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MEMORANDUM

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DATE: July 1, 2005

SUBJECT: FINDINGS ON THE HEALTH EFFECTS OF THE ACTIVE INGREDIENT: SULFURYL FLUORIDE

Enclosed please find a copy of the Office of Environmental Health Hazard Assessment's (OEHHA) findings for the active ingredient sulfuryl fluoride. These findings, which supercede our previous draft findings (dated December 23, 2004), were prepared in response to the final draft risk characterization document (RCD Volumes I and II, dated June 1, 2005) for sulfuryl fluoride prepared by the Department of Pesticide Regulation (DPR). The information contained in these documents served to identify sulfuryl fluoride as a candidate toxic air contaminant (TAC).

Pursuant to Food and Agricultural Code sections 14022 and 14023, OEHHA provides review, consultation and comments to DPR on the evaluation of the health effects of candidate toxic air contaminants (TAC) 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. This documentation is to be included as part of the DPR report.

Should you have any questions regarding OEHHA's draft findings on the health effects of sulfuryl fluoride, please contact Dr. David Rice at (916) 324-1277 (primary reviewer), Mr. Robert Schlag at (916) 323-2624, or Dr. Anna M. Fan at (510) 622-3165.

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Office of Environmental Health Hazard Assessment's Findings On the Health Effects of Sulfuryl Fluoride

Pursuant to Food and Agricultural Code Sections 14022 and 14023, the Office of Environmental Health Assessment (OEHHA) of the California Environmental Protection Agency provides consultation and technical assistance to the Department of Pesticide Regulation (DPR) on the evaluation of health effects of candidate toxic air contaminants (TAC) and prepares health-based findings. OEHHA previously reviewed and commented on the draft documents prepared by DPR on the evaluation of human health risks associated with potential exposure to sulfuryl fluoride. These documents are used by DPR in considering listing sulfuryl fluoride as a TAC. As part of its statutory responsibility, OEHHA has also prepared these findings on the health effects of sulfuryl fluoride which are to be included as part of DPR's Risk Characterization / Toxic Air Contaminant (RCD/TAC) documents.

Environmental Fate and Exposure

1. Sulfuryl fluoride (sulfuric oxyfluoride) is a fumigant used for structural and non-food commodity fumigations. Vikane is the registered trade name for the product that is used to control a variety of pests such as drywood termites, powder post beetles, old house borers, bedbugs, clothes moths, rodents, and cockroaches in dwellings, buildings, construction materials, furnishings, and vehicles. Use of sulfuryl fluoride increased from 1.7 million pounds in 1994 to 3 million pounds in 2002. The major use (>99%) is for structural pest control and the increase in use is attributed to the decline in the use of methyl bromide for the same purpose.

2. Relatively little is known about the environmental fate of sulfuryl fluoride. The chemical is hydrolyzed in water to fluorosulfuric acid and fluoride ion. Under neutral conditions, the reaction proceeds slowly, while under alkaline conditions the hydrolysis is rapid. Data addressing the fate of sulfuryl fluoride in soil and biota is unavailable.

3. Exposure was estimated for residents re-occupying fumigated dwellings (postclearance), and for bystanders during active structural fumigation and during the aeration phase using two different aeration techniques. Exposure was also estimated for bystanders during non-food commodity fumigations. Ambient air exposures for the general population other than bystanders were not estimated since they were assumed to be negligible.

4. Exposure to residents entering cleared, fumigated houses was based on the results of a 48-hour postclearance air monitoring study of seven homes (Shurdut, 1995). The 48-hour

data were used to estimate 24-hour sulfuryl fluoride air concentrations, which were then used to calculate the 24-hour acute absorbed daily dose (ADD). Since no longer-term data existed, the air concentration data was also used to generate dissipation curves, which provided air concentrations to estimate the short term (7-day) ADD, the annual ADD (AADD) and the lifetime average ADD (LADD). Ninety-fifth percentile upper bound air concentrations were used to derive acute, short-term and annual ADDs. An estimate of the average 7-day air concentration was used to calculate the lifetime ADD. Seven-day exposures, assumed as the dissipation curves for all residences in the study, show that air concentrations of sulfuryl fluoride were negligible at 7-days post clearance. Predicted air concentrations for sulfuryl fluoride of 1.78 ppm (7.42 mg/m^3), 0.42 ppm (1.75 mg/m^3), and 0.095 ppm (0.40 mg/m^3) were used to calculate acute ADDs, short-term/annual ADDs, and LADDs, respectively.

5. Bystander exposure during structural fumigations was estimated based on a study by Wright and co-workers (Wright et al., 2003) who monitored air levels of sulfuryl fluoride during an application of sulfuryl fluoride at the submaximal application rate of 16 g/m^3 and the structures' subsequent aeration. Data collected during the application phase was used to estimate acute 12 and 24-hour ADD (using upper 95^{th} percentile air concentrations), AADD (using upper 95^{th} percentile air concentrations) and the LADD (using average air concentration). Estimated air concentrations for sulfuryl fluoride of 1.60 ppm (6.67 mg/m^3), 1.12 ppm (4.67 mg/m^3), and 0.69 ppm (2.88 mg/m^3) were used to calculate 12-hour ADDs, 24-hour/annual ADDs, and LADDs, respectively. Estimates of air concentrations following use of sulfuryl fluoride at the maximum application rate of 160 g/m^3 were estimated by multiplying the estimated submaximal air concentrations by ten.

6. Wright et al.(2003) monitored air levels of sulfuryl fluoride following a structural fumigation during the aeration phase using the "Stack" method of aeration. Briefly, the stack method involves 12 hours of active ventilation via an exhaust stack with tarpaulin in place; the structure is then tested for clearance after the ventilation period. Data collected during this monitoring study was used to estimate acute 1 and 4-hour ADD (using upper 95^{th} percentile air concentrations), AADD (using upper 95^{th} percentile air concentrations) and the LAADD (using average air concentrations). Estimated air concentrations for sulfuryl fluoride of 7.99 ppm (33.32 mg/m^3), 1.97 ppm (8.21 mg/m^3), and 0.60 ppm (2.50 mg/m^3) were used to calculate 1-hour ADDs, 4-hour/annual ADDs, and LADDs, respectively. Estimates of air concentrations following use of sulfuryl fluoride at the maximum application rate of 160 g/m^3 were estimated by multiplying the estimated submaximal air concentrations by ten.

7. Bystander exposure during aeration using an alternate clearance method known as "TRAP", which involves 10 minutes active ventilation followed by tarpaulin removal, and then 60 minutes of active aeration, was estimated by using air concentrations of

sulfuryl fluoride calculated for worker exposure during general detarping activities. Estimated air concentrations for sulfuryl fluoride of 24 ppm (100 mg/m^3) and 6.2 ppm (26.7 mg/m^3) were used to calculate 2-hour ADDs/AADDs and LADDs, respectively. These estimates were made from air morning data following a sulfuryl fluoride application at the average application rate of 11 g/m^3. Estimates of air concentrations following use of sulfuryl fluoride at the maximum application rate of 160 g/m^3 were estimated by multiplying the estimated submaximal concentrations by 14.5.

8. No air monitoring data is available to estimate bystander exposures associated with nonfood commodity fumigation. Exposures were estimated assuming a maximum ambient air level of 5 ppm (20.9 mg/m^3), which is the maximum allowed by the Vikane label. Exposure over a 24-hour period was assumed.

9. Based on the results of a pharmacokinetic analysis in Fisher rats by Mendrala and co-workers (2002), inhalation absorption was estimated at 18%. Absorbed doses were calculated taking into consideration air concentration, inhalation rate (specific for age group and activity), the absorption factor (18%), and body weight. Exposure was estimated for several age groups (in years): <1, 1-2, 3-5, 6-8, 9-11, 12-14, 15-18, and > 18 (adults). Because of children's high breathing rate to body weight ratio, exposures were greatest for children less than one-year of age.

10. Human exposure to atmospheric sulfuryl fluoride can occur by both inhalation and dermal routes, but the predominant route for systemic exposure is inhalation. Dermal uptake of sulfuryl fluoride has not been quantitatively estimated in these studies but it is expected to provide less than 1 percent of the systemic dose received by inhalation.

Health Effects Studies

Humans

11. Several unintentional cases of human poisoning with sulfuryl fluoride have been reported in the literature. A number of these cases were fatalities, nearly all of which were cases associated with entering structures that were either undergoing active fumigation, were still tarped and not yet cleared for reentry, or were cleared for reentry and sulfuryl fluoride levels not yet measured. Symptoms included coughing, chest discomfort, hypotension, hyperexcitability, hyperventilation, tachycardia, and seizures. Post mortem evaluations typically reveal severe pulmonary edema, respiratory and lung mucosa and brain edema. A single non-lethal case has also been reported. In the latter case, reddened conjunctiva, pharyngeal and nasal mucosa and reversible paresthesia of the right leg was reported.

12. Sulfuryl fluoride exposure has resulted in serious illness in California. Between 1997 and 2001, a total of 32 incidents were reported to DPR associated with either sulfuryl

fluoride, chloropicrin or both and were due to spillage, drift or chemical residues. Short-term exposure typically resulted in irritation of the eyes, nose and throat along with respiratory symptoms of difficulty in breathing and shortness of breath. Nausea, dizziness, paresthesia, disorientation, headache, confusion and memory loss have also been reported. In a cross-sectional epidemiological study of 1234 structural fumigation workers, reduced performance on the pattern memory test and reduced olfactory function was noted in workers exposed with "high sulfuryl fluoride exposure."

Animals

13. The acute toxicity of sulfuryl fluoride has been evaluated in a variety of animal species including rats, mice, dogs, rabbits, and guinea pigs. Neurotoxiciy was observed in rats, mice, rabbits and dogs at non-lethal concentrations. With exposures up to two weeks, signs observed in these species included tremors, lethargy, respiratory effects, incapacitation, tetany, and convulsions. Renal effects (papillary necrosis, degeneration and regeneration of the collecting and proximal tubules) in rats, cerebral lesions (vacuolation, malacia, demyelination) in rabbits and mice and respiratory effects (tissue inflammation in nasal, trachea and bronchi/bronchioles) in rabbits and dogs were observed at the LOAELs in the two-week exposure studies. One-hour LC_{50}s were 3730 ppm and 3020 ppm in male and female rats, respectively. Four-hour LC_{50}s ranged from approximately 600 ppm in mice to 1500 ppm in rats. An acute NOAEL of 300 mg/kg/day (300 ppm; 6 hr/d x 2d) was observed in rats exposed for 6-hours/day over the course of two days, based on no effects observed in the FOB or electrodiagnostic tests at this, the highest dose tested. The lowest two-week NOAEL, 40 mg/kg/day (100 ppm; 6 hr/d x 5d/w x 2w), was established in rabbits based on brain and respiratory tract lesions at the next higher dose of 121 mg/kg/day (300 ppm; 6 hr/d x 5d/w x 2w).

14. Subchronic toxicity studies in laboratory animals provide information on adverse effects following inhalation exposure of rats, mice, rabbits and dogs to sulfuryl fluoride. The brain was the primary target for sulfuryl fluoride toxicity in all species studied and the most common lesion following subchronic exposure was vacuolation of the cerebrum. Other effects reported were nasal tissue inflammation in rats and rabbits, renal hyperplasia, pulmonary histocytosis and fluorosis in rats, and thyroid hypertrophy in mice. A NOAEL of 12 mg/kg/day (30 ppm; 6hr/d x 5d/w x 13w) was established in rabbits based on cerebral vacuolation and nasal inflammation at the next higher dose of 40 mg/kg/day (100 ppm).

15. Three chronic toxicity/oncogenicity inhalation studies are available for sulfuryl fluoride, one each in rats, mice and dogs. In all species tested, the brain and the respiratory tract were the primary target organs for sulfuryl fluoride toxicity. Similar to subchronic exposures, cerebral vacuoles were observed in the brains of treated animals. Respiratory tract lesions consisted of inflammation of the nasal passages, trachea, larynx, and lungs

and lung congestion. Dental fluorosis was also observed in rats and dogs. Progressive glomerular nephropathy was also observed in rats and was considered the cause of early mortality in the high dose groups (57 mg/kg/day, 80 ppm; 6hr/d x 5d/w x 2y) of both sexes. A NOAEL of 4 mg/kg/day (6hr/d x 5d/w x 2y) was identified in male rats based on dental fluorosis in the next higher dosed group, 14 mg/kg/day. No oncogenic responses were observed in any of the three species tested.

16. Reproductive toxicity of sulfuryl fluoride was tested in rats in a two-generation study. Maternal effects consisted of lung inflammation and alveolar macrophage aggregates and the formation of cerebral vacuoles. Effects on pups occurred at doses that were maternally toxic and consisted solely of reduced body weight. The maternal NOAEL was 4 mg/kg/day (5 ppm; 6 hr/d x 5d/w x 2generations) based on the effects on the lungs observed at the next higher dose of 14 mg/kg/day (20 ppm); the latter dose was the NOAEL for the brain lesions). The reproductive NOAEL was 14 mg/kg/day (20 ppm; 6 hr/d x 5d/w x 2generations), based on reduced body weight of pups at the next higher dose of 107 mg/kg/day (150 ppm).

17. Developmental toxicity studies have been conducted in rats and rabbits. No teratogenic effects were observed in either species. In rats, maternal toxicity was observed at 100 ppm (100 mg/kg/day) in a range finding study based on a decrease in body weight and body weight gain and decreases in food and water consumption at the highest dose of 300 mg/kg/day (300 ppm; 6 hr/dx10d; gestational days 6 to 15). No fetal effects were observed in the study. A NOAEL of > 225 mg/kg/day (the highest dose tested, 225 ppm; 6 hr/dx10d; gestational days 6 to 15) was established in the definitive rat study for maternal and fetal effects based on the absence of effects at this dose. In rabbits, a maternal and developmental NOAEL of 42 mg/kg/day (75 ppm; 6 hr/d x 13d; gestational days 6 to 18) was observed based on reduced body weights and body weight gain in the dams and reduced fetal body weights at the highest dose of 127 mg/kg/day (225 ppm) (Hanley et al., 1981, 1989). No histological examination of either maternal or pup brains was performed in either species.

Basis, Potency, and Range of Health Risks to Humans

18. Human health risks for acute exposures to sulfuryl fluoride are estimated in the RCD/TAC document using an NOAEL of 300 mg/kg/day (300 ppm; 6 hr/dx2d) based on no effects observed in rats in the FOB or electrodiagnostic tests at this highest dose level in the study. A short-term (2 week) NOAEL of 40 mg/kg/day (6 hr/d x 5d/w x 2w) based on lesions in the brain and respiratory tract in rabbits at the next higher dose of 121 mg/kg/day (300 ppm) was used for evaluating human exposures longer than acute, but shorter than subchronic durations.

19. Human health risks from subchronic exposure to sulfuryl fluoride are estimated in the RCD/TAC document based on a subchronic NOAEL of 12 mg/kg-day (30 ppm; 6 hr/d x 5d/w x 13w) identified in 13 week rabbit study and was based on brain lesions (cerebral vacuoles) and nasal inflammation at the next higher dose of 40 mg/kg-day (100 ppm).

20. Chronic exposure to airborne sulfuryl fluoride was evaluated in the RCD/TAC based on a NOAEL of 4 mg/kg-day (5 ppm; 6 hr/d x 5d/w x 2generations) from a two-generation reproduction study in rats based on lung inflammation and alveolar macrophage aggregates observed in the dams at the next higher dose of 14 mg/kg-day (20 ppm).

21. OEHHA agrees with the selection of the critical studies and identification of the endpoints and NOAELs found in the RCD/TAC document.

22. Margins of exposure (MOEs) were calculated in the RCD/TAC document for the various age groups and scenarios by dividing the NOAEL by the estimated exposure. Only variants of acute exposures were actually evaluated in the RCD/TAC, even though exposures for longer durations were estimated. Acute (24 hour) exposure was assessed for residents entering cleared, fumigated homes. Acute (12 and 24 hour) exposures were assessed for bystanders at structural fumigation sites during the application phase. For bystanders at structural fumigation sites during the aeration phase, two-hour exposures were evaluated for the TRAP aeration procedure while 1-hour and 4-hour exposures were evaluated for bystanders near structures aerated by the Stack method. Acute (24-hopur) exposures were evaluated for bystanders at or near a non-food commodity fumigation site.

23. MOEs exceeding 100 when based on NOAELs from animal studies are typically considered by DPR to be sufficiently protective of human health. In the case of sulfuryl fluoride, however, a higher benchmark of 1,000 was adopted for residential and bystander exposures because of a data gap resulting from the lack of a suitable developmental neurotoxicity study. In addition, DPR Regulations (Title 3, CCR Section 6890) specifies that a pesticide shall be listed as a toxic air contaminant if the ambient air concentrations are greater than: 1) 10-fold below the reference concentration for pesticides with threshold effects, or 2) 10-fold below the negligible risk concentration. Because of the relationship between MOEs and reference concentrations, MOEs lower than 10,000 meet the criterion #1, above.

24. MOEs presented in the RCD/TAC for acute (24 hour) exposure of residents entering cleared, fumigated homes range from 104 for children <1 year of age to 270 for 15-18 year-old children. We note that all MOEs for residents of fumigated homes are less than 1,000 and are therefore of potential human health concern.

25. For fumigations conducted at the submaximal application rate of 16 g/m3, MOEs presented in the RCD/TAC for acute (12 hour) exposure of bystanders at a structural fumigation site during the application phase were all less than 1,000 and ranged from 150 for infants <1year of age to 386 for 15-18 year-old children. MOEs presented for acute (24 hour) exposure were also all less than 1,000 and ranged from 108 for infants <1year of age to 270 for 15-18 year-old children. For fumigations occurring at the maximum application rate (160 g/m3), MOEs for acute (12 hour) exposure of bystanders at a structural fumigation site during the application phase were all less than 100 and ranged from 15 for infants <1 year of age to 39 for 15-18 year-old children. MOEs presented for acute (24 hour) exposure were also all significantly less than 100 and ranged from 11 for infants <1year of age to 27 for 15-18 year-old children. We note that all MOEs for bystanders under all scenarios near an active structural fumigation site are extremely low, and are therefore of potential human health concern.

26. For fumigations conducted at the submaximal application rate of 16 g/m3, MOEs presented in the RCD/TAC for acute (2 hour) exposure of bystanders at a structural fumigation site during the aeration phase utilizing the TRAP method were all less than 1,000 and ranged from 64 for infants <1year of age to 150 for 15-18 year-old children. Using the Stack aeration technique, MOEs presented for acute (1 hour) exposure were also all 1,000 or less and ranged from 386 for infants <1year of age to 1080 for 15-18 year-old children. Acute, 4-hour MOEs with Stack aeration ranged from 360 for infants <1year of age to 900 for 15-18 year old children. For fumigations occurring at the maximum application rate (160 g/m3), MOEs for acute (2 hour) exposure of bystanders during the aeration phase utilizing the TRAP method also all significantly less than 100 and ranged from 4 for infants <1year of age to 10 for 15-18 year-old children. Using the Stack aeration technique, MOEs presented for acute (1 hour) exposure also were all less than 100 and ranged from 39 for infants <1year of age to 108 for 15-18 year-old children. Acute, 4-hour MOEs with Stack aeration ranged from 36 for infants <1year of age to 90 for 15-18 year old children. We note that all MOEs for bystanders near structural fumigation sites utilizing either TRAP or Stack methodology for aeration were all under 1,000 and many were less than 100 and are therefore of potential human health concern. We are particularly concerned with bystander exposure at the maximum application rate using the TRAP aeration technique, where all MOEs were 10 or less.

27. MOEs presented in the RCD/TAC for acute (24 hour) exposure of bystanders at or near a non-food commodity fumigation site were all significantly less than 1,000 and ranged from 23 for infants <1year of age to 60 for 15-18 year-old children. We note that all MOEs for all age groups under this scenario are less than 100 and are therefore of potential human health concern.

28. Continuous and or repeated exposures to sulfuryl fluoride are considered unlikely; accordingly only acute exposures were evaluated in the RCD/TAC. Annual exposures

based on 1 – 7 day exposures were not evaluated in the document because they were considered acute exposures. Lifetime risks of sulfuryl fluoride exposure were also not evaluated since sulfuryl fluoride exposure is considered acute, there are no toxic endpoints unique to chronic exposure and there is no evidence that sulfuryl fluoride is oncogenic.

29. Reference concentrations (RfCs) are calculated in the RCD/TAC for acute (24-hour), short duration (up to two-weeks), subchronic (13-weeks) and chronic exposures to sulfuryl fluoride in ambient air. The RfC is calculated by dividing the oral NOAEL (in mg/kg-day) by the appropriate human breathing rate (in m^3/kg-day) and uncertainty factor (unitless). RfCs were calculated based on breathing rats of infants (0.59 m^3/kg-day) since that provided the most health-protective value. An uncertainty factor of 1000 was applied to each NOAEL in consideration of the variability between and within species (100) and for the lack of a developmental neurotoxicity study (10). RfCs presented in the RCD/TAC, along with the corresponding NOAELs and assumptions made in the calculations can be seen in Table 1.

Other Relevant Findings

30. U.S. EPA's Food Quality Protection Safety Factor Committee has recommended that the ten-fold safety factor be retained in the calculation of RfCs for chronic and dietary residential exposures. This is due to the lack of a suitable developmental neurotoxicity study for sulfuryl fluoride and concern regarding brain vacuolation observed in adult animals. Accordingly, an additional 10-fold uncertainty is applied when interpreting MOEs and in the RfC calculations presented in the RCD/TAC document.

31. Limited information is available regarding any potential environmental breakdown products of sulfuryl fluoride. The extent of or any toxicological significance of co-exposure to possible breakdown products cannot be evaluated.

32. Estimates of the contribution to total chronic fluoride exposure from all sources (drinking water, dietary and cryolite) from occupational fluoride sources ranged from a low of 5% to a high of 92%. A value of 46% contribution from occupational sources (0.05 mg/kg/day of a total 0.11 mg/kg/day) was proposed in the RCD as probably reflecting current exposures.

33. Cumulative exposure to other chemicals with similar mechanisms of action is possible. The extent of or any toxicological significance of cumulative exposure to these compounds has not and should be evaluated.

Table 1. Reference Concentrations (RfCs) Calculated in the RCD/TAC for Acute, Short Duration (1-2 weeks), Subchronic (13 weeks), and Chronic Exposures to Sulfuryl Fluoride

Exposure Duration	NOAEL[1] (mg/kg-day)	RfC[2] (mg/m^3)	Air Concentrations[3] (mg/m^3)
Acute (1 day)	54[4]	0.51	7.42
Short-term (1-2 weeks)	7.2[5]	0.10	1.75
Subchronic (13 weeks)	2.2[6]	0.03	n.a.[8]
Chronic	0.72[7]	0.01	n.a.[8]

1. Absorbed dose NOAELs, inhalation absorption was assumed to be 18%.
2. A breathing rate (infants) of 0.59 m^3/kg-day was used for the calculations. An uncertainty factor of 1000 was applied to all calculations.
3. Estimated concentrations of sulfuryl fluoride in indoor air following clearance of fumigated homes. Estimates based on the exposure study by Shurdut, 1995. See also Finding #4.
4. Albee et al., 1993a, NOAEL of 300 mg/kg-day based on no effect in the FOB or electrophysiological tests in rats at this, the highest dose tested.
5. Eisenbrandt et al., 1985, NOAEL of 40 mg/kg-day based on brain lesions in rabbits at the next higher dose of 121 mg/kg-day.
6. Nitschke et al., 1987b, NOAEL of 12 mg/kg-day based on brain lesions in rabbits observed at the next higher dose of 40 mg/kg-day.
7. Breslin et al., 1992, NOAEL of 4 mg/kg-day based on pulmonary effects observed in rats at the next higher dose of 14 mg/kg-day.
8. n.a. = not applicable as continuous exposure exceeding 7 days is not expected.