CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

Sulfuryl Fluoride
Chemical Code # 618, **Document Processing Number (DPN) #** 50223
SB 950 # 498
August 1, 1986
Revised 2/27/87, 8/25/89, 9/17/90, 1/30/91, 4/10/92, 7/24/92, 9/14/94, 11/17/98, 4/23/02, 6/2/04, 11/27/12 and 4/28/15

DATA GAP STATUS

Chronic toxicity, rat:	No data gap, possible adverse effect
Chronic toxicity, dog:	No data gap, no adverse effect
Oncogenicity, rat:	No data gap, no adverse effect
Oncogenicity, mouse:	No data gap, possible adverse effect (not oncogenic)
Reproduction, rat:	No data gap, no adverse effect
Developmental toxicity, rat:	No data gap, no adverse effect
Developmental toxicity, rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, possible adverse effect
Chromosome effects:	No data gap, no adverse effect
DNA damage:	No data gap, no adverse effect
Neurotoxicity:	Not required at this time (see special studies)

Toxicology one-liners are attached.

All record numbers for the above study types through 284097 (Document No. 50223-0130) were examined. This includes all relevant studies indexed by DPR as of 4/28/15.

In the 1-liners below:
indicates an acceptable study.
Bold face indicates a possible adverse effect.
indicates a study on file but not yet reviewed.

File name: T150428
Revised by [redacted], 4/28/15
NOTE: The following symbols may be used in the Table of Contents which follows:

* = data adequately address FIFRA requirement
† = study(ies) flagged as “possible adverse effect”
N/A = study type not currently required

This record contains summaries of studies. Individual worksheets may be useful for detailed assessment.

Table of Contents

METABOLISM AND PHARMACOKINETICS

**50223-0067 210013, "Sulfuryl Fluoride: Pharmacokinetics and Metabolism in Fischer 344 Rats", (A. L. Mendrala, *et.al.*, Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI, Study ID 001166, 22 May 2002). 4 jugular vein cannulated Fischer 344 male rats and 4 non-cannulated males per group received nose-only inhalation exposure (4 hours) to ^{35}S-Sulfuryl Fluoride at 30 and 300 ppm. Additionally, 18 non-cannulated males per group were exposed (4 hours, nose-only inhalation) to non-radiolabelled sulfuryl fluoride at 30 and 300 ppm and 8 non-cannulated males served as a vehicle control (dry, compressed air) group. Time-weighted actual exposure concentrations over the 4-hour treatment period with ^{35}S-sulfuryl fluoride were 28.4 ppm (0.26 µCi/l of atmosphere) and 274 ppm (2.8 µCi/l of atmosphere) at the 30 ppm and 300 ppm nominal levels respectively. Values were 31.2 ppm and 312 ppm at 30 ppm and 300 ppm respectively for non-radiolabelled sulfuryl fluoride exposures. Venous blood samples (~0.15 ml) were collected from cannulated rats at 0.25, 0.5, 1, 2, 3, and 4 hours during inhalation exposure and 0.5, 1, 2, 4, 6, 12, 24, 36, 48, 72, 96, 120, and 168 hours post-exposure. 3 animals per group exposed to non-radiolabelled sulfuryl fluoride were sacrificed after 2 and 4 hours of exposure and 2, 4, 8, and 20 hours post-exposure to measure fluoride ion content in plasma, brain, and kidney. Additionally, fluoride ion content was determined in plasma, brain, and kidney of 2 control rats per group at the beginning and end of exposure and 4 and 8 hours post-exposure. No radioactivity was detected in expired air of the 300 ppm group animals at 24 hours post-exposure, therefore, collection of expired air was not continued for the remaining sampling intervals of the group and not performed at all for 30 ppm animals. Plasma and RBC Radioactivity after ^{35}S-Sulfuryl Fluoride Exposure. Plasma levels of radioactivity peaked at 5.2 and 37.7 µg-equivalents/g (µg-eq./g) at 30 and 300 ppm respectively at the end of exposure. From the end of exposure to 24 hours post-exposure (α phase), half-lives were 2.6 and 2.4 hours at 30 and 300 ppm respectively, and from 24 hours post-exposure on (β phase), half-lives were 82.7 and 56.2 respectively. RBC radioactivity reached 4.7 and 40.3 µg-eq./q RBC at 30 and 300 ppm respectively at the end of exposure. α phase half lives were 2.5 and 1.1 hours and β phase half-lives were 222 and 139 hours at 30 and 300 ppm respectively. Urinary and Fecal Excretion after ^{35}S-Sulfuryl Fluoride Exposure. Urine contained 85.6% to 88.9% of excreted radioactivity through 7 days post-exposure (580.636 and 4618.051 µg-eq at 30 and 300 ppm respectively). 47% (273 µg-eq.) and 60% (2766 µg-eq) were excreted during the 4 hour exposure period at 30 and 300 ppm respectively. 73 and 777 µg-eq. of radioactivity were recovered in feces through 7 days post-exposure at 30 and 300 ppm respectively. 70 and 704 µg-eq. respectively were recovered through 48 hours

post-exposure. Tissue Distribution after ^{35}S-Sulfuryl Fluoride Exposure. The lungs had the highest concentration of radioactivity, 0.77 and 6.30 µg-eq./g at 30 and 300 ppm respectively 7 days post-exposure. Respiratory turbinates contained 0.312 and 3.491 µg-eq./g, olfactory turbinates - 0.285 and 3.233 µg-eq./g, spleen - 0.394 and 3.075 µg-eq./g, and kidneys - 0.368 and 2.756 µg-eq./g at 30 and 300 ppm respectively. Metabolites Identified Following ^{35}S-Sulfuryl Fluoride Exposure. Two radiolabelled metabolites, sulfate and fluorosulfate, both hydrolysis products of sulfuryl fluoride, were identified in whole blood and urine. Fluoride Ion Analysis Following Non-Radiolabelled Sulfuryl Fluoride Exposure. Metabolic release of fluoride ions was proposed as the cause of toxicity in sulfuryl fluoride exposure (Nitschke, *et. al.* (1986), and Nitschke and Eisenbrandt (2001)), therefore, quantification was performed. Elevated levels of fluoride ion were detected in urine, plasma, kidney, and brain during and after exposure to non-radiolabelled sulfuryl fluoride. Most returned to background levels at varying times post-exposure. Acceptable. ([redacted] and [redacted], 6/1/04).

50223-0105; 264593; "Sulfuryl Fluoride: Limited Pharmacokinetics and Metabolism in F344/DuCrl Rats"; (J.A. Hotchkiss, *et. al.*; Toxicology & Environmental Research and Consulting, The Dow Chemical Co., Midland, MI; Study No. 061180; 4/3/08, revised, 3/28/11); Four male Fischer 344 rats/group were exposed nose-only to 30, or 300 ppm of Sulfuryl Fluoride (lot no. PE13160101, purity: >99.8%) for 2 or 4 hours. Control groups of 4 animals each were euthanized at the time of exposure initiation and after 4 hours of exposure to chamber air. Plasma, kidney and brain samples were recovered from animals up to 8 hours post-exposure. Analysis of the fluoride and fluorosulfate content in the plasma and the fluorosulfate content in the kidneys and brain was performed. Free fluoride was not present in the plasma of the 30 ppm animals at any time during the exposure. The fluorosulfate concentration in the plasma peaked at the conclusion of the 4 hour exposure. No fluorosulfate was isolated in the kidneys or brain of these study animals. For the 300 ppm group, the free fluoride and fluorosulfate concentrations peaked at the conclusion of the 4-hour exposure. The free fluoride content was below limits of quantification by 8 hours post-dose. The fluorosulfate concentration in the kidneys peaked at the termination of the 4-hour exposure and had declined to a negligible level (< 10 nmol/ml) by 4 hours post-exposure. The fluorosulfate level in the brain was less than 10 nmol/ml or below the level of detection in all of the study animals even at the termination of the 4-hour exposure level. No characterization of the fluoride content in the kidneys or brain was available. **Study supplemental.** [redacted], 9/25/12)

50223-0106; 264594; "Nasal and Pulmonary Uptake and Metabolism of Inhaled Sulfuryl Fluoride in Male F344/DuCrl Rats"; (J.A. Hotchkiss, *et. al.*; Toxicology & Environmental Research and Consulting, The Dow Chemical Co., Midland, MI; Study No. 061056; 10/10/06); Young adult male F344/DuCrl rats were exposed nose-only to 0, 3, 30 or 300 ppm of Sulfuryl Fluoride (lot no. PE131601101, purity: >99.8%) for 4 hours. In one cohort, absorption of the test material was measured by limiting exposure to the compound to the upper respiratory tract (URT). These animals absorbed 4.9% of the dose to which they were exposed (300 ppm). This contrasted with the 12.5% of the dose which was absorbed for animals in which normal breathing parameters were maintained (based on results of another study). This observation was borne out in the comparison of the concentration of fluorosulfate recovered from the various tissues which were assayed. In the lung, lung lavagate, and nasal lavagate of the surgically-modified animals, fluorosulfate was not detected in contrast to the measurable levels noted in the unmodified animals. In the nasal area, the fluorosulfate concentration was nearly 10 fold greater for these animals than that the URT-modified rats. The plasma levels of fluorosulfate reflected an even greater difference, 16.8 to 0.9 ug FSO_3/ml, respectively. Only in the olfactory bulbs were the concentrations comparable, 0.8 (URT-modified) vs. 1.1 ug FSO_3/ml (unmodified). No fluorosulfate was detected in the cerebrum of either group. Fluoride was

isolated in the plasma and urine of the URT-unmodified rats exposed to 300 ppm sulfuryl fluoride. The mean concentrations were 2.95 and 68.98 ug F/ml, respectively. In a second assay, in which 4 animals/group were exposed to 3, 30 or 300 ppm of the test material, fluorosulfate and fluoride were recovered from the urine. For the two lower concentrations, fluorosulfate or fluoride were not detected after 6 hours post-exposure. The ratio of fluorosulfate to fluoride in the urine shifted from 0.14 to 1.37 between exposures of 3 and 300 ppm (based on data collected in the 1st 6 hours). The quantity of fluorosulfate recovered from the urine increased from 2.9 ug to 863 ug over the 24-hour collection period as the exposure level increased from 3 to 300 ppm. In an effort to assay the degree to which fluorosulfate further hydrolyzed to free fluoride and sulfate, 25 mg/kg of potassium fluorosulfate was injected iv into the study animals. Over the 48-hour collection period, 41% of the administered dose was recovered as fluoride in the urine (background fluoride was subtracted from the total). A final measure of exposure was explored in which the presence of fluorosulfate adducts to serum albumin was assayed. The levels of adducts to albumin in broncho-alveolar lavagate and plasma were determined after exposure to 3, 30 or 300 ppm of the test material for 4 hours. The presence of the adducts were noted in the 30 and 300 ppm groups and the concentration increased in an exposure-related manner. **Study supplemental.** [redacted], 9/27/12)

50223-0107; 264595; "Quantitation of Fluorosulfate and Fluoride in Selected Tissues Following Inhalation Exposure to Sulfuryl Fluoride in Male F344/DuCrl Rats"; (J.A. Hotchkiss, *et. al.*; Toxicology & Environmental Research and Consulting, The Dow Chemical Co., Midland, MI; Study No. 071193; 2/5/09, revised 6/9/11); Forty male F344/DuCrl rats/group were exposed nose-only to 3, 30 or 300 ppm of Sulfuryl Fluoride (lot no. PE13160101, purity: <99.8%) for 4 hours. Ten animals/group/time point were euthanized at 0, 2, 4, or 8 hours post-exposure. Selected tissues were assayed for the concentrations of fluorosulfate, net total fluoride or net free fluoride. A control group of 10 males were exposed for four hours to chamber air. Tissues from these animals were used to establish background levels for fluoride. For the 3 ppm group, fluorosulfate was present in the plasma, kidneys, and lungs at the end of the exposure period. By four hours post-exposure, the fluorosulfate could only be isolated in the lung tissue. At the 30 and 300 ppm exposure levels, the concentration of fluorosulfate increased in these tissues, in the plasma and in the nasal tissue in an exposure-related manner. No fluorosulfate was isolated in the cerebrum even at the highest exposure level. At the 3 ppm exposure level, the presence of net total fluoride was noted at the termination of the exposure in the plasma, kidney, lung, and nasal tissue. Only in the nasal tissue was net free fluoride present. For the 30 and 300 ppm exposure groups, the net total fluoride concentrations increased in an exposure-related manner in the plasma and all of the tissues assayed (including cerebrum and olfactory tissue). At 30 ppm, by 8 hours post-exposure, the net total fluoride was below the limits of detection for all of the assayed sites except for the nasal tissue. At the 300 ppm exposure level, net total and net free fluoride concentrations were sufficient to permit the calculation of elimination half-lives for all of the assayed sites except for the kidneys (due to technical difficulties in assessing the fluorosulfate content) and the nasal tissue (elimination was not readily evident up to 8 hours post-exposure). The elimination half-lives for fluorosulfate ranged from 1.07 to 1.80 hours for plasma, kidneys, lung and nasal tissue at the 300 ppm exposure level. The elimination half-lives for net free fluoride at the 300 ppm exposure level ranged from 2.14 to 2.61 hours for plasma, lung and cerebrum. Although elimination half-lives were calculated for some of the tissues at the 30 ppm exposure level, a greater degree of variability in the concentrations of the fluorosulfate and/or net free fluoride resulted in elimination values with much greater variability; 0.97 hours (cerebrum, net free fluoride) to 11.3 hours (lung, fluorosulfate). **Study supplemental** (non-guideline study). ([redacted], 10/2/12)

50223-0108; 264596; "Sulfuryl Fluoride: Limited Pharmacokinetics of Repeated 6-Hour/Day Inhalation Exposures, Conducted for Two Weeks, in F344/DuCrl Rats"; (J.A. Hotchkiss, *et. al.*; Toxicology & Environmental Research and Consulting, The Dow Chemical Co., Midland, MI; Study No. 101159; 6/30/11); Male F344 DuCrl rats were exposed whole body to 0, 3, 30 or 300 ppm of Sulfuryl Fluoride Technical (lot no. WH27160101; purity: 99.8%) for 6 hours/day, five days per week for two weeks. In Group 1, 25 animals/group were exposed and blood was drawn from the jugular vein of 5 animals/group/time point prior to exposure on study days 1, 5, 8, and 12. These animals were euthanized immediately after exposure on that designated day. Another cohort of 5 animals/group was scheduled to euthanized on study day 15 (more than 60 hours after the last exposure was completed). This sacrifice was not performed. The concentrations of net free fluoride and fluorosulfate were assayed in the plasma, kidneys and cerebrum of all of the Group 1 animals. In Group 2, 24 animals/group were exposed and urine was scheduled to be collected from 4 animals/group/time point after exposure on study days 1, 5, and 12. After 18 hours of urine collection, 8 animals/group/time were euthanized and blood was pooled from 4 animals each to assay for net free fluoride and fluorosulfate, respectively. No collection of urine or sacrifice was performed on study 5. Kidneys and cerebrum from each animal were dissected and retained for possible analysis for net free fluoride and fluorosulfate. The concentrations of net free fluoride in the plasma, kidneys and cerebrum were exposure-related. Fluorosulfate was present in the plasma in an exposure-related manner. However, it was recovered in the kidneys only at the highest exposure level and was not recovered in the cerebrum. There was no apparent retention of either analyte between the 1st and 10th exposures. This was borne out by the relatively short elimination half-lives of both net free fluoride and fluorosulfate in the plasma. The elimination half-lives for net free fluoride at the 300 ppm exposure level were 2.3 and 2.6 hours for the study days 1 and 12 (after 10th exposure) data respectively. The plasma elimination half-lives for fluorosulfate at the 300 ppm exposure level were 1.7 and 1.6 hours for the study days 1 and 12 data, respectively. Both analytes were eliminated via the urine. The rates of elimination were similar after both the 1st and 10th exposures with little apparent retention of either analyte between exposures. **Study supplemental.** ([redacted], 10/4/12)

50223-0109; 264597; "Sulfuryl Fluoride: Pharmacokinetics in Crl:CD(SD) Rat Dams, Fetuses and Pups Following Vapor Inhalation or Gavage Exposures during Gestation and Lactation"; (M.S. Marty, *et. al.*; Toxicology & Environmental Research and Consulting, The Dow Chemical Co., Midland, MI; Study No. 081144; 6/2/09, revised, 6/30/11); Perinatal pharmacokinetics of sulfuryl fluoride and its hydrolysis products, fluorosulfate and net free fluoride was assessed for rat dams and 10-day old pups. In phase I, twelve mated female Crl:CD rats/group were exposed to 0, 5, 30 or 150 ppm of Sulfuryl Fluoride Technical (lot no. WH27160101, purity: 99.8%) from gestation day 6 through day 20 for 6 hours/day. On gestation day 18, at the conclusion of the exposure, urine was collected overnight for 18 hours from 5 dams/group. At the conclusion of the exposure on gestation day 20, the dams were anesthetized and blood samples were collected. The number of fetuses/litter was recorded and blood was drawn from each fetuses. All of the blood from the fetuses in 3 litters was pooled for analysis. Brains from all of the fetuses within a litter and kidneys from all of the fetuses in 6 litters were pooled for analysis. Sulfuryl fluoride, fluorosulfate and fluoride content were analyzed in all of these tissues. In Phase II, part one, eight mated females/group were exposed to 0, 5, 30 or 150 ppm of sulfuryl fluoride for 6 hours/day from gestation day 6 through day 20 and from lactation day 5 through 10 (note: pups were not exposed during this time period). Immediately after exposure or 2 hours post-exposure on lactation day 10, 4 dams/group/time point were treated with 3 units of oxytocin ip, followed 10 minutes later with a second dose. Three mls of milk were collected from each dam. At this time, blood was drawn from each of the pups within a litter and pooled. Blood was collected from each of the dams prior to their being euthanized. The dams in the

post-2 hour cohort, nursed their pups during that time interval. In Phase II part two, 81 pups/group were dosed orally by gavage with 0, 4, 20 or 40 ug of an equal mass of Potassium Fluorosulfate (lot no. D25T015, purity: 78.7%) and Fluoride (lot no. 080513, purity: 98.9%). Twenty seven pups/group/time point were euthanized at 1, 3, or 6 hours post-dose. Blood was collected from each pup with the blood from each litter being pooled for analysis. The brain and kidneys from each litter were pooled for analysis, as well. Fluorosulfate and fluoride were analyzed in the plasma and both of the tissues. In phase I, the dams rapidly eliminated fluorosulfate and net free fluoride via the urine. The elimination half-life for fluorosulfate was 1.8 hours at the 150 ppm exposure level. The half-lives for fluoride ranged from 3.9 to 4.8 hours over the 5 to 150 ppm exposure range. Sulfuryl fluoride was not recovered from the plasma of the dams even when samples were analyzed as soon as possible after the last exposure. The concentrations of fluorosulfate and net free fluoride in the dams' plasma increased in an exposure-related manner. For the fetuses, the concentration of fluorosulate in the plasma was approximately 12% of that in the dam plasma at the 30 and 150 ppm exposure levels. The concentrations of fluorosulfate in the fetal brain and kidneys of the 150 ppm exposure group were 2.7 and 17 nmol/g of tissue, respectively. In Phase II, part one, fluorosulfate and net free fluoride increased in an exposure-related manner in the plasma and milk of dams. The concentrations declined over the 2-hour interval between analyses. The dam milk to plasma fluorosulfate ratio varied between 2.81 and 4.45 over the exposure range of 5 to 150 ppm. The pup plasma/dam plasma ratio for fluorosulfate was 0.15 and 0.16 for the 30 and 150 ppm exposure levels, respectively. The pup plasma/dam plasma ratio for net free fluoride was 0.12 and 0.04 for the 30 and 150 ppm exposure levels, respectively. In Phase II, part two, the elimination half-lives of orally administered fluorosulfate from the plasma of 10-day old pups were 2.25 and 5.05 hours for the 20 and 40 ug/pup treatment levels, respectively. The elimination half-lives for fluoride from the plasma of these pups were 1.94 and 3.12 hours, respectively. The fluorosulfate was not recovered from the pup brains at any of the dose levels. Net free fluoride was consistently present in the brain only at the 40 ug/pup treatment level and did not demonstrate first-order elimination kinetics. Fluorosulfate and net total fluoride were consistently present in the kidneys of the 20 and 40 ug/pup treatment groups over the time course of the assay. These pharmacokinetic data demonstrate a relatively rapid elimination of the two analytes from the plasma of both the dams and the pups and the urine of the dams, the higher concentration in the milk of the dams in comparison to that in the plasma and the lower concentration in the plasma of fetuses in comparison to that of the dams. **Study supplemental.** ([redacted], 10/10/12)

50223-0110; 264598; "Sulfuryl Fluoride: Pharmacokinetics in Crl:CD(SD) Rat Weanling Following Inhalation Exposure on Postnatal Day (PND) 22"; (M.S. Marty, *et.al.*; Toxicology & Environmental Research and Consulting, The Dow Chemical Co., Midland, MI; Study ID No. 081145; 7/10/09, 1st revision, 7/23/09, 2nd revision, 7/1/11); Forty eight 22-day old male weanling Crl:CD rats were exposed whole body to 0, 3, 30 or 300 ppm of Sulfuryl Fluoride Technical (lot no. WH27160101, purity: 99.8%) for 4 hours. Eight animals/group/time point were euthanized at 0, 2, 4, and 8 hours post-exposure. Plasma, brain and kidneys were assayed for fluorosulfate and net total and/or net free fluoride content. The elimination half-lives for fluorosulfate from the plasma were 2.01 and 2.33 hours for the 30 and 300 ppm exposure levels, respectively. There was a minimal presence of the analyte in the brain even at the 300 ppm exposure level. The concentrations of fluorosulfate in the kidneys were comparable to those in the plasma over the range of exposures. The net free fluoride concentration was greatest in the brain of these weanlings, demonstrating an exposure-related increase. Any characterization of free fluoride in the kidneys was impossible due the rapid hydrolysis of the fluorosulfate during the analytical preparations. The concentration of net free fluoride in the plasma was not determinable as well. **Study supplemental.** ([redacted], 10/11/12)

50223-0111; 264599; "Sulfuryl Fluoride: Probe Study to Evaluate Absorption and Limited Pharmacokinetics following a Single 6-Hour, 600 ppm Exposure in New Zealand White Rabbits"; (J.A. Hotchkiss, *et.al.*; Toxicology & Environmental Research and Consulting, The Dow Chemical Co., Midland, MI; Study No. 091139; 6/9/11); Six male New Zealand White rabbits were exposed nose-only to 600 ppm of Sulfuryl Fluoride technical (lot no. WH27160101, purity: 99.8%) for 6 hours. Blood samples were drawn from the jugular vein of each animal at 2, 4 and 6 hours of the exposure. Urine samples were collected from the animals during the exposure and up to 18 hours post-exposure. Three animals/time point were euthanized at the conclusion of the exposure and at 18 hours post-exposure. The kidneys, lungs brain, olfactory bulb, nasal mucosa, and nasal tissue were analyzed for fluoride and/or fluorosulfate. Three animals were included in the study as a control cohort and were euthanized at 18 hours post-exposure. Their tissues provided baseline values for fluoride. There was an increase in the concentrations of fluorosulfate and net free fluoride in the plasma over the course of the 6-hour exposure. During the 18-hour post-exposure period, both analytes demonstrated first-order elimination kinetics with the half-lives for fluorosulfate and fluoride being 2.06 and 3.39 hours, respectively. The fluoride (net total and/or net free) concentrations in the kidneys, lungs, cerebrum, and olfactory bulb declined over the time course of 0 to 18 hours post-exposure. For the nasal mucosa and nasal tissue, the concentrations of fluoride at 18 hours post-exposure was comparable to that at the termination of the exposure. The presence of fluorosulfate in these tissues declined to non-detectable levels by 18 hours post-exposure. The elimination of fluorosulfate and net free fluoride via the urine was demonstrable. However, sample collection was inconsistent and no half-lives for elimination could be determined. **Study supplemental.** ([redacted], 10/12/12)

50023-0112; 264600; "Sulfuryl Fluoride: Species Comparison of Limited Pharmacokinetics Following Single 6-Hour Inhalation Exposures of F344/DuCrl Rats and New Zealand White Rabbits"; (D.L. Rick, *et. al.*; Toxicology & Environmental Research and Consulting, The Dow Chemical Co., Midland, MI; Study No. 101161; 6/30/11); Five male F344/DuCrl rats and three female New Zealand White rabbits/group were exposed whole body to 0, 3, 30 or 300 ppm of Sulfuryl Fluoride technical (lot no. WH27160101; purity: 99.8%) for six hours. The concentrations of fluorosulfate and net free fluoride were analyzed in the plasma, kidneys and cerebrum at the termination of the exposure. The plasma levels of net free fluoride were approximately three fold greater for the rabbit than the rat across the exposure range. The net free fluoride concentrations in the cerebrum at the 300 ppm exposure level were comparable in the two species. However, at the two lower exposure levels, the fluoride content in the cerebrum of the rat increased in an exposure-related manner in contrast to there being no analyzable levels in the cerebrum of the rabbit. The net free fluoride content in the kidneys of the rabbits was higher by greater than a ten fold factor than that of the rat at the 30 ppm exposure level. The plasma levels for fluorosulfate were comparable for both species across the exposure range. The analyte could not be isolated in the cerebrum of the rat and at only the highest exposure level in the rabbit. In the kidneys, fluorosulfate content was much greater in the kidneys of the 300 ppm rabbits in comparison to that of the rats (127 nmol/g vs. 7.45 nmol/g). These data were procured for use in establishing a PBPK model for sulfuryl fluoride. **Study supplemental.** ([redacted], 10/16/12)

GUIDELINE ACUTE STUDIES ON ACTIVE INGREDIENT

Acute oral toxicity, rat

Study not required due to gaseous nature of the active ingredient under ambient conditions.

Acute dermal toxicity

Study not required due to gaseous nature of the active ingredient under ambient conditions.

Acute inhalation toxicity, rat

50223-0011; 71423; "Sulfuryl Fluoride (Vikane Fumigant): An LC50 Determination"; (R.R. Miller, L.L. Calhoun, D.G. Keyes, R.J. Kociba; Mammalian and Environmental Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical Company, Midland, MI; Study ID No. K-016399-013; 8/25/80); Ten Fischer 344 rats/sex/group (unless otherwise designated) were exposed whole-body to 320 (F only), 450, 700 (F only), 790 (F only), 1000, 1020 (F only), 1200 (F only), 1250 (M only), 1425, or 2025 ppm of Sulfuryl Fluoride Technical (lot no. 141; purity: 99.7%) for 4 hours. The following mortality resulted from the exposures: 320 (F:0/10), 450 (M/F: 0/10), 700 (F: 0/10), 790 (F: 0/10), 1000 (M: 1/10, F: 10/10), 1020 (F: 1/10), 1200 (F: 9/10), 1250 (M: 6/10), 1425 (M/F: 10/10), 2025 (M/F: 10/10). Clinical signs included lethargy, cyanosis, ocular irritation, prostration and convulsions. Deaths occurred within 6 days post-exposure. Reduced body weight gain was apparent for the animals in the lower exposure groups. For the animals which died during the study, the necropsy examination revealed the accumulation of red tinged secretory material near the eyes and nose, reddened, inflamed appearance of the nasal turbinates and a darkened, edematous appearance of the lungs. Secondary responses included a slight distension of the stomach, congested appearance of the liver and a reddened and inflamed appearance of the cecum. Those animals which survived the two-week observation period did not demonstrate any apparent treatment-related lesions. Histopathological examination of tissues/organs from the males in the 1250 ppm group and the females in the 1200 ppm group revealed the progression of centrilobular hepatocellular cytoplasmic vacuolar degeneration in the liver and renal tubular degeneration with sloughing of the tubular epithelium in the kidneys. **Rat Acute Inhalation LC50:** (M) 1122 ppm (4.69 mg/l at 1 atmosphere and 25^{o} C), (F) 991 ppm (4.14 mg/l at 1 atmosphere and 25^{o} C); Toxicity Category IV; **Study acceptable.** ([redacted], 4/29/15)

Acute inhalation toxicity, mouse

50223-027; 122419; Acute Inhalation Toxicity Study; 813; Mouse; Mammalian and Environmental Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical Company, Midland, MI; Study ID: HET K-016399-028; 3/22/89; 5 animals/sex/group; Exposure Concentrations: 400, 600, 1000 ppm, 4 hour exposure; Mortality: 400 (M/F:0/5), 600 (M/F:5/5), 1000 (M/F:5/5), 1000 ppm exposed animals died within 90 minutes, 600 ppm animals died within 5 days; Observations: (600) tremors, lethargy, (400) no treatment-related signs; Necorpsy: no treatment-related lesions; LC50 (M/F) > 400 ppm (1.67 mg/l), < 600 ppm (2.80 mg/l); Toxicity Category III; **Study acceptable**. ([redacted], 9/29/93)

50223-026,-037; 115231, 131311; Acute Inhalation Toxicity Study; 813; Mouse; The Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical Company, Midland, MI; Study No. K-016399-031; 12/21/90; Sulfuryl Fluoride; 5 animals/sex/group; Exposure concentrations (analytical): 596, 692, 806 ppm (estimated concentrations: 2.4, 3.2, 3.7 mg/l, respectively, based on ambient conditions), 4 hour, whole body; Mortality: 596 (M/F: 0/5), 692 (M:5/5; F:4/5), 806 (M:4/5; F:3/5); Observations: body tremors, lethargy; Necropsy: no treatment-related lesions; LC50 (M): 642 ppm (2.6 mg/l), (F): 660 ppm (2.7 mg/l); Toxicity Category III; (Study previously unacceptable, possibly upgradeable with the submission of

analytical data used to determine the analytical exposure concentration); submitted information in Rec.# 131311 was sufficient to upgrade study to **acceptable.** [redacted], 2/18/94, upgraded [redacted], 9/16/94)

Primary eye irritation, rabbit

Study not required due to gaseous nature of the active ingredient under ambient conditions.

Primary dermal irritation

Study not required due to gaseous nature of the active ingredient under ambient conditions.

Dermal sensitization

Study not required due to gaseous nature of the active ingredient under ambient conditions.

SUBCHRONIC STUDIES (units of mg/kg/day unless specified)

2-Week Inhalation toxicity, rat and rabbit:

50223-018 095932 Eisenbrandt, D. L., Nitschke, K. D., Streeter, C.M., Wolfe, E. L. "Sulfuryl fluoride (Vikane® Gas Fumigant): 2-Week inhalation toxicity probe with rats and rabbits". Dow Chemical Co., Midland MI, April 2, 1985. Dose levels were 0, 100, 300, or 600 ppm in both species. Animals were exposed for 6 hr/day for a total of 9 days. Nine out of 10 rats administered 600 ppm sulfuryl fluoride died. Kidneys of these rats were severely affected. Minor kidney damage was noted in 300 ppm rats. There were on other apparent effects at that dose level. Reviewed by [redacted] 1/30/91 in the context of a protocol review for a reproduction study scheduled to begin in Feb., 1991. (See CDFA protocol comments of 1/30/91).

Subchronic Inhalation Toxicity, rat:

****50223-012 071485** Nitschke, K. D., Dittenber, D.A., and Eisenbrandt, D. L. "Sulfuryl Fluoride (Vikane Gas Fumigant): 13-Week Inhalation Toxicity Study with Rats" (Mammalian and Environmental Toxicology Research Laboratory, Dow Chem. Co., Project ID K-016399-025R, 11/16/87). Vikane, sulfuryl fluoride, Lot TWP 830919-408, 99.8%, was administered by inhalation to Fischer 344 rats, 10/sex/group, at 0, 30, 100 or 300 ppm for 6 hours/day, 5 days/week, 13 weeks. NOEL = 30 ppm (based on mottled incisors in all rats at 100 and 300 ppm). A practical NOAEL relevant to adults likely to be exposed chronically is 100 ppm. Major findings at 300 ppm included: marked body weight decrements (M & F), cerebral vacuolation [caudate-putamen area, white fiber tracts of the internal capsule; (M and F)], kidney hyperplasia (F) and decreased protein droplets in kidneys (M), inflammation of nasal mucosae (M & F), and subpleural histiocytosis in the lungs (M & F). Brain findings constitute **possible adverse effects. Acceptable** as a subchronic study. [redacted]; 9/17/90.

Subchronic Inhalation Toxicity, rabbit:

****50223-012 071484** Nitschke, K. D., Zimmer, M.A., and Eisenbrandt, D. L. "Sulfuryl Fluoride (Vikane™ Gas Fumigant): 13-Week Inhalation Toxicity Study with Rabbits" (Mammalian and Environmental Toxicology Research Laboratory, Dow Chemical Company, Study ID K-016399-025B, 11/16/87). Vikane, sulfuryl fluoride, Lot No. TWP 830919-408, 99.8%, was administered to New Zealand White rabbits via inhalation for 6 hours/day, 5 days/week for 13 weeks at 0, 30, 100 or 300 ppm. Seven animals per sex per group. NOEL = 30 ppm; [cerebral vacuolation in regions of internal and external capsules, putamen, and globus pallidus of one female: and nasal tissue inflammation in one male]. At 300 ppm, common brain findings were vacuolation to severe malacia of cerebrum (both sexes, in the above regions), and gliosis and/or hypertrophy of vascular endothelial cells in some females in the same regions. Common nasal tissue findings at 300 ppm in both sexes were degeneration and inflammation of epithelial

tissues. Collectively, these findings are **possible adverse effects. Acceptable subchronic study**. [redacted], 9/10/90.

Two-Week inhalation Toxicity, mice:

****50223-055 186125** Nitschke, K. D. and J. F. Quast, "Sulfuryl fluoride: two-week inhalation toxicity study in CD-1 mice," The Dow Chemical Co., Midland, MI, 2/11/02. Laboratory Project Study # K-016399-029. Five mice/sex/group were dosed 6 hr/day, 5 days/wk, for 9 exposures at 0, 30, 100, and 300 ppm sulfuryl fluoride, 99.6% purity. Associated exposures of treated groups were 0.13, 0.42, and 1.3 mg/l of chamber air. Mice were sacrificed 1 day after the last exposure, at which time they were subjected to limited hematology and clinical chemistry studies, gross necropsy and histopathology. NOEL = 30 ppm ("very slight" cerebral vacuolation in six of ten 100 ppm mice). The 300 ppm exposure proved to be excessive: 9/10 of these mice did not survive the 11-day duration of the study. Deaths were preceded by inanition (statistically significantly body weight losses, decreased ingesta in digestive tract, decreased body fat), and associated pathology (stomach erosions/ulcers, hepatocellular atrophy judged to be due to inanition). Most decedents had "roughened hair coat" and at least 3 of the males had whole body tremors. All high dose mice, except for 2 with sufficient autolysis to impede microscopic evaluation, showed cerebral vacuolation, usually of "moderate" degree. Five high dose mice had very slight vacuolation of the medulla. These brain lesions are **"possible adverse effects."** Also, nine high dose mice had lacrimal/Harderian gland atrophy. **Acceptable**. [redacted], 4/23/02.

Subchronic Inhalation Toxicity, mice:

50223-034; 128669; Sulfuryl Fluoride: Thirteen-Week Inhalation Toxicity Study in CD-1 Mice, Nitschke, K.D. and J.F. Quast; 824; Mouse; The Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical Company, Midland, MI; Study ID: K-016399-032; 12/28/93; Sulfuryl Fluoride (purity: 99.6%); 14 animals/sex/group; Exposures: 0, 10, 30, 100 ppm, 6 hr/day, 5 days/wk, 13 weeks; Mortality: 0-1F, 10-1F, 100-1M (all not treatment-related); Observations: 10% reduction in body weight gain (100 ppm), reduced absolute brain, heart, kidney (M only), liver weights (100 ppm), no effects detailed in functional observational battery; Hematology: no treatment-related effects; Clinical Chemistry: increased triglycerides, alkaline phosphate (100 ppm, M only); Necropsy: no treatment-related lesions; Histopathology: multifocal vacuoles in cerebrum, thalamus/hypothalamus, hypertrophy of follicular epithelial cells and decrease in colloid in thyroid gland; target organ: brain; **possible adverse effect:** multifocal vacuoles in brain; NOEL can not be determined; Study unacceptable, possibly upgradeable with the submission of the analytical data used to determine the analytical exposure concentration. ([redacted], 4/29/94)

Two-Week Inhalation Toxicity, dog:

50223-020 097246 Nitschke, K. D. and Quast, J. F., "Sulfuryl fluoride: Two-week inhalation toxicity study in beagle dogs". The Toxicology Research Laboratory, Health and Environmental Sciences, Dow (Midland), 4/30/91. Beagles, 1/sex, were dosed with nine 6-hr inhalation treatments of sulfuryl fluoride (SO_2F_2) over two weeks. Concentrations were 0, 30, 100, or 300 ppm. The major clinical observation was intermittent tremors and tetany in both 300 ppm dogs from day 5 onward. The effects were severe enough on day 9 that exposure was terminated after 5.5 hr. Dogs rapidly recovered to normal appearance and behavior at the end of each exposure period. Nasal turbinates of 300 ppm dogs had a slightly greater degree of inflammation than background level, and a similar slight inflammatory response in mucosa of the trachea was noted in the 300 ppm female. The NOEL was 100 ppm. No separate DPR written review is needed for this study. [redacted], 4/1/91

Subchronic Inhalation Toxicity, dog:

50223-023 113430 Nitschke, K. D., Beekman, M. J., and Quast, J. F., "Sulfuryl fluoride: 13-week inhalation toxicity study in beagle dogs". The Toxicology Research Laboratory, Health and Environmental Sciences, Dow (Midland), 2/24/92. Four beagles/sex were dosed with SO_2F_2 by inhalation for 6 hr/day, 5 days/wk for 13 weeks. Doses were 0, 30, 100, and 200 ppm as whole body exposures in dynamic airflow chambers. High dose males and females gained less weight than other groups (final body weights of 200 ppm males and females were 12% and 4% lower than respective controls). The only clinical signs noted were one 200 ppm male with "lateral recumbency, tetany, tremors, salivation, and incoordination" noted on day 19 of the study only. Histopathology attributed to treatment was gliosis and vacuolation of focal areas of the putamen in one male and one female at 200 ppm. Microscopic changes are "possible adverse effects", however the presence of predictable clinical signs at the same dose level suggest that dose levels which do not elicit transient clinical signs are unlikely to cause marked histopathologic changes. The NOEL was 100 ppm. Results suggest that the chronic study should employ comparable dose levels to this subchronic study. [redacted], 4/1/92 (no separate worksheet).

CHRONIC STUDIES

Chronic, rat

****50223-029 125637** "Sulfuryl Fluoride: 2-Year Inhalation Chronic Toxicity/ Oncogenicity Study in Fischer 344 Rats", (J. F. Quast, G. J. Bradley and K. D. Nitschke, The Dow Chemical Co., Toxicology Research Laboratory, Lab Project Study ID K-016399-040, 8/18/93). Sulfuryl fluoride, stated purity 99.8%, was administered via inhalation at concentrations of 0, 5, 20, or 80 ppm to 50 Fischer 344 rats/sex/group for 6 hours/day, 5 days/week (except holidays) for 24 months. Fifteen additional rats/sex/dose level were included for a 12- month neurotoxicity study (Record No. 130056). Formally, the NOEL = 5 ppm, based on "very slight" degree of dental fluorosis (statistically significant in males). Since the fluorosis is considered as a biomarker of exposure rather than as an adverse effect, a practical NOAEL is 20 ppm, based on a host of changes at 80 ppm. The primary target organ was kidney. An exacerbation of the normal process of chronic progressive glomerulonephropathy was the primary cause of premature deaths in both sexes at that dose, with mineralization in a variety of tissues as common secondary effects. High dose females had increased incidence of brain vacuolation in cerebral cortex and in thalamic and hypothalamic areas, limited to "very slight" degree. Possible direct responses of respiratory tissues would include aggregates of alveolar macrophages in lungs (already evident at 1 year interim sacrifice), and inflammation of larynx and trachea. Findings in this study had either not appeared or had not reached advanced degree until well beyond the first year of the study, consistent with the majority of effects being secondary to renal toxicity. **Acceptable, with "possible adverse effect"** (chronic renal disease). No oncogenicity was evident. [redacted] and [redacted] 9/14/94.

50223-042 161152 U.S. EPA review of Record #125637, above. Recent reviews of 3 study types were included in this record. The review corresponding to the above record agreed with the 1994 DPR review above in acceptability status, and in the determination that no oncogenic effect was indicated. There are no fundamental differences in study interpretation between the DPR and U.S. EPA reviews, except that the U.S. EPA placed the NOEL at 20 ppm whereas the DPR review placed the NOEL at 5 ppm. The difference was based on the use of dental fluorosis as a determinant of the LOEL by DPR, which finding was not considered by either reviewer as a pivotal endpoint for chronic/oncogenicity outcomes. [redacted], 11/17/98.

Chronic, dog

** 50223-033 126744 "Sulfuryl Fluoride: One-Year Inhalation Toxicity Study in Beagle dogs", (J. F. Quast, M. J. Beekman, and K. D. Nitschke; Dow Chemical Company, Midland, MI; Report # K-016399-044; 21 October 1993). Sulfuryl fluoride, 99.8% purity. Four beagle dogs per sex per group were exposed via whole-body inhalation at 0, 20, 80, and 200 ppm for 6 hours per day, 5 days per week, for 1 year. High dose animals were killed at 9 months due to severe clinical signs of toxicity. NOEL = 20 ppm (very slight degree of chronic active inflammation in alveoli of the lungs of two 80 ppm females, multifocal aggregates of alveolar macrophages in both sexes, and very slight dental fluorosis). Alveolar inflammation was the main cause of rapid deterioration of health of most high dose dogs by about 9 months. A focal malacia in the caudate nucleus of the brain was identified in 5 high dose dogs, without apparent functional sequelae. **Acceptable**. **No adverse effects** are indicated, since subacute studies (see especially Record No. 097246) had already shown marked functional toxicity at 300 ppm, whereas about one-fourth of that daily dose in this chronic study caused only slight chronic effects. [redacted] and [redacted], July 5, 1994.

Oncogenicity, rat

See Chronic, rat above.

Oncogenicity, mouse

** **50223-028 125636** "Sulfuryl Fluoride: 18-Month Inhalation Oncogenicity Study in CD-1 Mice", (J. F. Quast, G. J. Bradley and K. D. Nitschke, Dow Chemical Co., Toxicology Research Laboratory, Lab Project Study ID K-016399-039, 8/19/93). Sulfuryl fluoride, 99.8% purity, was administered via inhalation at concentrations of 0, 5, 20, or 80 ppm to 50 CD-1 mice/sex/group for 6 hours/day, 5 days/week for 18 months. Ten additional mice/sex per dose level were included for sacrifice at 12 months. NOEL = 20 ppm. Primary concern was increased mortality in females (mainly due to increased incidence of severe degree of bilateral amyloidosis in glomeruli). Possibly treatment-related findings in males were food impaction in esophagus and inflammation and/or abscesses in the head and/or oral cavity at 80 ppm. Lesser changes at 80 ppm included very slight vacuolation of brain, particularly of cerebral external capsule (M and F), and very slight hypertrophy of thyroid epithelial cells (especially in males). This study is considered to indicate a "**possible adverse effect**", based on the exacerbation of geriatric renal disease in high dose females. Considering how high the NOEL and LOEL of this study are to levels which cannot be tolerated in acute and subacute toxicity exposure, this flagging of a "possible adverse effect" should not be taken to indicate unusual concern. No oncogenicity effects. **Acceptable**. [redacted] and [redacted] Sept. 14, 1994.

GENOTOXICITY

Gene mutation

** 016 091291 "Evaluation of Sulfuryl Fluoride in the Ames Salmonella/Mammalian-Microsome Bacterial Mutagenicity Assay." (Gollapudi, B. B., Samson, Y. E. and Zempel, J. A.; Health and Environmental Sciences-Texas, Dow, TXT:K-016399-037, 8/17/90). Sulfuryl fluoride gas, lot 874, 99.6%, was tested with Salmonella typhimurium strains TA1535, TA1537, TA98 and TA100 with and without activation with rat liver S9. Overnight cultures were plated in top agar, then exposed without lids for 4 hours in glass desiccators. Atmospheres of 0, 300, 1000, 3000, 10,000 and 30,000 ppm were tested. After exposure, plates were incubated an additional 2 days, then the colonies were counted. Triplicate plates per concentration and two trials were studied. There was no evidence of an increase in reversion rate. The number of revertants was decreased somewhat at 30,000 ppm suggesting cytotoxicity. The positive controls were acceptable. ACCEPTABLE. ([redacted] 9/14/90).

**** 50223-0101; 264589**; " Evaluation of Sulfuryl Fluoride in the Mouse Lymphoma (L5178Y $TK^{+/-}$) Forward Mutation Assay"; (B.B. Gollapudi, *et. al.*; Toxicology & Environmental Research and Consulting, The Dow Chemical Co., Midland, MI; Study ID No. 001144; 5/16/02); Mouse lymphoma L5178Y cells (clone 3.7.2 ($TK^{+/-}$)) were treated with Sulfuryl Fluoride (lot no. OC16160101; purity: 99.8%) at concentrations ranging from 100 to 6000 ppm under conditions of (+/-) activation in Assay No. 1, from 500 to 6000 ppm under (+/-) activation in Assay No. 2 and from 1000 to 7000 ppm under conditons of (+/-) activation in Assay No. 3 for 4 hours at 37^{o} C. There were duplicate cultures/treatment level. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. Cell viability and mutation frequency for each treatment level were determined and compared to those of the solvent control. In each of the assays, the mutant colonies were sized. In both the non-activated and activated assays, there was a treatment-related increase in the mutation frequency. **Adverse effect indicated.** Chemical analysis of the sulfuryl fluoride content in the media revealed that the molecule was hydrolyzed to the fluoride and fluoryl sulfate ions over the course of the 4-hour incubation and that the fluoride ion was the likely cause of the genotoxic response. Positive controls were functional. **Study acceptable.** ([redacted], 9/19/12)

Chromosome damage

**014, 017 090476, 091576 "Evaluation of Sulfuryl Fluoride in the Mouse Bone Marrow Micronucleus Test" (Gollapudi, B. B., McClintock, M. L. and Nitschke, K. D., Toxicology Research Laboratory, Dow, Project ID: TXT:K-016399-033, 2/16/90). Sulfuryl fluoride, Lot WP880329 752 MAR/88, 99.6%, was administered to CD-1 mice in an inhalation chamber for a 4 hour exposure period. Actual concentrations of sulfuryl fluoride were 0, 48, 180 and 520 ppm, TWA. Benzene was a positive control with a target concentration of 9000 ppm. Cyclophosphamide was an additional positive control at 120 mg/kg by gavage. The positive controls were sampled 24 hours after exposure, the negative control and treated animals were sampled 24, 48 or 72 hours after exposure, 5/sex/group for each time point. 1000 PCE/animal were evaluated and the percent PCE determined. No increase in the number of micronucleated cells. ACCEPTABLE. ([redacted] and [redacted], 9/14/90).

025 115686 "Response to U. S. EPA Comments on the Study Entitled 'Evaluation of Sulfuryl Fluoride in the Mouse Bone Marrow Micronucleus Test' Laboratory Project ID: TXT:K-016399-033" (K. D. Nitschke and B. B. Gollapudi, DowElanco, 1991) The U. S. EPA rejected the study as unacceptable based on the following: 1) No evidence for an MTD and 2) several parameters of exposure were not provided, namely, identity of the inhalation chamber, use of Miran-1A infrared spectrophotometry, no location for sampling devices or placement of animals in the chamber. The submission contains DowElanco's response. The study was ACCEPTABLE to DPR. No change in status. No worksheet. [redacted], 7/24/92.

**** 50223-0102; 264590**; "Revised Report for Evaluation of Sulfuryl Fluoride in an *In Vitro* Chromosomal Aberration Assay Utilizing Rat Lymphocytes"; (B.B. Gollapudi, *et. al.*; Toxicology & Environmental Research and Consulting, The Dow Chemical Co., Midland, MI; Study No. 001133; 5/20/02, revised, 7/29/05); Primary lymphocyte cultures, procured from the whole blood of male Sprague-Dawley rats (stimulated with PHA for 48 hours), were treated with 500 to 50000 ppm of Sulfuryl Fluoride (lot no. OC16160101; purity: 99.8%) for 4 hours (both non-activation and activation), followed by 20 hours of incubation in assay A2. In Assay B1, the cells were exposed to 2500 to 40000 ppm of the active ingredient under the same conditions. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. A treatment-related increase in chromosomal aberration was evident under conditions of (+/-)

activation. **Adverse effect indicated.** The positive controls were functional. Chemical analysis of the sulfuryl fluoride content in the media revealed that the molecule was hydrolyzed to the fluoride, fluoryl sulfate and sulfate ions over the course of the 4-hour incubation and that the fluoride ion was the likely cause of the genotoxic response. **Study acceptable.** ([redacted], 9/20/12)

DNA damage or miscellaneous effects

** 50223-021 093262, "Evaluation of Sulfuryl Fluoride in the Rat Hepatocyte Unscheduled DNA Synthesis (UDS) Assay", (B. Bhaskar Gollapudi, et al., Health and Environmental Sciences-Texas, The Dow Chemical Co., Report # K-016399-043, 10/7/91). Sulfuryl fluoride (gas fumigant), 97.4% purity, was tested in the unscheduled DNA synthesis assay using hepatocytes of Sprague-Dawley outbred Crl:CD BR male rats at concentrations of 0 (air), 204, 408, 612, 816, 1020, or 1530 ppm. No increase in unscheduled DNA synthesis by autoradiography. ACCEPTABLE. ([redacted] and [redacted] 4/10/92)

REPRODUCTIVE TOXICITY, RAT

** 50223-022 112308 Breslin, W. J., Liberacki, A.B., Kirk, H. D., Bradley, G. J., and Crissman, J. W. "Sulfuryl fluoride: Two-generation inhalation reproduction study in Sprague-Dawley rats". The Toxicology Research Laboratory, Health and Environmental Sciences, Dow (Midland), Jan. 7, 1992. Sprague-Dawley rats were dosed 6 hr/day, 5 days/wk with sulfuryl fluoride at doses of 0, 5, 20, or 150 ppm. Thirty rats/sex/group were dosed for 10 wk or 12 wk prior to mating (F0 and F1 parents, respectively): dosing was continued to end of weaning period for both sexes, except that females were taken off treatment for 5 days beginning shortly before expected parturition. Pups were not exposed to sulfuryl fluoride prior to weaning. Parental NOEL = 5 ppm (aggregates of alveolar macrophages in lungs of both sexes, both generations: dose related). At 150 ppm, adults of both generations had body weight decrements of about 10% (generally statistically significant). This group had discolored teeth (fluorosis), chronic inflammation of lungs, and "very slight" to "slight" vacuolation of myelinated fiber tracts of the caudate putamen. Reproductive effects NOEL = 20 ppm (reduced pup body weights in F1 and F2 generations). Study is ACCEPTABLE. No adverse reproductive effects. The comparatively low NOEL for systemic effects may nevertheless be useful in eventual risk assessment. [redacted] 4/8/92.

DEVELOPMENTAL TOXICITY

Rat

**006 36089 Rat Teratology, 833. (Toxicology Research Laboratory, Dow Chemical, 10/26/81). "Vikane: Inhalation teratology study in rats and rabbits." Vikane = sulfuryl fluoride = SO_2F_2 (99.8% purity) at 0, 25, 75, or 225 ppm by inhalation for 6 hours/day on days 6 through 15 of gestation. Dose levels based on a probe study. Maternal and developmental NOEL's > 225 ppm (HDT). [redacted] evaluation (7/24/86) found study unacceptable but possibly upgradeable; [redacted] evaluation (2/6/87) was complete and ACCEPTABLE with supplemental data (007:051087).

007 051087 Data supplemental to a rat teratology study 006:036089, above. (Toxicology Research Laboratory, Dow Chemical, 11/19/80). "Vikane: Probe teratology study in Fischer 344 rats and New Zealand white rabbits." Vikane = sulfuryl fluoride = SO_2F_2 (99.8% purity). Results from a range-finding study show decreases in maternal body weight, body weight gain, and food consumption, and increases in water consumption and kidney weights at the 300 ppm exposure level, with no toxicity at 100, 30, or 0 ppm. Summary and individual antemortem observations,

individual necropsy data, and individual litter and fetal data are provided. This supplement removes all deficiencies and the teratology is complete and acceptable. [redacted] 2/6/87.

Rabbit

006 36089 Rat Teratology, 833. (Toxicology Research Laboratory, Dow Chemical, 10/26/81). "Vikane: Inhalation teratology study in rats and rabbits." Vikane = sulfuryl fluoride = SO_2F_2 (99.8% purity) at 0, 25, 75, or 225 ppm by inhalation for 6 hours/day on days 6 through 15 of gestation. Dose levels based on a probe study. Maternal and developmental NOEL's > 225 ppm (HDT). [redacted] evaluation (7/24/86) found study unacceptable but possibly upgradeable; [redacted] evaluation (2/6/87) was complete and **ACCEPTABLE with supplemental data (007:051087).

007 051087 Data supplemental to a rat teratology study 006:036089, above. (Toxicology Research Laboratory, Dow Chemical, 11/19/80). "Vikane: Probe teratology study in Fischer 344 rats and New Zealand white rabbits." Vikane = sulfuryl fluoride = SO_2F_2 (99.8% purity). Results from a range-finding study show decreases in maternal body weight, body weight gain, and food consumption, and increases in water consumption and kidney weights at the 300 ppm exposure level, with no toxicity at 100, 30, or 0 ppm. Summary and individual antemortem observations, individual necropsy data, and individual litter and fetal data are provided. This supplement removes all deficiencies and the teratology is complete and acceptable. [redacted] 2/6/87.

NEUROTOXICITY

Acute, rat

50223-030 126302 "Sulfuryl Fluoride: Electrodiagnostic, FOB and Motor Activity Evaluation of Nervous System Effects from Short-Term Exposure", (R. R. Albee, P. J. Spencer, and G. J. Bradley, Dow Chemical Co., Toxicology Research Laboratory, Lab. Project ID K-016399-045, K-016399-045D, K-016399-045E, K-016399-045F, and K-016399-045G, 5/3/93). This study was requested by U.S. EPA to achieve limited objectives as indicated in the title. Previous studies had addressed histopathology and other features commonly included in neurotoxicity studies. Sulfuryl fluoride, purity 98.3-99.8%, was administered via whole-body inhalation (6 hours/day for 2 consecutive days) at concentrations of 0, 100 or 300 ppm to 12 non-pregnant female Fischer rats/group. NOEL = 300 ppm. Functional observational battery, grip performance, landing foot splay, motor activity and electrodiagnostic responses were examined within 24 hr of the final exposure. There was no evidence of neurotoxicity. Not applicable to fill guideline FIFRA study data gaps, but useful information. ([redacted] and [redacted] 9/7/94).

90-day, rat

50223-010 071482 Mattsson, J. L., Albee, R. R., Eisenbrandt, D. L., and Nitschke, K. D. "Neurological examination of Fischer 344 rats exposed to sulfuryl fluoride (Vikane™ gas fumigant) for 13 weeks". (Mammalian and Environmental Toxicology Research Laboratory, Dow, study ID K-016399-026, 11/21/86). Vikane, Lot TWP 830919-408, 99.8%, was administered to Fischer 344 rats, 7/sex/group, 6 hours/day, 5 days/week, for 13 weeks at 0, 30, 100 or 300 ppm. Rats were implanted with epidural electrodes, and a battery of neurological tests was performed on the rats after 13 weeks of exposure. At 300 ppm, rats had increased latencies of certain components of various evoked response wave patterns (visual, somatosensory, cerebellar, auditory). In addition, visual and somatosensory evoked responses were noted as statistically significantly slowed in females at 100 ppm, and the latency of the auditory brainstem response in 100 ppm males appeared to be increased. Thus the NOEL was 30 ppm. The only brain microscopic findings at the end of the treatment period were vacuoles in the white fiber tracts of the caudate-putamen. Auditory brainstem response was tested in

controls and high dose rats (2/dose/sex) after 2 months of recovery, at which time rats were sacrificed and brains were examined microscopically. After recovery, 300 ppm rats had normal evoked responses and normal brain histology. Brain functional changes are **possible adverse effects. Useful supplemental data.** [redacted] / [redacted], 9/13/90.

Chronic Neurotoxicity, rat:

50223-035 130056 "Sulfuryl Fluoride: Chronic Neurotoxicity Study in Fischer 344 Rats-Final Report" (P. J. Spencer, G. J. Bradley and J. F. Quast, Dow Chemical Co., Toxicology Research Laboratory, Lab. Project ID K-016399-040B 3/24/94). Sulfuryl fluoride (purity 99.8%, lots WP 880329-752, WP 901011-907, WP 910321-918, WP 910826-929 and WP 920131-940) was administered via whole-body inhalation (6 hours/day, 5 days/week) for 1 year at concentrations of 0, 5, 20 or 80 ppm to 15 Fischer 344 rats/sex/group (satellite rats from concurrent 2-year chronic toxicity/oncogenicity study). NOEL (for neurotoxicity) = 80 ppm. **No Adverse Effects. Functional observational battery, grip performance, landing foot splay and motor activity tests showed no evidence of neurotoxicity. ACCEPTABLE. Supplemental information. [redacted] and [redacted], 9/14/94.

Developmental neurotoxicity, rat

50223-0130; 284097; "Sulfuryl Fluoride: Neurotoxicity and Toxicokinetic Assessment in Crl:CD(SD) Rats Following Inhalation Exposure from Postnatal Days 11-21"; (M.S. Marty *et. al.*, Toxicology and Environmental Research and Consulting, The Dow Chemical Company, Midland, MI; Study ID. 141074; 3/31/15); Multiple cohorts of Crl:CD (SD) rats of both sexes were exposed whole body to 0, 5, 20 or 150 ppm of Sulfuryl Fluoride Technical (lot no. ZE27160101; purity: 99.7%) 6 hours/day from post-natal day 11 through post-natal day 21 (0, 0.02, 0.08, 0.63 mg/l at 25^{o} C, 1 atmosphere). In the neurotoxicity cohort, 12 animals/sex/group were observed twice in a functional observational battery (FOB) on post-natal days 22 and 54 to 56. Motor activity was assessed at the same time intervals. On post-natal day 78, the young adults were euthanized and their brains were weighed and subjected to morphometric analysis and histopathological examination. In the weanling toxicokinetic cohort (TK), 15 males and 16 females/group were included. The low dietary F toxicokinetic cohort included 16 animals/sex/group. In both cohorts, on post-natal day 21, blood and brain samples were recovered from each animal and analyzed for fluorosulfate and free and total fluoride. The mean body weight gain of both sexes in the 150 ppm exposure group of the three cohorts was less than that of the control animals between post-natal day 17 and 21 ($p<0.01$). There was no apparent effect on the food consumption of the animals in the neurotoxicity cohort after post-natal day 22. The only effect in the FOB which demonstrated a possible treatment-related effect was the reduction in hind limb grip strength of both sexes in the 150 ppm exposure group on post-natal day 22 ($p<0.01$). The report author surmised that this effect was more likely due to the lower mean body weights of these animals than any neurologically-relevant factor. By post-natal day 55, the deficit was no longer apparent. There was no treatment-related effect on motor activity at either time point of assessment. The mean absolute or relative brain weights were not affected by the treatment. Gross brain measurements were not affected by the treatment. Brain morphometrics did not reveal any treatment-related effect upon the dimensions of various regions. No treatment-related lesions were evident in the histological examination of the brain. For the TK cohort, fluorosulfate was detected in the plasma of rats at all concentrations of sulfuryl fluoride with supralinear concentrations (nonlinear TK) at the highest exposure level of 150 ppm. Other analytes (brain fluorosulfate, brain fluoride and plasma fluoride) were only quantifiable in the 150 ppm group in the presence of nonlinear TK. The fluorosulfate and total and free fluoride plasma levels in the low dietary F TK cohort were comparable to those levels noted in the plasma and brain of the rats on the regular diet. **No adverse effect evident. Neonate Rat Multiple Exposure NOEL:** (M/F) 20 ppm (0.08 mg/l)

(based upon the lower mean body weight gain between post-natal 17 and 21 of both sexes in the 150 ppm group); **Study supplemental** (non-guideline protocol). ([redacted], 4/23/15)

IMMUNOTOXICITY

Not required at this time.

ENDOCRINE DISRUPTOR STUDIES

Not required at this time.

SUPPLEMENTAL STUDIES

50223-027; 122417; Sulfuryl Fluoride: Effects of Acute Exposure on Respiration in Rats; Non-guideline; Rat; Mammalian and Environmental Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical Company, Midland, MI; Study ID: HET K-016399-020; 12/19/83; 4 male animals/group; Exposure concentrations: 0, 4,000, 10,000 ppm, 20 minute exposure, head-only; Obseservations: 4,000 ppm-initial increase in respiratory frequency (max. 39%), decrease in mean tidal volume (max. 40%) and mean minute volume (max. 23%), returning to baseline levels by 10 minutes; 10,000 ppm-increased respiratory rate (max. 60%), decreased mean tidal volume (max. 59%) and minute volume (max. 53%), parameters tended to return to baseline levels, animals quite ill at the conclusion of the exposure; **Study supplemental**. ([redacted], 9/28/93)

50223–0103; 264591; "*In Vitro* Determinations of the Sites and Rates of Hydrolysis of Sulfuryl Fluoride and Fluorosulfate in the Rat and Human"; (D.L. Rick, M.J. Filiary; Toxicology & Environmental Research and Consulting, The Dow Chemical Co., Midland, MI; Study ID. No. 061145; 7/7/09); Sulfuryl fluoride (lot no. PE13160101, purity: > 99.8%) was incubated *in vitro* for typically 1 hour with preparations of rat liver and lung S9 and S3 fractions, rat whole blood, plasma and red blood cells, rat nasal tissue S3 fraction, rat lung lavage fluid, rat pup (post-natal day 10) whole blood, human liver and lung S9 fraction, and human whole blood. The preparations were fortified with from 8 to 208 ug of sulfuryl fluoride. The incubations were performed in which the test material was introduced into a head space or was injected into the aqueous media. In the second type of assay, no headspace was present in the vial. Minimal hydrolysis of sulfuryl fluoride was noted in cellular subfractions when exposed via the headspace. An exception was noted for the rat liver and lung S3 fractions. However, the report authors stated that they believed these results to be artifactitious. Hydrolysis of the test material was more extensive in the presence of blood components (whole blood, red blood cells and plasma) with 60 to 80% of the initial load being hydrolyzed. In the no-headspace configuration, the experimental results were more difficult to interpret because hydrolysis occurred in the presence of physiological saline alone. The report authors attempted to elucidate the net rate of hydrolysis in the presence of whole blood by subtracting out the background saline-alone hydrolysis. In this experiment, at the 42 ug fortification level, hydrolysis of the test material occurred within the first minute. At the higher fortification level of 208 ug, additional hydrolysis occurred after the 1st minute, but the rate was not linear over the 10-minute time interval. In the first minute, the rate of hydrolysis in whole blood (diluted 20 ul into 5 ml of saline) was similar for both the adult rat and 10-day post-natal pup. For the human blood, the rate of hydrolysis under these artificial conditions was double that of the rat. Overall, hydrolysis of sulfuryl fluoride in subcellular fractions was negligible. In the presence of blood components and particularly whole blood, some characterization of the hydrolysis was possible, but under very artificial conditions. **Study supplemental.** ([redacted], 9/24/12)