This HIARC report supercedes the previous HIARC report dated 5/22/01 (TXR No. 014568).

TXR NO.: 0052208

DATE: October 31, 2003

MEMORANDUM


FROM: Jessica Kidwell, Executive Secretary
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

THROUGH: Jess Rowland, Co-Chair
and
Karen Whitby, Co-Chair
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: Ed Budd, Toxicologist
Michael Doherty, Risk Assessor
Registration Action Branch 2
Health Effects Division (7509C)

PC Code: 078003

On April 11, 2001, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed the recommendations of the toxicology reviewer for SULFURYL FLUORIDE with regard to the acute and chronic Reference Doses (RfDs) and the toxicological endpoint selection for occupational/residential exposure risk assessments. The potential for increased susceptibility of infants and children from exposure to sulfuryl fluoride was also evaluated as required by the Food Quality Protection Act (FQPA) of 1996. On October 21, 2003, the potential for increased susceptibility of infants and children from exposure to SULFURYL FLUORIDE was re-evaluated as required by the Food Quality Protection Act (FQPA) of 1996 according to the 2002 OPP 10X Guidance Document. The conclusions drawn at both of these meetings are presented in this report.
Committee Members in Attendance

Members present were: Ayaad Assaad, William Burnam, Jonathan Chen, William Dykstra (alternate), Ray Kent (RARC Rep.), Jessica Kidwell (Executive Secretary), John Liccione, Jess Rowland (Co-Chair), Brenda Tarplee, Karen Whitby (Co-Chair)

Member(s) in absentia were: Pamela Hurley, Susan Makris, Elizabeth Mendez

Also in attendance were: Edwin Budd (HED/RAB2), Jeffrey Herndon (HED/RAB2)
INTRODUCTION

Sulfuryl fluoride, also known as Vikane™ Gas Fumigant, has been registered since 1959 for non-food uses. It is marketed as a liquified gas in pressurized steel cylinders and is used for the fumigation of closed (sealed) structures and their contents, such as buildings, dwellings, garages, barns, storage buildings, and other structures infested with a variety of insects such as drywood termites, powder post beetles, old house borers, bedbugs, and clothes moths. A Registration Standard for this chemical was completed in June 1985 and a Reregistration Eligibility Decision (RED) was published in September 1993. In response to Data-Call-Ins in 1990 and 1992, and in anticipation of future toxicology requirements, the registrant (Dow AgroSciences) has submitted several new subchronic and chronic toxicology studies on this chemical.

Sulfuryl fluoride is a potential alternative for methyl bromide for uses involving the post-harvest fumigation of food commodities. Toward this end, the registrant has requested an Experimental Use Permit (EUP) for the use of ProFume™ Gas Fumigant, which is identical to the presently registered Vikane Gas Fumigant, to evaluate control of insects in and on walnuts and raisins in storage and processing facilities. This would be the first food use for this chemical. A toxicology data base sufficient to support food uses is available for sulfuryl fluoride.

On April 11, 2001, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed the recommendations of the toxicology reviewer for sulfuryl fluoride with regard to the acute and chronic Reference Doses (RfDs) and the toxicological endpoint selection for occupational/residential exposure risk assessments. The potential for increased susceptibility of infants and children from exposure to sulfuryl fluoride was also evaluated as required by the Food Quality Protection Act (FQPA) of 1996. On October 21, 2003, the potential for increased susceptibility of infants and children from exposure to sulfuryl fluoride was re-evaluated as required by the Food Quality Protection Act (FQPA) of 1996 according to the 2002 OPP 10X Guidance Document. The conclusions drawn at both of these meetings are presented in this report.

I. FQPA HAZARD CONSIDERATIONS

1. Adequacy of the Toxicity Data Base

The available toxicology data base for sulfuryl fluoride is adequate for FQPA assessment and includes the following acceptable studies:

1. Acute neurotoxicity study, rats
   OPPTS 870.6200, MRID 42772001
2. Subchronic neurotoxicity study, rats
   OPPTS 870.6200, MRID 40839902
3. Chronic neurotoxicity study, rats
   OPPTS 870.6200, MRID 43216702
4. Developmental toxicity study, rats
   OPPTS 870.3700, MRID 00090015
5. Developmental toxicity study, rabbits
   OPPTS 870.3700, MRID 00090015
2. Evidence of Neurotoxicity

The HIARC concluded that there is a concern for neurotoxicity resulting from exposure to sulfuryl fluoride.

Acute Neurotoxicity

Executive Summary: In a specially designed acute neurotoxicity inhalation toxicity study (MRID 42772001), four epidural electrodes were implanted, using stereotaxic instruments, into the skulls of female Fischer 344 rats 3 weeks before exposures. Twelve female rats/exposure group were then exposed to technical grade sulfuryl fluoride gas (lot # WP 920619-953, 99.8% active ingredient) at exposure concentrations of 0, 100, or 300 ppm for 6 hours/day for 2 consecutive days (calculated to be equivalent to 0, 118, or 354 mg/kg/day). The parameters evaluated included functional observational battery (FOB), motor activity, and the electrophysiological parameters affected at the LOAEL in a previously conducted 90-day subchronic neurotoxicity study in rats (MRID 40839902). These parameters were visual evoked response (VER), somatosensory evoked response (SER), and auditory brain stem response (ABR). Microscopic neuropathology was not examined due to the lack of effects in a previously conducted 2-week inhalation study in rats at 100 or 300 ppm (MRID 148956).

At 300 ppm (354 mg/kg/day), the highest exposure concentration tested in this study, and at 100 ppm (118 mg/kg/day), no treatment-related general clinical effects were observed in any of the rats. Also, no treatment-related effects on functional observational battery, motor activity or electrophysiological parameters were observed. The systemic and neurotoxic NOAEL in this study is 300 ppm (354 mg/kg/day), the highest exposure concentration tested. A LOAEL was not observed (>300 ppm).

This acute neurotoxicity study in female rats is classified as an Acceptable study and satisfies the Subdivision F guideline requirements for an acute neurotoxicity study in rats (OPPTS 870.6200). Although it does not strictly meet guideline requirements, it satisfies the data requirements as modified by agreement between the Agency and the registrant prior to initiation of the study. The protocol modifications were intended to provide a reasonable NOAEL for short-term inhalation exposure to sulfuryl fluoride (as might be expected during reentry by residential persons or occupational workers into fumigated/aerated structures) and to minimize unnecessary tests (e.g. where results of previously conducted studies indicated that no effects would be expected). Testing in male rats was not required because females appeared to be more sensitive in the 90-day neurotoxicity study. Also, achievement of toxicity at the highest exposure concentration tested was not required.
Subchronic Neurotoxicity

Executive Summary: In a specially designed subchronic neurotoxicity study (MRID 40839902), 7 Fischer 344 rats/sex/exposure group were exposed to sulfuryl fluoride gas (Vikane Gas Fumigant) at exposure concentrations of 0, 30, 100, or 300 ppm for 6 hours/day, 5 days/week for 13 weeks (calculated to be equivalent to 0, 24, 80, or 240 mg/kg/day in males and 0, 25, 83, or 250 mg/kg/day in females). Two months into the study, each rat was withheld from exposure for a day to permit surgical implantation of four epidural electrodes, using stereotaxic instruments, into their skulls. At the conclusion of dosing, a functional observation battery (FOB) and electrophysiological testing were conducted. The electrophysiological parameters evaluated were visual-evoked response (VER), cortical flicker fusion (CFF), auditory brain stem response (ABR), somatosensory evoked response (SER), cerebellar evoked response (CER), and caudal nerve evoked action potential (CNAP). Microscopic examination of nervous system tissues was also performed, but only in the 300 ppm animals. Adequate daily observations of clinical signs, weekly observation of forced motor activity, and functional observation batteries prior to the conclusion of the dosing were absent from this study.

At 300 ppm, a slowing of all the waveforms except for CNAP was observed. There was also a decrease in the power of the ABR. Vacuolation of the white fiber tracts in the caudate putamen was also observed in all the rats exposed to 300 ppm. Decreased body weights, excessive salivation, poor grooming, histopathology in the lungs and dental fluorosis were also noted at 300 ppm. At 100 ppm, disturbances in the electrophysiological parameters were also observed. These disturbances were a slowing of the VER and SER waveforms in females and a slowing of the ABR waveform in males. Histopathology in the lungs and dental fluorosis were also noted at 100 ppm. The neurotoxic LOAEL in this study is 100 ppm (80/83 mg/kg/day) based on disturbances in electrophysiological parameters in males and females. The neurotoxic NOAEL is 30 ppm (24/25 mg/kg/day). The systemic LOAEL is 100 ppm (80/83 mg/kg/day) based on histopathology in the lungs and dental fluorosis in males and females. The systemic NOAEL is 30 ppm (24/25 mg/kg/day).

This subchronic neurotoxicity study, when considered together with the results from the chronic neurotoxicity study in rats (MRID 43216702), is classified as an Acceptable/Guideline study and satisfies the Subdivision F guideline requirement for a subchronic neurotoxicity study in rats (OPPTS 870.6200).

Chronic neurotoxicity study, rats

Executive Summary: In a chronic inhalation neurotoxicity study (MRID 43216702), technical grade sulfuryl fluoride gas (lot #s WP 880329-752, WP 901011-907, WP 910321-918, WP 910826-929, WP 920131-940; 93.6% to 99.7% a.i.) was administered to 15 Fischer 344 rats/sex/group by whole body inhalation exposure at concentrations of
0, 5, 20 or 80 ppm (equivalent to 0, 0.021, 0.085 or 0.334 mg/L) for 6 hours per day, 5 days/week for 1 year (calculated to be equivalent to 0, 3.5, 14, or 56 mg/kg/day in males and to 0, 3.9, 16, or 62 mg/kg/day in females). Functional observational battery (FOB) and motor activity testing were conducted at 3, 6, 9 and 12 months. Neuropathological evaluation was conducted on 5 perfused animals/sex/dose at 12 months. This study was conducted concurrently with a chronic toxicity/carcinogenicity study as a satellite group and some data for these animals are presented in the report for that study (MRID 43354902), including daily observations, clinical pathology, organ weights, and standard microscopic pathology evaluations for the remaining 10 unperfused animals/sex/dose.

No treatment-related neurotoxic or other effects on FOB parameters, motor activity testing or neuropathological examinations were observed. Other treatment-related effects reported at 1 year included: at 20 ppm, very slight to slight bilateral dental fluorosis in 3/10 males, increasing to 10/10 at 80 ppm; at 80 ppm, slight effects in both sexes on several clinical chemistry parameters consistent with progressive kidney disease; slightly increased relative kidney and liver weights (7%); increased severity (slight vs. very slight, controls) of chronic progressive glomerulonephropathy in both sexes and increased incidence in females (100% vs. 30%, controls); and all animals showed pale bilateral foci of the lung and multifocal aggregates of alveolar macrophages. The neurotoxicity LOAEL is >80 ppm (>56/62 mg/kg/day). The neurotoxicity NOAEL is 80 ppm (56/62 mg/kg/day). The systemic LOAEL is 20 ppm (14/16 mg/kg/day) based on very slight to slight fluorosis in teeth of male rats. The systemic NOAEL is 5 ppm (3.5/3.9 mg/kg/day).

This chronic neurotoxicity study, together with the previously submitted subchronic neurotoxicity study (MRID 40839902), is considered Acceptable/Guideline and satisfies the guideline requirement for a subchronic neurotoxicity screening study in the rat (82-7ss). Most of the issues raised in the previous review of the subchronic study were adequately addressed in this study. No additional studies are required to satisfy the subchronic neurotoxicity requirement since there are sufficient data for purposes of human risk assessment.

Evidence of neurotoxicity from other toxicity studies on Sulfuryl Fluoride

In numerous subchronic and chronic inhalation toxicity studies on rats, mice, dogs and rabbits, a treatment-related neurotoxic lesion described as malacia (necrosis) and/or as vacuolation of the white fiber tracts in the brain was regularly reported at dose levels as low as 90 mg/kg/day in a 2-week study in rabbits (MRID 148956), at dose levels as low as 28 mg/kg/day in a 90-day study in rabbits (MRID 40890901), at dose levels as low as 50 mg/kg/day in a 90-day study in dogs (MRID 42256601), at dose levels as low as 50 mg/kg/day in a 1-year study in dogs (MRID 43354901), and as low as 56 mg/kg/day in a 2-year study in rats (MRID 43354902). In these studies, clinical signs of neurotoxicity (e.g. tremors, tetany, incoordination, excessive salvation) were sometimes observed at
dose levels below those at which malacia and/or vacuolation was observed in the brain, sometimes at higher dose levels, and sometimes not at all at any of the dose levels tested. The parts of the brain in which these lesions were present were frequently the caudate-putamen nucleus in the basal ganglia of the cerebrum, and the white fiber tracts of the internal and external capsules and globus pallidus of the cerebrum.

3. Developmental Toxicity Study Conclusions

**Developmental toxicity study in rats**

Executive Summary: In a developmental toxicity study (MRID 00090015), 35-36 presumed pregnant Fischer 344 rats/exposure group were exposed to technical grade sulfuryl fluoride gas (lot # 217, 99.8% active ingredient) at exposure concentrations of 0, 25, 75, or 225 ppm for 6 hours/day on days 6-15 of gestation for a total of 10 exposures (calculated to be equivalent to 0, 27, 81, or 243 mg/kg/day). On GD 21, all surviving dams were sacrificed and necropsied and all fetuses were weighed, sexed, measured for crown-rump length, and examined for external malformation/variations. One-half of the fetuses were randomly chosen for soft tissue examinations by dissection (including examination by serial sectioning of heads). All fetuses were eviscerated, stained, and examined for skeletal malformations/variations.

No treatment-related clear maternal toxicity or significant developmental or teratogenic effects were observed in any of the dams or fetuses at any of the exposure concentrations tested in this study. Although an LOAEL was not achieved, 225 ppm approached the LOAEL based on the results of a previously conducted range-finding study in rats (DOW Chemical Co., Lab. No. HET K-16399-(14), 11/19/80), which demonstrated toxicologically significant maternal toxicity at 300 ppm. In this range-finding study, treatment-related statistically significant (p<0.05) decreased body weight (8.6% on GD 16), body weight gain (86% on GD 6-15), and food consumption (21-27% at various times during the treatment period); and treatment-related statistically significant (p<0.05) increased water consumption (68-118% at various times during the treatment period), absolute kidney weights (7.5% on GD 16) and relative/kidney body weight ratios (18.3% on GD 16) were noted. In addition, gross necropsies revealed subcapsular foci or areas of paleness in the kidneys of 7/10 dams at 300 ppm compared to 0 in all the other groups, including the controls; and diffuse paleness in the liver of 7/10 dams at 300 ppm compared to 0 in all the other groups, including the controls. The kidney has been shown in other studies to be a major target organ for sulfuryl fluoride in rats. The maternal toxicity NOAEL and the developmental toxicity NOAEL are both 225 ppm (243 mg/kg/day). No LOAEL was observed in the study (>225 ppm).

This developmental toxicity study in rats is classified Acceptable/Guideline and satisfies the Subdivision F guideline requirement for a developmental toxicity study in rats (OPPTS 870.3700).
Developmental toxicity study in rabbits

Executive Summary: In a developmental toxicity study (MRID 00090015), 28-29 presumed pregnant New Zealand white rabbits/exposure group were exposed to technical grade sulfuryl fluoride gas (lot # 217, 99.8% active ingredient) at exposure concentrations of 0, 25, 75, or 225 ppm for 6 hours/day on days 6-18 of gestation for a total of 13 exposures (calculated to be equivalent to 0, 9.5, 29, or 86 mg/kg/day). On GD 29, all surviving does were sacrificed and necropsied and all fetuses were weighed, sexed, measured for crown-rump length, and examined for external malformation/variations. One-half of the fetuses were randomly chosen for soft tissue examinations by dissection (including examination by serial sectioning of heads). All fetuses were eviscerated, stained, and examined for skeletal malformations/variations.

At 225 ppm, statistically significant reductions in body weight were observed on GD 29 and in body weight gain on GD 12-14, GD 19-28, and GD 6-28. Overall, for GD 6-28, the mean body weight gain for controls was 240 grams, whereas the 225 ppm group lost 60 grams. Food consumption was unaffected. The maternal toxicity LOAEL is 225 ppm (86 mg/kg/day) based on decreased body weight and body weight gain. The maternal toxicity NOAEL is 75 ppm (29 mg/kg/day).

A statistically significant decrease in fetal body weight (14%) was noted at 225 ppm. A small non-statistically significant decrease in crown-rump length (4%) was also noted as well as a slightly increased incidence of fetal liver pathology (pale livers) in 3 fetuses from 2 litters at 225 ppm. The decrease in crown-rump length could not be attributed to treatment with sulfuryl fluoride because of the small magnitude of the decrease and the lack of statistical significance. Similarly, the slight increase in incidence of fetal liver pathology was insufficient to attribute this observation to treatment with sulfuryl fluoride. The developmental toxicity LOAEL is 225 ppm (86 mg/kg/day) based on decreased fetal body weight. The developmental toxicity NOAEL is 75 ppm (29 mg/kg/day).

This developmental toxicity study in rabbits is classified Acceptable/Guideline and satisfies the Subdivision F guideline requirement for a developmental toxicity study in rabbits (OPPTS 870.3700).

4. Reproductive Toxicity Study Conclusions

2-Generation reproduction inhalation toxicity study in rats

Executive Summary: In a 2-generation reproduction inhalation toxicity study (MRID 42179801), 30 male and 30 female Sprague-Dawley rats/exposure group were exposed to sulfuryl fluoride gas (99.8% active ingredient) at exposure concentrations of 0, 5, 20, or 150 ppm for 6 hours/day, 5 days/week for the premating period and for 6 hours/day 7 days/week for the mating, gestation and lactation periods. The dams were not exposed
from GD 20 to day 4 postpartum. Pups were separated from dams and exposed for 6 hours/day on days 5-21 postpartum. The doses of test material were calculated to be 0, 3.6, 14, or 108 mg/kg/day for both the males and females in this study. One litter was produced in each generation. F0 parents were exposed for 10 weeks prior to mating. F1 litters (and F2 litters) were culled to a total of 8 pups on day 4 of lactation and 30 F1 pups/sex were selected for the next generation. F1 animals were exposed for 12 weeks prior to mating. F2 pups were sacrificed after weaning. Adults and pups were necropsied in accordance with standard procedures for a 2-generation reproduction study.

At 150 ppm (108 mg/kg/day), treatment-related vacuolation of the caudate putamen white fiber tracts in the cerebrum of parental F0 and F1 rats was observed. In addition, decreased body weights (up to 16%), dental fluorosis and histopathology in the lungs were also noted at 150 ppm. At 20 ppm (14 mg/kg/day), treatment-related pale, gray foci in the lungs were observed at gross necropsy and histopathology in the lungs (increased alveolar macrophages) during microscopic examination. The LOAEL for parental toxicity is 20 ppm (14 mg/kg/day) based on pathological changes in the lungs. The NOAEL for parental toxicity is 5 ppm (3.6 mg/kg/day).

No treatment-related changes in reproductive parameters were observed in this study. The LOAEL for reproductive toxicity is >150 ppm (>108 mg/kg/day). The NOAEL for reproductive toxicity is 150 ppm (108 mg/kg/day), the highest concentration tested in this study.

At 150 mg/kg/day (108 mg/kg/day), pup body weights in the F1 and F2 generation were decreased. This decrease may have been secondary to the decreased maternal body weights at this exposure concentration. The LOAEL for offspring toxicity is 150 ppm (108 mg/kg/day) based on decreased pup body weights in the F1 and F2 generations. The NOAEL for offspring toxicity is 20 ppm (14 mg/kg/day).

This study is classified Acceptable/Guideline and satisfies the Subdivision F guideline requirements for a 2-generation reproduction study in rats (OPPTS 970.3800).

5. Additional Information from Literature Sources

None available.

6. Pre- and/or Postnatal Toxicity

The HIARC concluded that there is not a concern for pre- and/or postnatal toxicity resulting from exposure to sulfuryl fluoride.
A. Determination of Susceptibility

In the developmental toxicity study in rats, neither quantitative nor qualitative evidence of increased susceptibility of fetuses to *in utero* exposure to sulfuryl fluoride was observed.

In the developmental toxicity study in rabbits, neither quantitative nor qualitative evidence of increased susceptibility of fetuses to *in utero* exposure to sulfuryl fluoride was observed.

In the 2-generation reproduction toxicity study in rats, neither quantitative nor qualitative evidence of increased susceptibility of fetuses to sulfuryl fluoride was observed.

B. Degree of Concern Analysis and Residual Uncertainties

There are no concerns or residual uncertainties for pre- and/or post-natal toxicity following exposure to sulfuryl fluoride.

C. Special FQPA Safety Factor

Based upon the above data, no special FQPA safety factor is needed (i.e. 1X) since there are no residual uncertainties for pre- and/or post-natal toxicity.

*NOTE:* The Special FQPA Safety Factor recommended by the HIARC assumes that the exposure databases (dietary food, drinking water, and residential) are complete and that the risk assessment for each potential exposure scenario includes all metabolites and/or degradates of concern and does not underestimate the potential risk for infants and children.

7. Recommendation for a Developmental Neurotoxicity Study

The HIARC concluded that there is a concern for developmental neurotoxicity resulting from exposure to sulfuryl fluoride.

A. Evidence that suggest requiring a Developmental Neurotoxicity study:

In numerous subchronic and chronic inhalation toxicity studies on rats, mice, dogs and rabbits, a treatment-related neurotoxic lesion described as malacia (necrosis) and/or as vacuolation of the white fiber tracts in the brain was regularly reported at dose levels as low as 90 mg/kg/day in a 2-week study in rabbits (MRID 148956), at dose levels as low as 28 mg/kg/day in a 90-day study in rabbits (MRID 40890901), at dose levels as low as 50 mg/kg/day in a 90-day study in dogs (MRID 42256601), at dose levels as low as 50 mg/kg/day in a 1-year study in dogs (MRID 43354901), and at dose levels as low as 56 mg/kg/day in a 2-year study in rats (MRID 43354902). In these studies, clinical signs of
neurotoxicity (e.g. tremors, tetany, incoordination, excessive salvation) were sometimes observed at dose levels below those at which malacia and/or vacuolation was observed in the brain, sometimes at higher dose levels, and sometimes not at all at any of the dose levels tested. In a specially designed 90-day neurotoxicity study in rats, disturbances in electrophysiological waveforms (EEG patterns) were observed at a dose level (80 mg/kg/day) lower than the dose level at which malacia/vacuolation was observed in the brain (240 mg/kg/day). The parts of the brain in which these lesions were present were frequently the caudate-putamen nucleus in the basal ganglia of the cerebrum, and the white fiber tracts of the internal and external capsules and globus pallidus of the cerebrum.

B. Evidence that do not support the need for a Developmental Neurotoxicity study:

In the developmental toxicity study in rats, neither quantitative nor qualitative evidence of increased susceptibility of fetuses to in utero exposure to sulfuryl fluoride was observed.

In the developmental toxicity study in rabbits, neither quantitative nor qualitative evidence of increased susceptibility of fetuses to in utero exposure to sulfuryl fluoride was observed.

In the 2-generation reproduction toxicity study in rats, neither quantitative nor qualitative evidence of increased susceptibility of fetuses to sulfuryl fluoride was observed.

Based on consideration of the evidence presented above, HIARC recommends that an inhalation developmental neurotoxicity (DNT) study in rats (Guideline No. 870.6300) be required in order to more clearly and fully characterize the potential for neurotoxic effects in young animals. HIARC also recommends that the registrant consult with the Agency regarding the protocol for this study prior to initiation of the study.

HIARC determined that a 10X database uncertainty factor (UF_{DB}) is needed to account for the lack of the DNT study since the available data provide no basis to support reduction or removal of the default 10X factor. The following points were considered in this determination:

- The current regulatory dose for chronic dietary risk assessment is the NOAEL of 8.5 mg/kg/day (0.13 mg/L; 30 ppm) selected from a 90-day inhalation toxicity study in rabbits. This dose is also used for intermediate- and long-term inhalation exposure risk assessments. The current dose for the short-term inhalation exposure risk assessment is the NOAEL of 0.42 mg/L (100 ppm) from a 2-week inhalation toxicity study in rabbits.

- After considering the dose levels used in the neurotoxicity studies and in the 2-generation reproduction study, it is assumed that the DNT study with sulfuryl fluoride will be conducted at dose levels similar to those used in the 2-generation reproduction study (0, 0.02, 0.08, 0.6 mg/L). It is considered possible that the results of the DNT study could
impact the endpoint selection for risk assessments because the lowest dose that may be tested in the DNT (5 ppm or 0.02 mg/L), based on the HIARC’s dose analysis, could become an effect level which would necessitate an additional factor resulting in doses which would then be lower than the current doses used for chronic dietary (8.5 mg/kg/day), intermediate and long-term inhalation (30 ppm or 0.13 mg/L) and short term inhalation (100 ppm or 0.42 mg/L) risk assessments. Given these circumstances, the HIARC does not have sufficient reliable data justifying selection of an additional safety factor for the protection of infants and children lower than the default value of 10X. Therefore, a UF_{DB} of 10X will be applied to repeated dose exposure scenarios (i.e. chronic RfD, and residential short, intermediate and long term inhalation) to account for the lack of the DNT study with sulfuryl fluoride.

II. HAZARD IDENTIFICATION

1. Acute Reference Dose (RfD)

Study Selected: None

Guideline No.: None

MRID No.: None

Executive Summary: None

Dose and Endpoint for Establishing RfD: Not applicable

Uncertainty Factor (UF): Not Applicable

Comments about Study/Endpoint: No toxicological endpoint attributable to a single exposure was identified in the available toxicology studies on sulfuryl fluoride that would be applicable to females (13-50 years old) or to the general population (including infants and children). In an inhalation acute neurotoxicity study in rats (MRID 42772001), no treatment-related effects were observed at the highest concentration tested (300 ppm; equivalent to 354 mg/kg/day). In the inhalation developmental toxicity study in rabbits (MRID 00090015), decreased body weight and body weight gain observed in the dams and decreased body weight observed in the fetuses were not considered to be attributable to a single exposure. Treatment-related effects observed in a 2-week subchronic inhalation toxicity study in rabbits (MRID 148956) also were not appropriate endpoints for an acute RfD. In this study, focal malacia and vacuolation of the cerebrum were not attributable to a single exposure and inflammation of the nasal tissues and trachea (in an inhalation study) were not considered to be appropriate endpoints on which to base an oral RfD. Poisonings and fatalities have been reported in humans following inhalation

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exposure to sulfuryl fluoride. The severity of these effects has depended on the concentration of sulfuryl fluoride and the duration of exposure. Short-term inhalation exposure to high concentrations has caused respiratory irritation, pulmonary edema, nausea, abdominal pain, central nervous system depression, and numbness in the extremities. In addition, there have been two reports of deaths of persons entering houses treated with sulfuryl fluoride. One person entered the house illegally and was found dead the next morning. A second person died of cardiac arrest after sleeping in the house overnight following fumigation. A plasma fluoride level of 0.5 mg/L (10 times normal) was found in this person following exposure. The HIARC did not consider these poisonings in humans to be appropriate endpoints on which to base an acute oral RfD because all of these incidents only occurred following gross violations of the label directions and only after exposure to high concentrations of sulfuryl fluoride.

2. Chronic Reference Dose (RfD)

Study Selected: 90-Day Subchronic Inhalation Toxicity Study in Rabbits

Guideline No.: 870.3465

MRID No.: 40890901

Executive Summary: In a 90-day subchronic inhalation toxicity study (MRID 40890901), seven New Zealand white rabbits/sex/exposure group were exposed to sulfuryl fluoride gas (Vikane Gas Fumigant, lot #TWP 830919-408, 99.8% active ingredient) at exposure concentrations of 0, 30, 100, or 600/300 ppm for 6 hours/day, 5 days/week for 13 weeks (calculated to be equivalent to 0, 8.6, 29, or 86 mg/kg/day for males and to 0, 8.5, 28, or 85 mg/kg/day for females). The initial exposure concentration of 600 ppm was reduced to 300 ppm after 9 exposures due to convulsions in one male and one female and hind leg paralysis in another female. Mortality, clinical signs, body weights, hematology, clinical chemistries (including serum fluoride), and organ weights were evaluated and gross and microscopic examinations were performed.

At 300 ppm, microscopic malacia (necrosis) and/or vacuolation of the internal and external capsules, putamen and globus pallidus of the brain was observed in males and females. Decreased body weight gain, decreased liver weights, dental fluorosis, and histopathology in the nasal epithelium and lungs (alveolar histiocytosis) were also


observed at 300 ppm in both males and females. At 100 ppm, vacuolation of the caudate-putamen nuclei of the brain was observed in females. Decreased body weights and dental fluorosis were also noted at 100 ppm. Serum fluoride levels were increased at all exposure concentrations tested (including 30 ppm). The systemic LOAEL in this study is 100 ppm (29/28 mg/kg/day) based on vacuolation of white matter in the brain of females, and decreased body weights, decreased liver weights and dental fluorosis in males and females. The systemic NOAEL is 30 ppm (8.6/8.5 mg/kg/day).

This subchronic inhalation toxicity study in rabbits is classified as Acceptable/Guideline and satisfies the Subdivision F guideline requirement for a 90-day subchronic inhalation study (OPPTS 870.3465).

Dose and Endpoint for Establishing RfD: NOAEL = 8.5 mg/kg/day, based on vacuolation of white matter in the brain of females at the systemic LOAEL of 28 mg/kg/day.

Uncertainty Factors (UFs): 3000, based on 10X for intraspecies variation, 10X for interspecies extrapolation, 3X Uncertainty Factor for using a subchronic (90-day) study for chronic risk assessment (UF_s), and 10X Database Uncertainty Factor (UF_DB) for lack of a DNT study.

Comments about Study/Endpoint/Uncertainty Factor: For sulfuryl fluoride, the endpoint from an inhalation toxicity study was used to calculate the chronic RfD which is to be used to perform risk assessments for oral exposures. HIARC believes this is a very conservative methodology which is supported by the following considerations:

- The absorption of test material from inhalation exposure is generally presumed to be 100%, whereas absorption after oral exposure is oftentimes determined to be less than 100%.

- A higher and more persistent level of parent test material in the body may occur following inhalation exposure as compared to an oral exposure because the parent test material is immediately distributed throughout the circulatory system following inhalation, rather than first being directly shunted to the liver (where most metabolism occurs) as in the case of oral exposure.

- In addition, for sulfuryl fluoride, the NOAEL on which the chronic RfD was calculated is from a study in rabbits (which is the most sensitive species for neurotoxic effects) and the LOAEL in this study was close to a threshold effect level (the effect was observed in only one female rabbit).

The LOAEL of 100 ppm (equivalent to 28 mg/kg/day) in the 90-day rabbit study, which was used to calculate the chronic RfD, was considered to be close to a threshold effect level because only one female rabbit at this concentration had vacuolation of the white
matter in the brain. The HIARC considered applying an additional uncertainty factor to the NOAEL in this study due to the severity of the effect at the LOAEL, but concluded that application of an additional uncertainty factor would not be necessary since the LOAEL was an approximate threshold effect level.

For the purpose of determining a chronic oral RfD, the HIARC believes that an endpoint based on a well-defined morphological/pathological effect, such as the neurological effect observed in the 90-day rabbit study, is preferable to one based on a more equivocal and/or dubious effect such as dental fluorosis (mottling of teeth). The HIARC also believes that it is not appropriate to utilize an effect on the respiratory system in an inhalation study as the basis for calculating an oral RfD. Therefore, the NOAEL of 5 ppm (equivalent to 3.5 mg/kg/day) for male rats in the combined 2-year chronic/carcinogenicity inhalation study in rats (MRID 43354902) was not used to calculate the chronic RfD because the effect observed at the LOAEL of 20 ppm (equivalent to 14 mg/kg/day) was dental fluorosis. Also, the parental NOAEL of 5 ppm (equivalent to 3.6 mg/kg/day) in the 2-generation reproduction inhalation study in rats (MRID 42179801) was not used because the effect observed at the parental LOAEL of 20 ppm (equivalent to 14 mg/kg/day) was pathological changes in the lungs. In addition, the NOAEL of 20 ppm (equivalent to 5.0 mg/kg/day) in the 1-year chronic inhalation toxicity study in dogs (MRID 43354901) was not used because the effect observed at the LOAEL of 80 ppm (equivalent to 20 mg/kg/day) was decreased body weight gain, dental fluorosis, and histopathological changes in the lungs.

Therefore, the chronic RfD for sulfuryl fluoride is considered to be a very conservative RfD for the purpose of oral risk assessments. In addition, oral exposure to sulfuryl fluoride at the time of consumption is expected to be extremely low (due to prior dissipation of sulfuryl fluoride from the ingested commodities).

\[
\begin{align*}
\text{Chronic RfD} & \quad = \quad \frac{8.5 \text{ mg/kg/day (NOAEL)}}{3000 \text{ (UF)}} \\
& \quad = \quad 0.003 \text{ mg/kg/day}
\end{align*}
\]

### 3. Incidental Oral Exposure (All Durations)

Sulfuryl fluoride is a gas at ordinary temperatures and pressures and because of its use pattern as a fumigant in enclosed structures and spaces only, it is not anticipated that toxicologically significant residues of sulfuryl fluoride or its degradates will remain in/on the contents of residential or other structures after the aeration period is completed. Consequently, there is no potential for incidental ingestion by toddlers. Therefore, HIARC did not select endpoints for this exposure scenario.
4. **Dermal Absorption**

No dermal absorption study on sulfuryl fluoride is available. Because of its use pattern, the likelihood of dermal exposure to toxicologically significant amounts of sulfuryl fluoride is very low. See *Section 5 Dermal Exposure (All Durations)* below.

5. **Dermal Exposure (All Durations)**

Sulfuryl fluoride is a gas at ordinary temperatures and pressures and because of its use pattern as a fumigant in enclosed structures and spaces only, it is not anticipated that toxicologically significant residues of sulfuryl fluoride or its degradates will contact the skin of applicators, bystanders or others as a result of its use, except possibly by accidental direct exposure to the skin of applicators as it is released from pressurized steel cylinders. Under these conditions, however, the exposed skin would be immediately frozen. Nevertheless, there is a study (described below) which assessed the potential toxicity resulting from dermal exposure to high concentrations of sulfuryl fluoride.

**Study: Dermal Vapor Exposure Study in Rats**

**Guideline No.:** None

**MRID No.:** 41712001

**Executive Summary:** In a specially designed dermal vapor exposure study (MRID 41771201), five Fischer 344 rats/sex were dermally exposed (body only) to sulfuryl fluoride gas (Vikane Gas Fumigant, lot # 880329752, 99.7% active ingredient) at an exposure concentration of 9599 ppm for a single exposure of 4 hours. An additional 5 male or 5 female rats were also exposed in a similar manner to an exposure concentration of 1013 or 987 ppm for 4 hours. Prior to the exposure, the dorsal surface of each rat was shaved. The rats were then placed in an inhalation exposure chamber with their bodies inside the chamber and their heads outside in a reversed head only exposure position. Thus, the bodies were dermally exposed to sulfuryl fluoride gas but inhalation exposure was prevented. During a 2 week postexposure period, the rats were frequently weighed and detailed clinical examinations were conducted. Behavior patterns and nervous system activity were also assessed by carefully observing the rats for any signs of altered CNS function. The rats were sacrificed and necropsied on postexposure day 15. Samples of brain and of clipped and unclipped skin from the 9599 ppm group were microscopically examined.

No treatment-related adverse effects were observed in any of the rats during or after the 4-hour dermal only exposure at exposure concentrations up to 9599 ppm. This concentration (9599 ppm) is approximately 15-fold greater than the 4-hour whole body
inhalation LC50 for mice (642 ppm). The NOAEL for dermal exposure to sulfuryl fluoride in rats in 9599 ppm. A LOAEL was not observed (>9599 ppm).

This study is Acceptable as a non-guideline study. It was well performed, characterized and reported. It met its objective of assessing the possible toxicity from dermal exposure to high concentrations of sulfuryl fluoride.

No hazard identified. Quantification of risk is not necessary.

6. Short-term Inhalation (1 - 30 days) Exposure

Study Selected: 2-Week Inhalation Toxicity Study in Rabbits

Guideline No.: None

MRID No.: 148956

Executive Summary: In a 2-week subchronic inhalation toxicity study (MRID 148956), three New Zealand white rabbits/sex/exposure group were exposed to sulfuryl fluoride gas (Vikane Gas Fumigant, lot #TWP 830919-408, 99.8% active ingredient) at exposure concentrations of 0, 100, 300, or 600 ppm for 6 hours/day, 5 days/week for a total of 9 exposures (calculated to be equivalent to 0, 0.42, 1.25, or 2.5 mg/L, respectively, for both males and females). The animals were sacrificed and examined the day after the last exposure. Mortality, clinical signs, body weights, hematology, clinical chemistries and organ weights were evaluated and gross and microscopic examinations were performed.

At 600 ppm, one female rabbit convulsed after 5 exposures, which caused a fractured tibia, and another female rabbit may have convulsed after 6 exposures because it had a fractured vertebrum (a convulsion was not actually observed). Both animals were euthanized. The surviving rabbits were noted to be slightly hyperactive during the treatment period. At necropsy, treatment-related focal malacia (necrosis) was observed in the cerebrum of all surviving 600 ppm animals and in 1 male and 1 female animal at 300 ppm. In addition, vacuolation of the same part of the cerebrum was observed in all surviving 600 ppm animals and all 300 ppm animals. The lesion in the cerebrum was restricted to the globus pallidus and putamen (basal nuclei) and external and internal capsules (myelinated tracts). Most rabbits at 600 ppm and 300 ppm had moderate inflammation of the nasal tissues and some had acute inflammation of the trachea. One female at 600 ppm had inflammation of the bronchi and bronchioles also. No exposure-related changes were observed in rabbits in the 100 ppm exposure group.

The LOAEL is 300 ppm (1.25 mg/L), based on focal malacia and vacuolation in the cerebrum and on inflammation of the nasal tissues and trachea. The NOAEL is 100 ppm (0.42 mg/L).
This subchronic inhalation toxicity study is classified as an **Acceptable/Non-Guideline** study. Only 3 rabbits/sex/dose level were used and the duration of the study was only 2 weeks (9 exposures). The study was well conducted and reported.

**Dose and Endpoint for Risk Assessment:** NOAEL = 0.42 mg/L (100 ppm), based on malacia (necrosis) in the cerebrum in 1 male and 1 female, vacuolation in the cerebrum in all male and females, and moderate inflammation of nasal tissues in most animals and acute inflammation of the trachea in some animals at the LOAEL of 1.25 mg/L (300 ppm).

**Comments about Study/Endpoint:** The results of this study provide the best information available pertaining to assessment of the potential short-term (1 - 30 days) risk via inhalation exposure.

**Comment:** The HIARC determined there is no need to quantify the inhalation risk resulting from a single residential or occupational inhalation exposure to sulfuryl fluoride. No treatment-related neurotoxic or other effects were observed in a specially designed acute neurotoxicity inhalation study (MRID 42772001) in which rats were exposed on two consecutive days for 6 hours/day to concentrations up to 300 ppm of sulfuryl fluoride (equivalent to 1.25 mg/L). Further, no appropriate endpoints resulting from a single inhalation exposure were identified in any of the available toxicity studies on sulfuryl fluoride. Therefore, no hazard attributable to a single inhalation exposure was identified and quantification of risk for single inhalation exposures was determined to be unnecessary. The HIARC noted that poisonings and fatalities have been reported in humans following inhalation exposure to sulfuryl fluoride. The severity of these effects has depended on the concentration of sulfuryl fluoride and the duration of exposure. Short-term inhalation exposure to high concentrations has caused respiratory irritation, pulmonary edema, nausea, abdominal pain, central nervous system depression, and numbness in the extremities. In addition, there have been two reports of deaths of persons entering houses treated with sulfuryl fluoride. One person entered the house illegally and was found dead the next morning. A second person died of cardiac arrest after sleeping in the house overnight following fumigation. A plasma fluoride level of 0.5 mg/L (10 times normal) was found in this person following exposure. These acute poisonings in humans, however, occurred only after label directions were grossly violated and persons were subsequently exposed to extremely high concentrations of sulfuryl fluoride.

7. **Intermediate-term Inhalation (1-6 Months) Exposure**

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Study Selected: 90-Day Subchronic Inhalation Toxicity Study in Rabbits

Guideline No.: 870.3465

MRID No.: 40890901

Executive Summary: See *Chronic Reference Dose (RfD)*

Dose and Endpoint for Risk Assessment: NOAEL = 0.13 mg/L (30 ppm), based on vacuolation of white matter in the brain of females at the systemic LOAEL of 0.42 mg/L (100 ppm).

Comments about Study/Endpoint: The route and dosing regimen of this study is appropriate for the route and duration of exposure of concern.

8. **Long-term Inhalation (Several Months to Lifetime) Exposure**

Study Selected: 90-Day Subchronic Inhalation Toxicity Study in Rabbits

Guideline No.: 870.3465

MRID No.: 40890901

Executive Summary: See *Chronic Reference Dose (RfD)*

Dose and Endpoint for Risk Assessment: NOAEL = 0.13 mg/L (30 ppm), based on vacuolation of white matter in the brain of females at the systemic LOAEL of 0.42 mg/L (100 ppm).

Comments about Study/Endpoint: This study was used to establish the chronic RfD. See comments under the Chronic Reference Dose (RfD) section.

9. **Margins of Exposure for Occupational/Residential Risk Assessments**

Summary of target Margins of Exposure (MOEs) for risk assessment.

<table>
<thead>
<tr>
<th>Route Duration</th>
<th>Short-Term (1-30 Days)</th>
<th>Intermediate-Term (1 - 6 Months)</th>
<th>Long-Term (&gt; 6 Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occupational (Worker) Exposure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhalation</td>
<td>100</td>
<td>100</td>
<td>300</td>
</tr>
<tr>
<td>-----------</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>Residential (Non-Dietary) Exposure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhalation</td>
<td>1000</td>
<td>1000</td>
<td>3000</td>
</tr>
</tbody>
</table>

For Occupational Exposure:

For short-term (1 - 30 days) and intermediate-term (1-6 months) inhalation exposure risk assessments, a MOE of 100 is required. This is based on the conventional uncertainty factor of 100X (10X for intraspecies extrapolation and 10X for interspecies variation).

For long-term (>6 months) inhalation exposure risk assessments, a MOE of 300 is required. An extra uncertainty factor of 3X should be applied to the conventional uncertainty factor of 100X to account for using a subchronic (90-day) study, rather than a chronic study, for this long-term risk assessment (UF$_S$). A 3x (as opposed to a 10x) is adequate because the LOAEL (100 ppm) in the subchronic study is similar to the LOAELs established following long-term exposures (1-2 years) in mice (80 ppm), rats (80 ppm) and dogs (80 ppm).

For Residential Exposure:

For short-term (1 - 30 days) and intermediate-term (1-6 months) inhalation exposure risk assessments, a MOE of 1000 is required. This is based on the conventional uncertainty factor of 100X (10X for intraspecies extrapolation and 10X for interspecies variation) and an additional database uncertainty factor (UF$_{DB}$) of 10X for lack of a DNT study.

For long-term (>6 months) inhalation exposure risk assessments, a MOE of 3000 is required. This is based on the conventional uncertainty factor of 100X (10X for intraspecies extrapolation and 10X for interspecies variation), an additional database uncertainty factor (UF$_{DB}$) of 10X for lack of a DNT study, and an extra factor of 3X to account for using a subchronic (90-day) study, rather than a chronic study, for this long-term risk assessment (UF$_S$). A 3x (as opposed to a 10x) is adequate because the LOAEL (100 ppm) in the subchronic study is similar to the LOAELs established following long-term exposures (1-2 years) in mice (80 ppm), rats (80 ppm) and dogs (80 ppm).

10. **Recommendation for Aggregate Exposure Risk Assessments**
For short-, intermediate-, and long-term aggregate exposure risk assessments, the oral and inhalation exposures can be combined due to the common end point (vacuolation of white matter) via these routes. Dermal risk assessments are not required.

III. CLASSIFICATION OF CARCINOGENIC POTENTIAL

1. Combined Chronic Toxicity/Carcinogenicity Study in Rats  

Executive Summary: In a combined chronic toxicity/carcinogenicity study (MRID 43354902), groups of 50 male and 50 female Fisher 344 rats were subjected to whole-body inhalation exposure to sulfuryl fluoride (93.6 - 99.7% a.i.; Lot No. WP 880329-752, WP 901011-907, WP 910321-918, WP 910826-929, WP 920131-940) at concentrations of 0, 5, 20, or 80 ppm for 6 hours/day, 5 days/week for 2 years (calculated to be equivalent to 0, 3.5, 14, or 56 mg/kg/day for males and to 0, 3.9, 16, or 62 mg/kg/day for females). Fifteen animals of each sex per group were similarly exposed to sulfuryl fluoride for 12 months (satellite study) for interim evaluation of toxicity. The satellite study identified the kidneys, lungs, and teeth as targets of sulfuryl fluoride.

All main study male and female rats exposed to 80 ppm of sulfuryl fluoride died before termination at 2 years; the death in more than 90% of each sex was due to very severe chronic glomerulonephropathy (advanced chronic renal disease), which resulted in renal failure. Other effects related to renal failure or directly to exposure to 80-ppm of the test material included decreased body weight gain, decreased specific gravity of urine, serum chemistry changes indicative of renal failure (elevated urea nitrogen, creatinine, triglycerides, and cholesterol, and phosphorus and depressed levels of total protein, albumin, and chloride). Pathologic lesions in 80-ppm group rats related to renal failure included parathyroid hyperplasia, osteodystrophy, splenic and lymph node atrophy, gastric erosion, cardiac thrombosis, lung congestion, and mineralization in a variety of tissues. Pathologic lesions considered to be related directly to exposure to 80 ppm of sulfuryl fluoride in male and female rats included adrenal cortical hemorrhage, hepatocellular atrophy, reactive hyperplasia and inflammation of the respiratory epithelium of the nasal turbinates, vacuolation of the cerebrum and thalamus/ hypothalamus, adrenal cortical hemorrhage, aggregates of alveolar macrophages, and dental fluorosis. The only treatment-related effects occurring at 20 ppm was a significantly increased incidence of dental fluorosis in males (10/50 vs 0/50 in controls, p<0.01). There was no increase in histopathologic lesions in females exposed to 20 ppm of sulfuryl fluoride. No exposure-related toxic effects occurred in male or female rats exposed to 5 ppm of sulfuryl fluoride.

The LOELs are 20 ppm (14 mg/kg/day) for male rats based on dental fluorosis and 80 ppm (62 mg/kg/day) for female rats based on primary and secondary renal
toxicity; effects in the adrenal cortex, brain, eyes, liver, nasal tissue, respiratory tract; and dental fluorosis. The corresponding NOELs are 5 ppm (3.5 mg/kg/day) for male rats and 20 ppm (16 mg/kg/day) for female rats.

At the concentrations tested, there were no increases in exposure-related tumor incidences when compared with control incidences. Dosing was considered adequate based on the survival of adequate numbers of animals in the 20-ppm groups (76% in males and 66% in females) at study termination despite the fact all 80-ppm group rats died before termination of the study.

This combined chronic/oncogenicity study in the rat is classified as Acceptable/Guideline and satisfies the Subdivision F guideline requirement for a combined chronic/oncogenicity study in rats (§83-5).

Discussion of Tumor Data: At the concentrations tested in this study, there were no increases in exposure-related tumor incidences when compared with control incidences.

Adequacy of the Dose Levels Tested: Dosing was considered adequate based on the survival of adequate numbers of animals in the 20 ppm groups (76% in males and 66% in females) at study termination despite the fact that all 80 ppm group rats died before termination of the study.

2. Carcinogenicity Study in Mice

Guideline No.: 870.4200

MRID No.: 43354903

Executive Summary: In a carcinogenicity toxicity study (MRID 43354903), sulfuryl fluoride (99.8% a.i., Lot #WP 880329-752, WP 901011-907, WP 910321-918, WP 910826-929) was administered by inhalation to 50 CD-1 mice/sex/dose at dose levels of 0, 5, 20, and 80 ppm in air 6 hours/day, 5 days/week for 18 months (estimated doses of 0, 4.96, 19.84, and 79.35 mg/kg/day). An additional 10 animals/sex/dose were treated for 12 months in a satellite study.

Mortality was significantly increased (p < 0.05) in females after treatment for 18 months at 80 ppm sulfuryl fluoride. Mortality was also increased in males, but the increase was not statistically significant (mortality: 80 ppm females, 72%; controls, 36%; 80 ppm males, 64%; controls, 46%). The mean body weight gain was decreased in both sexes at 80 ppm (males decreased 37%; females 35% compared to controls). The absolute weights of brain, kidney, and liver were significantly (p < 0.05) decreased in both sexes at 80 ppm compared to controls. Increased incidence of vacuolation in the cerebrum of the brain were seen in both sexes at 80 ppm (13/50 and 12/50 for males and females, respectively; 0/50 for both controls; p < 0.001). An increased incidence of thyroid epithelial hypertrophy was seen in both sexes compared to the control group, but was
observed more frequently in males (p ≤ 0.01) than females (p ≤ 0.05) (males: 80 ppm, 20/50; females: 80 ppm, 6/50; controls, 1/50 for both sexes). Thymus atrophy was significantly increased (p ≤ 0.05) in males at 80 ppm (80 ppm, 6/50; control 1/50). Significantly (p ≤ 0.01) increased incidences of heart thrombus and chronic lung congestion were seen in females at 80 ppm (heart thrombus: 80 ppm, 14/50; controls, 4/50; lung congestion: 19/50; controls, 6/50). Amyloidosis, commonly seen in aging CD-1 mice was a major cause of death in the study. The incidence of severe to very severe kidney glomerular amyloidosis was significantly (p ≤ 0.05) increased in females at 80 ppm (80 ppm, 32/50; control, 20/50).

The LOEL is 80 ppm (79.35 mg/kg/day) for both sexes, based on decreased survival, especially in females, decreased body weight gain and cerebral vacuolation in the brain in both sexes, thyroid epithelial hypertrophy, especially in males, and increased incidences of heart thrombus and lung congestion in females. The NOEL is 20 ppm (19.84 mg/kg/day) for both sexes.

At the doses tested, there was not a treatment related increase in tumor incidence when compared to controls. Major organs examined included liver, thyroid, kidney, testes, ovary, bladder, lung, and brain. Dosing was considered adequate based on decreased weight gain and increased microscopic brain lesions in both sexes, increased thyroid hypertrophy in males, and increased heart thrombus and lung congestion in females at the high dose.

This carcinogenicity study in the mouse is Acceptable, and does satisfy the guideline requirement for a carcinogenicity study (83-2b) in mice.

Discussion of Tumor Data: At the concentrations tested in this study, there were no increases in exposure-related tumor incidences when compared with control incidences.

Adequacy of the Dose Levels Tested: Dosing was considered adequate based on decreased body weight gain and increased microscopic brain lesions in both sexes, increased thyroid hypertrophy in males, and increased heart thrombus and lung congestion in females at the high dose.

3. **Classification of Carcinogenic Potential**

Sulfuryl fluoride is classified as “not likely to be carcinogenic to humans” according to the EPA *Draft Proposed Guidelines for Carcinogen Risk Assessment* (July 2, 1999). This classification is based on the lack of evidence of carcinogenicity in male and female rats as well as in male and female mice and on the lack of genotoxicity in an acceptable battery of mutagenicity studies performed on the technical grade product.
IV. MUTAGENICITY

There are three acceptable mutagenicity studies on technical grade sulfuryl fluoride. Results in all three studies were negative for mutagenic potential. These three mutagenicity studies satisfy the mutagenicity guidelines originally published in the 1982 Pesticide Assessment Guidelines, Subdivision F, Hazard Evaluation: Human and Domestic Animals, Series 84; Mutagenicity; and published again in 1984. These ‘old’ guidelines for mutagenicity testing are applicable to sulfuryl fluoride because this chemical has been registered since 1959.

1. **Ames Assay (Salmonella typhimurium)**

   **Guideline No.: 870.5100**

   **MRID No.: 41603001**

   **Executive Summary:** In a reverse gene mutation assay in bacteria (MRID 41603001), strains TA98, TA100, TA1535 and TA1537 of *S. typhimurium* were exposed to sulfuryl fluoride gas (Lot No. 874, 99.6% a.i.) diluted in sterile compressed air. Tester strains in open Petri dishes were each exposed for 4 hours to six concentrations of the gas in sealed desiccators modified for use as exposure chambers. After exposure, cultures were removed, covered, and reincubated for an additional 2 days. In the absence and in the presence of mammalian metabolic activation (S9-mix), the TA-strains were exposed to sulfuryl fluoride concentrations of 0, 300, 1000, 3000, 10000 and 30000 ppm. All platings were in triplicate. The mammalian metabolic activation system (S9-mix) was provided by commercially purchased hepatic microsomes rat liver homogenate (prepared from adult Sprague-Dawley male rats pretreated with Aroclor 1254) plus NADPH(H)-generating cofactors added just before use. Sham-treated (compressed air only) and untreated cultures served as negative controls. Other groups of cultures treated with strain-specific mutagens served as positive controls.

   No toxicologically significant increase in the mutant frequency was consistently seen in testing up to toxic concentrations (30000 ppm) of sulfuryl fluoride, with and without metabolic activation. The negative and positive controls induced the appropriate responses in the corresponding strains. **There was no consistent evidence of induced mutant colonies over background.**

   This study is classified as Acceptable/guideline. It satisfies the requirement for FIFRA Test Guideline [OPPTS 870.5100] for *in vitro* mutagenicity (bacterial reverse gene mutation) data.

2. **UDS Assay (Unscheduled DNA synthesis in primary male rat hepatocytes)**

   **Guideline No.: 870.5550**

   **MRID No. 42179802**
Executive Summary: In an unscheduled DNA synthesis (UDS) assay in rat primary hepatocytes (MRID 42179802), cultures of primary hepatocytes from male Sprague Dawley (Crl:CD BR strain) rats were exposed to sulfuryl fluoride gas (Lot No. 874, 97.4% a.i.) at concentrations of 102, 204, 408, 612, 816, 1020 and 1530 ppm. The gas was injected into cultures and the cells were exposed to the gas for 18-19 hours. Doses of 1530 ppm and higher were too cytotoxic to assay for UDS. Sham-treated (air only) cultures served as negative controls. Cultures treated with 2-acetylaminofluorene served as positive controls.

Sulfuryl fluoride did not cause an increase in unscheduled DNA synthesis above negative controls at any of the dose levels tested and none of the test cultures contained cells in repair. Mean nuclear counts were lower than cytoplasmic counts for all doses tested. The positive control produced a marked increase in nuclear grain count over negative controls and 100% of these cells were in repair. **No evidence of increased unscheduled DNA synthesis over negative controls was observed at concentrations of sulfuryl fluoride up to 1020 ppm.**

This study is classified as **Acceptable/guideline.** It satisfies the requirement for FIFRA Test Guideline [OPPTS 870.5550] for unscheduled DNA synthesis in mammalian cells in culture data.

3. **In vivo Cytogenetics (Micronucleus assay in mouse bone marrow cells)**

   Guideline No.: 870.5395

   MRID No.: 41769102, 41448601

   Executive Summary: In a mouse bone marrow micronucleus assay (MRID 41769102, 41448601), five CD-1 mice/sex/dose were exposed to sulfuryl fluoride gas (Lot No. WP880329 752 Mar/88, 99.6% a.i.) in compressed air. The mice were exposed for 4 hours to 48, 180 or 520 ppm TWA concentrations of the gas. Bone marrow cells were harvested 24, 48 and 72 hours post-treatment. The highest concentration of sulfuryl fluoride tested in this study (520 ppm) was determined in a separate study (MRID 41448601) to be approximately 80% of the LC50 (660/642 ppm in male/female CD-1 mice, respectively). Sham-treated (compressed air only) animals served as negative controls and additional animals exposed to heated benzene (8696 or 8872 ppm) served as positive controls. A final group of animals given cyclophosphamide (120 mg/kg) once by oral gavage served as an additional positive control. All positive control animals were sacrificed 24 hours post-treatment and bone marrow cells were harvested at that time. One thousand polychromatic erythrocytes (PCE) per animal were examined for the presence of micronucle (MN-PCE), and the ratio of PCE to normochromatic erythrocytes (NCE) was determined.

   Two test females died shortly after exposure to 520 ppm sulfuryl fluoride, but all other treated test animals survived without visible clinical effects. Three of the benzene-exposed
males also died, while several others showed transient respiratory deficits. No adverse clinical effects were observed in the animals treated with cyclophosphamide. In neither males nor females treated with sulfuryl fluoride were any significant differences from negative controls in MN-PCE counts found, nor in ratios of PCE to NCE. In contrast, significantly elevated MN-PCE counts were recorded for benzene-exposed males, but only a slight increase was recorded for females (consistent with other published results). Both sexes responded with highly significant positive results to orally administered cyclophosphamide. There was no significant increase in the frequency of micronucleated polychromatic erythrocytes in bone marrow at any sulfuryl fluoride concentration or treatment time used in this study.

This study is classified as Acceptable/guideline. It satisfies the requirement for FIFRA Test Guideline [OPPTS 870.5395] for in vivo cytogenetic mutagenicity data.

V. HAZARD CHARACTERIZATION

Technical grade sulfuryl fluoride (Vikane Gas Fumigant, Profume Gas Fumigant, 99.8% active ingredient) is marketed as a liquified gas in pressurized steel cylinders. The acute oral LD$_{50}$ of sulfuryl fluoride has been estimated to be approximately 100 mg/kg in rats (Toxicity Category II). The acute inhalation LC$_{50}$ in mice (4 hour exposure) is 660 ppm (2.56 mg/L) in males and 642 ppm (2.49 mg/L) in females. The acute inhalation LC$_{50}$ in rats (1 hour exposure) is 17.5 mg/L. Based on the use pattern for sulfuryl fluoride and several reported incidences of human poisonings in the RED (published in September, 1993), the Agency has classified sulfuryl fluoride as Toxicity Category I for acute inhalation toxicity. The acute dermal toxicity study (assumed Toxicity Category of IV), the primary skin irritation study (assumed Toxicity Category of IV), the primary eye irritation study (assumed Toxicity Category of I), and the dermal sensitization study (assumed to be a non-sensitizer) have been waived. In a non-guideline study in which rats were dermally exposed (with no inhalation exposure) to vapors of sulfuryl fluoride gas at an exposure concentration of 9599 ppm for 4 hours, no treatment-related adverse effects were observed.

In 2-week inhalation studies in rats, dogs and rabbits, different target organs were affected. In rats, the primary target organ was the kidneys, in which severe histopathological lesions were observed. In dogs, the primary target organ was the upper respiratory tract, in which minimal inflammation was observed. Intermittent tremors and tetany were also noted in dogs. In rabbits, the primary target organ was the brain, in which malacia (necrosis) and vacuolation were observed in the cerebrum. Inflammation of the upper respiratory tract was also noted in rabbits. In 90-day inhalation studies in rats, dogs, rabbits and mice, the brain was the major target organ. Malacia and/or vacuolation were observed in the white matter of the brain in all four species. The portions of the brain most often affected were the caudate-putamen nucleus in the basal ganglia, the white fiber tracts in the internal and external capsules, and the globus pallidus of the cerebrum. In dogs and rabbits, clinical signs of neurotoxicity (including tremors, tetany, incoordination, convulsions and/or hind limb paralysis) were also observed. Inflammation of the nasal passages
and histiocytosis of the lungs were observed in rats and rabbits; but not in dogs, in which species inflammation of the upper respiratory tract was more prominent in the 2-week study. In rats, kidney damage was also observed. In mice, follicular cell hypertrophy was noted in the thyroid gland. Decreased body weights and body weight gains were also observed in rats, dogs and mice.

In 1-2 year inhalation studies in rats, dogs and mice, target organs were the same as in the 90-day studies. In rats, severe kidney damage caused renal failure and mortalities in many animals. Additional gross and histopathological lesions in numerous organs and tissues were considered to be secondary to the primary effect on the kidneys. Other treatment-related effects in rats included effects in the brain and respiratory tract. In dogs and mice, increased mortalities, malacia and/or vacuolation in the white matter in the brain, histopathology in the lungs, and follicular cell hypertrophy in the thyroid gland were observed. Decreased body weights and body weight gains were also noted in all three species. No evidence of carcinogenicity was observed in either the combined chronic toxicity/carcinogenicity study in rats or in the 18-month carcinogenicity study in mice.

In many subchronic and chronic inhalation studies in rats, dogs, and rabbits, dental fluorosis was the most sensitive toxic effect observed in the study. In two 90-day studies in rats and rabbits, in which serum fluoride levels were determined, an increased serum level of fluoride anions was observed at even lower dose levels. The increased serum fluoride levels were due to the conversion of sulfuryl fluoride to fluoride anions in the body.

In specially designed acute and subchronic inhalation neurotoxicity studies in rats, several electrophysiological parameters (EEGs) were recorded in addition to observations for clinical signs of neurotoxicity, functional observational battery (FOB) and motor activity testing, and/or neurohistopathologic examination. Following two exposures on consecutive days for 6 hours/day at 300 ppm of sulfuryl fluoride (354 mg/kg/day), no treatment-related neurotoxic effects were noted. In a 90-day study, changes in some EEG patterns were observed at 100 ppm (80 mg/kg/day) and in several additional patterns at 300 ppm (240 mg/kg/day). Vacuolation of the white matter in the cerebrum was also observed at 300 ppm in this study. In a specially designed 1-year chronic inhalation neurotoxicity study in rats, no treatment-related neurotoxic effects were observed at 80 ppm (56 mg/kg/day). EEGs were not recorded in this study.

In a developmental toxicity inhalation study in rats, no developmental toxicity was observed in the pups. Although no maternal toxicity was observed in this study at the highest dose tested, significant maternal toxicity (decreased body weight body weight gain and food consumption) was observed in a previously conducted range-finding study at a slightly higher dose level. In a developmental toxicity inhalation study in rabbits, decreased fetal body weights were observed in the pups. At the same dose level, decreased body weight and body weight gain were observed in the dams. In a 2-generation reproduction inhalation study in rats, vacuolation of the white matter in the brain, pathology in the lungs, and decreased body weights were observed in the parental animals. Decreased pup body weights in the F1 and F2 generations were observed in the offspring. No effects on reproductive parameters were noted in this study. No quantitative or
qualitative evidence of increased susceptibility of fetuses or pups was observed in the
developmental toxicity or reproduction studies on sulfuryl fluoride.

A battery of mutagenicity studies was negative for genotoxic potential. The studies included an
Ames assay in Salmonella typhimurium, an unscheduled DNA synthesis assay in primary rat hepatocytes, and a micronucleus assay in mouse bone marrow cells.

Sulfuryl fluoride is classified as a “not likely to be carcinogenic to humans” according to the EPA Draft Proposed Guidelines for Carcinogen Risk Assessment (July 2, 1999).

Poisonings and fatalities have been reported in humans following inhalation exposure to sulfuryl fluoride. The severity of these effects has depended on the concentration of sulfuryl fluoride and the duration of exposure. Short-term inhalation exposure to high concentrations has caused respiratory irritation, pulmonary edema, nausea, abdominal pain, central nervous system depression, and numbness in the extremities. In addition, there have been two reports of deaths of persons entering houses treated with sulfuryl fluoride. One person entered the house illegally and was found dead the next morning. A second person died of cardiac arrest after sleeping in the house overnight following fumigation. A plasma fluoride level of 0.5 mg/L (10 times normal) was found in this person following exposure. Prolonged chronic inhalation exposure to concentrations of sulfuryl fluoride gas significantly above the threshold limit value (TLV) of 5 ppm have caused fluorosis in humans because sulfuryl fluoride is converted to fluoride anion in the body. Fluorosis is characterized by binding of fluoride anion to teeth (causing mottling of the teeth) and to bone.

VI. DATA GAPS

A general metabolism and pharmacokinetics study in rats (Guideline No.: 870.7485) is not available. The requirement for this study was waived in the Reregistration Eligibility Document (RED) published in 1993.

An inhalation developmental neurotoxicity study in rats (Guideline No. 870.6300) is required to be performed and submitted in order to more clearly and fully characterize the potential for neurotoxic effects in young animals. It is recommended that the registrant consult with the Agency regarding the protocol for this study prior to initiation of the study.

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Sulfuryl fluoride is marketed as a liquified gas in pressurized steel cylinders and causes freezing of skin and eye tissues on contact. Therefore, no dermal or eye irritation studies are required.

<table>
<thead>
<tr>
<th>GDLN</th>
<th>Study Type</th>
<th>MRID</th>
<th>Results</th>
<th>Tox Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>81-1</td>
<td>Acute Oral (1959)</td>
<td></td>
<td>M: LD₅₀ = 100 mg/kg</td>
<td>II*</td>
</tr>
<tr>
<td></td>
<td>Rats</td>
<td>43314</td>
<td>F: LD₅₀ = 100 mg/kg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Supplementary**</td>
<td></td>
<td>(See TXR 2673)</td>
<td></td>
</tr>
<tr>
<td>81-2</td>
<td>Acute Dermal</td>
<td>-----</td>
<td>Study Waived *</td>
<td>IV*</td>
</tr>
<tr>
<td>81-3</td>
<td>Acute Inhalation (1990)</td>
<td>41769101</td>
<td>M: LC₅₀ = 660 ppm (2.56 mg/L)</td>
<td>I*</td>
</tr>
<tr>
<td></td>
<td>Mice</td>
<td></td>
<td>F: LC₅₀ = 642 ppm (2.49 mg/L)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acceptable***</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>81-3</td>
<td>Acute Inhalation (1959)</td>
<td>238663</td>
<td>LC₅₀ = 17.5 mg/L</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>Rats</td>
<td>(See TXR 2673)</td>
<td>1 hr exposure</td>
<td></td>
</tr>
<tr>
<td>81-4</td>
<td>Primary Eye Irritation</td>
<td>-----</td>
<td>Study Waived *</td>
<td>I*</td>
</tr>
<tr>
<td></td>
<td>Rabbits</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>81-5</td>
<td>Primary Skin Irritation</td>
<td>-----</td>
<td>Study Waived *</td>
<td>IV*</td>
</tr>
<tr>
<td></td>
<td>Rabbits</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>81-6</td>
<td>Dermal Sensitization</td>
<td>-----</td>
<td>Study Waived *</td>
<td>Non-</td>
</tr>
<tr>
<td></td>
<td>Guinea Pigs</td>
<td></td>
<td></td>
<td>Sensitizer</td>
</tr>
<tr>
<td>----</td>
<td>Dermal Vapor Study</td>
<td>41712001</td>
<td>No treatment-related</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>(non-guideline)</td>
<td></td>
<td>adverse effects</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rats</td>
<td></td>
<td>LC₅₀ &gt; 9599 ppm (&gt;40.3 mg/L)</td>
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</tr>
<tr>
<td></td>
<td>4 hr dermal expos</td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acceptable</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Memorandum by M. Lewis (SRRD) to V. Dutch (SRRD), 11/17/99, HED Doc. No. 078003 states the following: “This product is sold as a pressurized liquefied gas. On contact with water, it hydrolyzes initially to chlorosulfonic acid and hydrogen fluoride and ultimately to sulfuric acid and hydrogen fluoride. Accordingly, it must be contained and used with caution. Based on this and other information, the Agency will waive the primary eye irritation study (81-4) and classify this product as Toxicity Category I. Based on the route of application for this product and other information available, the Agency will waive and assign toxicity categories to the following studies: acute dermal study (81-2) -Toxicity Category IV, primary dermal irritation study (81-5)-Toxicity Category IV, skin sensitization study (81-6)-non-sensitizer. PR Notice 84-5 requires labeling which adequately addressed these routes of exposure”. No further rationale was provided.

** A new acute oral study is not required. See M. Lewis (SRRD), above.

*** See also TXR 0008392.


**VIII. SUMMARY OF TOXICOLOGY ENDPOINT SELECTION**

The doses and toxicological endpoints selected for various exposure scenarios are summarized below.

<table>
<thead>
<tr>
<th>Exposure Scenario</th>
<th>Dose Used in Risk Assessment, UF</th>
<th>Special FQPA SF and Level of Concern for Risk Assessment</th>
<th>Study and Toxicological Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Dietary</td>
<td>None, UF = N/A</td>
<td>Not applicable</td>
<td>No toxicological endpoint</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>attributable to a single exposure</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>was identified in the available</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>toxicology studies on sulfuryl</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>fluoride.</td>
</tr>
<tr>
<td>Chronic Dietary (All populations)</td>
<td>NOAEL = 8.5 mg/kg/day, UF = 3000</td>
<td>FQPA SF = 1X Cpad = Chronic RfD = 0.003 mg/kg/day</td>
<td>90-Day Inhalation - Rabbit</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>LOAEL = 28 mg/kg/day based on</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>vacuolation of white matter in</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>the brain of females.</td>
</tr>
<tr>
<td>Incidental Oral (All durations)</td>
<td>None</td>
<td>Not applicable</td>
<td>Due to sulfuryl fluoride being a</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>gas and pattern of use, no</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>significant incidental oral</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>exposure is anticipated.</td>
</tr>
<tr>
<td>Dermal (All durations)</td>
<td>None</td>
<td>Not applicable</td>
<td>Due to sulfuryl fluoride being a</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>gas and pattern of use, no</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>significant dermal exposure is</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>anticipated. No hazard identified,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>therefore, no quantification is</td>
</tr>
<tr>
<td>Short-Term Inhalation (1 to 30 days)</td>
<td>Inhalation study NOAEL = 0.42 mg/L</td>
<td>Residential LOC for MOE = 1000</td>
<td>2-Week Inhalation - Rabbit</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>LOAEL = 1.25 mg/L based on</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>malacia (necrosis) and vacuolation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>in brain, inflammation of nasal</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>tissues and trachea.</td>
</tr>
<tr>
<td>Intermediate-Term Inhalation (1 to 6 months)</td>
<td>Inhalation study NOAEL = 0.13 mg/L</td>
<td>Residential LOC for MOE = 1000</td>
<td>90-Day Inhalation - Rabbit</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>LOAEL = 0.42 mg/L based on</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>vacuolation of white matter in</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>the brain of females.</td>
</tr>
<tr>
<td>Exposure Scenario</td>
<td>Dose Used in Risk Assessment, UF</td>
<td>Special FQPA SF and Level of Concern for Risk Assessment</td>
<td>Study and Toxicological Effects</td>
</tr>
<tr>
<td>---------------------------------------</td>
<td>----------------------------------</td>
<td>-------------------------------------------------------</td>
<td>---------------------------------</td>
</tr>
<tr>
<td>Long-Term Inhalation (&gt;6 months)</td>
<td>Inhalation study NOAEL = 0.13 mg/L</td>
<td>Residential LOC for MOE = 3000</td>
<td>90-Day Inhalation - Rabbit LOAEL = 0.42 mg/L based on vacuolation of white matter in the brain of females.</td>
</tr>
<tr>
<td>Cancer (oral, dermal, inhalation)</td>
<td></td>
<td>Occupational LOC for MOE = 300</td>
<td>Classified as “Not likely to be carcinogenic to humans”</td>
</tr>
</tbody>
</table>

UF = uncertainty factor, FQPA SF = Special FQPA safety factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD = population adjusted dose (a = acute, c = chronic) RfD = reference dose, MOE = margin of exposure, LOC = level of concern, NA = Not Applicable

**NOTE:** The Special FQPA Safety Factor recommended by the HIARC assumes that the exposure databases (dietary food, drinking water, and residential) are complete and that the risk assessment for each potential exposure scenario includes all metabolites and/or degradates of concern and does not underestimate the potential risk for infants and children.