-fold uncertainty factor to account for current lack of developmental neurotoxicity study and potential increased sensitivity of infants and children to sulfuryl fluoride exposures.
2. We recommend a decrease in the reentry levels (air concentration) of sulfuryl fluoride.
3. We suggest that the label for Vicane be included in the documentation of risk characterization and exposure assessment documents.
4. We support the choices of critical studies and toxicological endpoints used in the DPR RCD for sulfuryl fluoride.
5. We suggest that DPR provide further justification for not assessing health risks from lifetime exposures to sulfuryl fluoride.
6. Discussion of sulfuryl fluoride data gaps and related uncertainties in the risk characterization part of the RCD would enhance the quality of the risk assessment documents.
7. Available information or data on possible interaction of sulfuryl fluoride and chloropicrin, a warning agent that is required in Vicane, would be useful. We suggest that information be included regarding the range of chloropicrin concentrations in Vicane.
8. Justification of choice of default breathing rate for rabbits used in risk assessment, which is different than U.S. EPA's default rate, should be provided.
9. Brief discussion of potentially sensitive subpopulations (young, elderly, and those with medical conditions, particularly asthma) would improve the document.
10. We suggest that DPR consider evaluating chronic and subchronic exposures to bystanders, since it is plausible that a family could live adjacent to more than one home being fumigated over the course of a year.

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Thank you for providing the document for our review. If you have any questions about our comments, please contact Dr. Jolanta Bankowska (RCD reviewer), (510) 622-3162, Dr. David Rice (916) 324-1277 (exposure assessment reviewer), Robert Schlag (916) 323-2624, or Dr. Anna Fan at (510) 622-3165.

## ATTACHMENT

### COMMENTS ON THE DEPARTMENT OF PESTICIDES REGULATION'S SULFURYL FLUORIDE RISK CHARACTERIZATION AND EXPOSURE ASSESSMENT DRAFT DOCUMENTS

#### *RISK CHARACTERIZATION DOCUMENT*

##### *BACKGROUND INFORMATION*

Only one product is currently registered in California that contains sulfuryl fluoride as the active ingredient. This product, Vicane, is used for structural and non-food commodity fumigation. It controls a variety of pests such as dry wood termites, powder post beetles, old house borers, bedbugs, clothes moths, rodents, and cockroaches in dwellings, buildings, construction materials, furnishings, and vehicles. Vicane contains chloropicrin as a warning agent. According to information derived from the DPR website, the total statewide use of sulfuryl fluoride was 3,045,084 pounds, a vast majority of which was used in structural pest control applications. In 2002, one definite/probable and eight possible acute sulfuryl fluoride-related illnesses were reported. Additionally, 9 of 27 (33%) of reported fumigant illnesses were attributed to sulfuryl fluoride. Sulfuryl fluoride is a candidate for consideration as a toxic air contaminant under AB 1807, the Toxic Air Contaminant Act. Sulfuryl fluoride is not listed under Proposition 65, the Safe Drinking Water Act because it is not considered a developmental/reproductive toxicant or carcinogen.

Our comments provided below focus on issues that in our evaluation require further discussions and/or explanations.

#### COMMENTS

##### *Uncertainties*

Uncertainties involved in risk assessments in general and some uncertainties specific for sulfuryl fluoride are mentioned in various appropriate different parts of the documents. We suggest that a brief summary of all uncertainties relevant to sulfuryl fluoride risk assessment be included under the "Risk Characterization" section of the document. This section could also address but not be limited to: the current status of sulfuryl fluoride risk assessment, possible

future requirements of new data that would allow further refinements of the risks and possible underestimations of the current sulfur dioxide risk assessment because of the lack of developmental neurotoxicity study, unknown mechanism of action, lack of data on metabolite/s and their contribution to sulfur dioxide toxicity, lack of the methods to measure the impact of cumulative toxicity of sulfur dioxide and other chemicals that degrade or metabolize to fluoride ion.

### ***Absence of Important Study Data***

Throughout the RCD a number of potentially useful studies that have not been conducted or are unavailable were identified. We suggest that these studies specific to sulfur dioxide be summarized in one section. We refer not only to the data that are required under SB 950, but also to the data that would facilitate and improve health risk assessment. Such data for sulfur dioxide include but may not be limited to; developmental neurotoxicity study, pharmacokinetic studies, metabolic studies that would help to determine the role of fluoride ion in overall toxic effects of fluoride sulfate, and ecological effects of sulfur dioxide or fluoride ion. Absence of particular studies that relate to specific uncertainties in health risk assessment and a brief discussion of this issue in the risk characterization part of the RCD would be useful.

### ***Sensitive Subpopulations***

No potentially sensitive subpopulations are discussed in the RCD other than a mention of infants and children, who are not considered in this document to be more sensitive than the general population. OEHHA disagrees and believes infants and children should be regarded as potential sensitive subpopulation due to the neurotoxic effects of sulfur dioxide. In the light of the results of the RCD that show the brain is a primary target for sulfur dioxide toxicity we are concerned that younger populations may be especially sensitive to sulfur dioxide exposures. The developing organism with rapid cell proliferation, migration, and differentiation is uniquely sensitive to any kind of disruptions. In the brain these processes are unidirectional and occur at very specific times for different structures. Prenatal events include closure of the neural tube, proliferation of neurons, and migration of cortical neurons. During infancy and early childhood, proliferation and migration continue along with synaptogenesis, myelination, and development of the blood-brain barrier. Structural maturation of neural pathways, including an increase in the diameter and myelination of axons, continues through adolescence. During adolescence the rate of synaptic pruning peaks. Sulfur dioxide exposures can have profound effects on all of these neurologic developmental processes (OEHHA, 2001). OEHHA also recommends a brief discussion of other potentially sensitive subpopulations (elderly and others with medical conditions, such as asthma) be added to the document even though there are no mandated requirements or methods available to assess this probable higher sensitivity.

## *Risk Appraisal*

In general, human health risks associated with the current use of sulfuryl fluoride in structural and non-food commodity fumigation was determined in the RCD as being too high. As a general rule, a margin of exposure greater than 100 is considered protective of human health when it is calculated from a NOEL derived from an animal study. The MOEs were less than 100 for the following exposure scenarios: Structural fumigation

- a. Workers at submaximal application rate: introducing fumigant (chronic), total fumigator activities (subchronic and chronic), fumigator and tent crew tasks (all durations), ground seam opening (subchronic and chronic), roof seam opening (1-2 weeks, subchronic and chronic) ground snake removal (chronic), tarpaulin folding (chronic), and general detarping (all durations).
- b. Workers at maximal application rate: introducing fumigant (all durations), total fumigator activities (all durations), fumigator and tent crew tasks (all durations), and all tent crew activities for all durations.
- c. Residents following clearance: < one year old (acute), <one year old to eight years old (one to two weeks).
- d. Bystanders during maximal rate application phase: three to five years old (acute).
- e. Bystanders during aeration: < one and three to eleven years old (acute, TRAP method, submaximal rate), all age groups (acute, both methods, maximal application rates).

1. Non-food commodity fumigation: handlers (one to two weeks, chronic).

Because of the high probability that infants and children are more sensitive to neurotoxic effects of this fumigant than adults, health risks resulting from current use of sulfuryl fluoride may be even higher (i.e., MOEs may be lower than those determined by DPR), especially for younger subpopulations. At present, this has not been demonstrated because of the absence of required developmental neurotoxicity study, and also because in currently available developmental toxicity studies in rats and rabbits (see pg. 36), no histological examination of the brain was not performed. These examinations might have shown the presence of vacuoles that were observed in studies of adult rats, rabbits, and dogs exposed to sulfuryl fluoride.

Although the currently available (or lack of) data do not trigger the Food Quality Protection Act criterion for applying a ten-fold uncertainty factor in risk assessment (due to the absence of studies for potential increased sensitivity by infants and children to the pre- and post-natal toxicity) the ten-fold uncertainty factor was used by U.S. EPA in sulfuryl fluoride risk assessment to account for database uncertainty (lack of developmental neurotoxicity study). We agree with that decision and strongly urge that DPR apply an additional ten-fold uncertainty factor in calculating risks from current exposures to sulfuryl fluoride.

### **Lifetime risk of sulfuryl fluoride exposure**

Lifetime exposure assessment is a part of different exposures of sulfuryl fluoride determined in the Exposure Assessment document. However, lifetime risk from this exposure is not evaluated. The reason given in the RCD for this is that: "...sulfuryl fluoride has not been shown to be oncogenic in either humans or experimental animals" (see pg. 55 of the RCD). This explanation does not seem to be adequate, since other toxic effects of sulfuryl fluoride, e.g. neurotoxicity, should justify such evaluation. We suggest either performing risk assessment from lifetime exposures to sulfuryl fluoride or providing further convincing justifications for not performing it.

### ***Comparison between DPR and US EPA Risk Assessment of sulfuryl fluoride***

As mentioned above, the major difference between the U.S. EPA and DPR health risk assessment of sulfuryl fluoride is that U.S. EPA includes a ten-fold database uncertainty factor to account for the lack of developmental neurotoxicity study, while DPR does not in this document. The U.S. EPA health risk assessment of sulfuryl fluoride was based on dietary and inhalation exposures of "Profume," another sulfuryl fluoride product being considered for food uses registration. DPR documents under review refer to non-food uses of Vicane and only inhalation exposures.

Both DPR and U.S. EPA selected the same studies and the same NOELs (expressed in ppm) to address repeated exposures of less than one year. The NOELs expressed in mg/kg/day were different due to different default breathing rates used for rabbits by the two agencies. DPR used  $0.54 \text{ m}^3/\text{kg}/\text{day}$  and U.S. EPA used  $0.38 \text{ m}^3/\text{kg}/\text{day}$ . No explanation was provided within the DPR documents supporting the use of the breathing rate of  $0.54 \text{ m}^3/\text{kg}/\text{day}$  as a more appropriate factor for the risk assessment. Such an explanation would be useful.



For chronic inhalation exposure, both agencies used different studies, different NOELs and different toxicological endpoints. OEHHA supports DPR's approach, even though the resulting risk estimates may imply that EPA was more conservative in its assessment. Overall, comparing risk assessment approaches used by the two agencies enhances the quality of the risk and exposure assessment documents.

### ***Reentry Clearance Level***

The reentry air level for Vicane, according to the California and U.S. EPA product label, is 5 ppm. In the past, this level raised health concerns that it is insufficiently health protective (U.S. EPA, 1993). At that time U.S. EPA suggested the reentry (clearance) air concentration of 2 ppm for adults and 1 ppm for children. Subsequently, Dow Elanco provided data to support the 5 ppm reentry air level (see pg. 3 of the DPR Exposure Document).

Results of the sulfuryl fluoride risk assessment showed an unacceptably high risk (low MOE estimates) for most of the exposure scenarios for adults and for children. In light of these results, OEHHA recommends that the Dow Elanco data supporting higher reentry level of sulfuryl fluoride for Vicane be reevaluated and a lower air concentration of sulfuryl fluoride as the reentry levels be reconsidered. Additionally, page three, paragraph one of the Exposure Document states; "*In subsequent reports to be discussed in more detail later in this assessment, Dow Elanco provided data to support the 5 ppm reentry air level....*" It would be much more useful and transparent if these important data were summarized and discussed in detail in a single place in the document, rather than in different sections. It also would help if the bibliography could be provided when the Dow Elanco data are initially referenced.

### **Selection of critical studies and endpoints for risk assessment in RCD**

We support the choices of critical studies and toxicological endpoints used in the DPR RCD for sulfuryl fluoride.

### ***Conclusion***

Thorough evaluation of health risks from current non-food uses of sulfuryl fluoride shows that the risks are too high (non-protective of human health) for the majority of exposure scenarios. In OEHHA's opinion these risks may be underestimated by about ten-fold. We are concerned that DPR is considering the expanded use of sulfuryl fluoride in the near future that could result in even more situations where unacceptable health risks could occur.

## **References:**

U.S. EPA 1993. Reregistration eligibility decision, sulfuryl fluoride, list A, Case 0176. Washington DC: Office of Pesticide Programs, Special Review and Reregistration Division, Environmental Protection Agency.

OEHHA, 2001. Prioritization of Toxic Air Contaminants - Children's Environmental Health Protection Act - Final Report).

## **EXPOSURE ASSESSMENT DOCUMENT**

In general, we find the exposure assessments reasonable and scientifically defensible, with an exception is noted below. Exposure assessments were conducted for three general classes of potential receptors: workers (occupational exposure), residents (in fumigated homes) and bystanders (general public). Exposure durations of short-term (7 days or less), intermediate-term (7 days - one year), annual (one year), and lifetime (75 years) were evaluated for all receptor types. We assume that exposure of bystanders is considered ambient exposure and, therefore, relevant to the TAC statutes.

### *Occupational exposures:*

Task-specific exposure estimates were based on actual worker activities that were monitored during residential fumigations conducted in California in 1993 and 1994. Analytical results were appropriately corrected for recovery using the most conservative estimate of recovery available (66.1%). Exposure estimates were normalized (increased) to simulate applications of the material at the maximum allowable concentration (160 oz/1000 cf). Scenarios were evaluated with and without personal protective devices. Workers handling post-fumigation commodities were also evaluated; exposures were assessed based on the maximum sulfuryl fluoride levels allowed under the label (5 ppm as an 8 hour TWA).

### *Residential exposures:*

Residential exposure estimates were based from sampling of several California homes fumigated with sulfuryl fluoride. Analytical results were appropriately corrected for recovery using the most conservative estimate of recovery available (66.1%). Estimates were not adjusted for maximum application rates since it was assumed that residues left after ventilation were not based on the application rate. This is a reasonable assumption since the structure must be aerated to less than 5 ppm to be cleared regardless of the application concentration.

Based on the collected data, air concentrations for hypothetical fumigations were modeled to predict average and upper-bound exposure estimates. Modeling was necessary to predict air concentrations of sulfuryl fluoride for the various exposure scenarios since the actual sampling lasted only for 48 hours. Modeled results (for the first 48 hours) compared favorably with actual measured values. Assumptions of inhalation rates and proportion of hours spent indoors and outdoors for various age groups were standard and appropriate.

*Bystanders:*

Ambient air monitoring data collected during two different types of structural sulfuryl fluoride applications were used for estimating exposure of bystanders. Samples were corrected for an experimentally verified 83% recovery. Exposure estimates were normalized (increased) to simulate applications of the material at the maximum allowable concentration (160 oz/1000 cf). We suggest that DPR consider evaluating chronic and subchronic exposures to bystanders, since it is plausible that a family could live adjacent to more than one home being fumigated over the course of a year.

Exposure of bystanders to sulfuryl fluoride in ambient air as a result of commodity fumigation was also evaluated. No monitoring studies were available, so the 5 ppm maximum level allowed by the label was used to estimate exposures.

Two human occupational exposure studies (Anger *et al.*, 1986; Calvert *et al.*, 1998 - described in section III.H.2. Occupational Exposure) report reduced performance on cognitive, pattern memory, and olfactory tests. These studies are not directly applicable to quantitative risk assessment because of the lack of quantitative exposure assessment. However, they are applicable to human hazard identification, and should be discussed in this section.

OEHHA has developed a chronic (REL) for fluorides of  $13 \mu\text{g F}/\text{m}^3$  based on a benchmark dose evaluation of human occupational skeletal fluorosis data. Since fluoride is substantially metabolically available from absorbed sulfuryl fluoride, this section would be improved by a short description of the OEHHA chronic fluoride REL. We would be happy to provide you that additional information, which can also be found at:

[http://www.oehha.ca.gov/air/chronic\\_rels/pdf/2apna\\_fluoride\\_final.pdf](http://www.oehha.ca.gov/air/chronic_rels/pdf/2apna_fluoride_final.pdf))

The U.S. EPA and DPR Reference Concentrations (RfC) are listed in Table 29 on a mg/kg-day basis. Unfortunately, US EPA actually publishes its RfCs on a  $\text{mg}/\text{m}^3$  basis. Also, OEHHA lists its Reference Exposure Levels (RELs) on a mg or  $\mu\text{g}/\text{m}^3$  basis. It would be less confusing if DPR would include a listing for its sulfuryl fluoride RfC on a  $\text{mg}/\text{m}^3$  basis.

**References:**

Anger, W. K., Moody, L., Burg, J., Brightwell, W.S., Taylor, B.J., Russo, J.M., Dickerson, N., Setzer, J.V., Johnson, Bl., and Hicks, K. 1986. Neurobehavioral evaluation of soil and structural fumigators using methyl bromide and sulfuryl fluoride. *Neurotoxicology* 7(3): 137-56.

Calvert, G.M., Mueller, C.A., Fajen, J.M., Chrislip, D.W., Russo, J., Briggie, T., Fleming, L.E. Suruda, A.J., and Steenland, K. 1998. Health effects associated with sulfuryl fluoride and methyl bromide exposure among structural fumigation workers. *Am. J. Public Health* 88(12):1774-80.