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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

Subject: SULFURYL FLUORIDE. ID NO. 078003. Evaluation of 90-Day Mouse Inhalation Toxicity Study.

Tox. Chem. No.	816A
PC Code No.	078003
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Submission No.	S449380

From: Linnea J. Hansen, Ph.D.
Section IV, Toxicology Branch I
Health Effects Division (7509C)

Linnea J. Hansen 8/10/95

To: Larry Schnaubelt, Manager, PM Team 72
Robert Richards, Reviewer, PM Team 72
Special Review and Reregistration Division (7508W)

Through: John Doherty, Ph.D., D.A.B.T., Acting Section Head
Section IV, Toxicology Branch I
Health Effects Division (7509C)

John Doherty 8/15/95
M Copley 8/21/95

I. CONCLUSIONS

TB-I has reviewed the 13-week inhalation toxicity study conducted in mice by Dow Chemical Company. This study was submitted as additional information on inhalation toxicity of sulfuryl fluoride and was not required to support reregistration. Results are summarized below:

EXECUTIVE SUMMARY: In a 13-week inhalation toxicity study (MRID 43129401), sulfuryl fluoride gas (99.6% a.i.) was administered by inhalation to 14/sex/dose CD-1 mice (6 hr/day, 5 days/week) at levels of 0, 10, 30 or 100 ppm (0, 0.042, 0.125 or 0.416 mg/l, respectively). Of these, 4 animals/sex/dose were assessed only for serum fluoride and for examination of nervous system tissues following perfusion.

At 30 ppm, serum fluoride concentration was increased in males and females compared to controls (+50%; significant in females). At 100 ppm, body weight/weight gain was reduced

(-11%/-61%, males and -9%/-35%, females). Vacuolization of the caudate putamen and external capsule (graded very slight to slight, observed in all animals) and follicular cell hypertrophy in the thyroid (graded very slight, observed in most animals) were observed. **The LOEL for systemic toxicity is 100 ppm, based on decreased body weight and microscopic lesions in the brain (caudate putamen, external capsule) and thyroid. The NOEL for systemic toxicity is 30 ppm.** The LOEL for increased serum fluoride is 30 ppm and the NOEL is 10 ppm.

This study is Core-Minimum and satisfies the guideline requirements for 82-4, a 13-week inhalation toxicity study in mice. (Some clinical chemistry and hematologic parameters were not examined, food consumption not measured; some organs not weighed).

II. ACTION REQUESTED

On February 9, 1994, DowElanco submitted for review a 13-week inhalation toxicity study in mouse (MRID 43129401) as additional information on the toxicity of sulfuryl fluoride. The study was conducted as a range-finding study for a 18-month mosue inhalation study (MRID 43354903, in review).

Primary Review: Linnea J. Hansen, Ph.D. Linnea J. Hansen 8/10/95
Review Section IV, Tox. Branch I
Secondary Review: John Doherty, Ph.D., Acting Section Head
Review Section IV, Tox. Branch I John Doherty 8/15/95

DATA EVALUATION RECORD

STUDY TYPE: 13-week inhalation toxicity
Species: Mouse
Guideline: 82-4

TOX. CHEM. NO.: 816A

MRID NO.: 43129401

PC NO.: 078003

TEST MATERIAL: Sulfuryl Fluoride, technical

SYNONYMS: Vikane®

SPONSOR: DowElanco, Indianapolis, IN

STUDY NO.: K-016399-032

TESTING FACILITY: The Toxicology Research Laboratory, Health and Environmental Sciences, Dow Chemical Co., Midland, MI

TITLE OF REPORT: Sulfuryl Fluoride: Thirteen-Week Inhalation Toxicity Study in CD-1 Mice

AUTHORS: K.D. Nitschke and J.F. Quast

REPORT ISSUED: December 28, 1993

EXECUTIVE SUMMARY: In a 13-week inhalation toxicity study (MRID 43129401), sulfuryl fluoride gas (99.6% a.i.) was administered by inhalation to 14/sex/dose CD-1 mice (6 hr/day, 5 days/week) at levels of 0, 10, 30 or 100 ppm (0, 0.042, 0.125 or 0.416 mg/l, respectively). Of these, 4 animals/sex/dose were assessed only for serum fluoride and for examination of nervous system tissues following perfusion.

At 30 ppm, serum fluoride concentration was increased in males and females compared to controls (+50%; significant in females). At 100 ppm, body weight/weight gain was reduced (-11%/-61%, males and -9%/-35%, females). Vacuolization of the caudate putamen and external capsule (graded very slight to slight, observed in all animals) and follicular cell hypertrophy in the thyroid (graded very slight, observed in most animals) were observed. **The LOEL for systemic toxicity is 100 ppm, based on decreased body weight and microscopic lesions in the brain (caudate putamen, external capsule) and thyroid. The NOEL for systemic toxicity is 30 ppm.** The LOEL for increased serum fluoride is 30 ppm and the NOEL is 10 ppm.

This study is Core-Minimum and satisfies the guideline requirements for 82-4, a 13-week inhalation toxicity study in mice. (Some clinical chemistry and hematologic parameters were not examined, food consumption not measured; some organs not weighed).

A. MATERIALS

Test Compound: Sulfuryl fluoride, technical
Purity: 99.6%
Description: colorless gas
Lot No.: WP 880329 752 MAR/88
Contaminants: [redacted]

Vehicle: air

Test Animal: Species: mouse
Strain: CD-1
Source: Charles River Breeding Laboratories, Inc., Kingston, NY
Age: approx. 8 weeks at study start
Weight: males 26.4 - 38.3 g;
females 19.6 - 28.9 g

B. STUDY DESIGN

1. Animal Assignment

Following a 14-day acclimatization period, animals were randomly assigned by body weight to the following test groups:

TABLE 1: ANIMAL ASSIGNMENT

Test Group	Exposures (ppm)	(mg/l)[1]	Main study males	Main study females	Satellite group[1] males	Satellite group[1] females
Control	0	0.000	10	10	4	4
Low Dose	10	0.042	10	10	4	4
Mid Dose	30	0.125	10	10	4	4
High Dose	100	0.416	10	10	4	4

1 Satellite group assessed at termination for serum fluoride and perfused for examination of nervous system tissues.

[1] mg/l calculated using the following formulae:
(1) mg/m^3 = [ppm x mol.wt.] ÷ 24.5, where mol. wt = 102
(2) mg/l = mg/m^3 ÷ 1000

Animals were exposed in test chambers for 6 hr/day, 5 days/week over 13 weeks. In addition to standard daily clinical observations, all animals of the main study group were evaluated by functional observational battery testing at weeks 4, 8 and 12. Four animals/sex/group were selected randomly for perfusion with fixative and examination of nervous system tissues. Serum fluoride was also assayed in these 4 animals. The remaining 10 animals were sacrificed and evaluated according to standard procedures for a subchronic inhalation toxicity study.

The study report did not describe housing conditions during non-exposure periods except to state that "animals were placed in rooms designed to maintain adequate environmental conditions concerning temperature, relative humidity and photocycle for the specific species under test." Food (Purina Rodent Chow #5002) and tap water were provided ad libitum throughout the study except during exposures or neurobehavioral testing.

2. Rationale for Dose Selection

Dose selection was based on the results of a 2-week inhalation study in CD-1 mice, in which 5/sex/exposure group were exposed to sulfuryl fluoride over 2 weeks (9 exposures) at chamber concentrations of 30, 100 or 300 ppm. No effects were observed at 30 or 100 ppm but 5 male and 4 females died during the second week of the study; inanition was cited as the cause of death. The 4 hr LC_{50} for CD-1 mice is 650 ppm.

3. Generation and Analysis of Test Atmosphere

Test Chambers and Exposure Conditions: Stainless steel and glass inhalation chambers with pyramidal top and bottom, volume of 1000 L and dynamic chamber airflow of 225 l/min (no. air changes/hr not indicated in report) were used for all exposures. Sulfuryl fluoride gas was introduced into the chambers and appropriate concentrations were generated by the glass J-tube method of Miller et al. (Am. Ind. Hyg. Assoc. J. 4:844, 1980). Sulfuryl fluoride was metered into the J-tubes from SARAN bags and diluted with compressed air, then further diluted and mixed in the main chamber airstream. Chamber airflow was monitored with a Sierra 830 Mass Flow Meter.

Prior to initiation of animal exposure, distribution of the test material in the chambers was determined at each exposure level by measuring concentration at 5 different sampling points within the chamber breathing zone and at the

reference point of the chamber. At 10 ppm, all sample concentrations were within 11% or 1 ppm of target concentration and at 30 and 100 ppm, all values were within 3% of the mean reference point value.

Analysis of Test Atmosphere Concentration: Chamber test material concentrations were analyzed once or twice/hr using a calibrated MIRAN 1A infrared spectrophotometer at a wavelength of 11.8 μm. Chamber temperature and humidity were recorded twice/hour. Particle size (MMAD) was not determined since sulfuryl fluoride is a respirable gas and nominal concentration was not determined.

Results - Analytically determined daily mean test chamber concentrations were 10±0.3, 30±0.05 and 100±1.4 ppm for the 10, 30 and 100 ppm groups, respectively. Daily mean time-weighted averages for each exposure group ranged from 9.0 - 10.9 ppm, 28.6 - 31.8 ppm and 91.0 - 103.2 ppm, respectively. All daily time-weighted average concentrations were within 10% of target concentration, usually better. Sporadic individual chamber concentration measurements varied by more than 10% in the 10 ppm chambers on 4 different exposure days, but these variations did not exceed 18% and daily means were all acceptable (data not shown; see Tables 4, p 32 and A1, p. 83 of study report).

Daily exposure chamber temperature ranged between 19.8 - 23.1°C and relative humidity ranged between 24.9 - 68.8%. For the 0, 10, 30 and 100 ppm exposure chambers, mean temperature was 21.3, 21.2, 21.3 and 21.4°C and mean humidity was 50.2, 46.9, 53.8 and 48.0%, respectively.

4. Statistical Analysis

Bartlett's test was used to examine parameters for equality of variance, followed by parametric or non-parametric ANOVA. Dunnett's test or the Wilcoxon Rank-Sum test with Bonferroni correction for multiple comparisons were then performed. A sequential test was used to identify statistical outliers. Statistical analysis of serum fluoride values was forced to parametric ANOVA because of the small sample size. No statistical analyses were performed on chamber concentrations, humidity or temperature, white blood cell differential and nucleated red blood cell counts.

5. Signed quality assurance and good laboratory practices statements were present.

C. METHODS AND RESULTS:

1. Clinical Observations and Mortality

Animals were observed once daily for mortality and clinical signs of toxicity and a second time for mortality and maintenance animal husbandry (only the mortality check was conducted on weekends). Detailed physical exams were performed weekly, beginning just prior to the study start. An ophthalmologic examination using a penlight was conducted prior to study start to ensure that animals were within normal limits.

Results - A male (100 ppm) and female (10 ppm) died due to accidental trauma during handling. One female (control) died on day 17, reportedly due to a tongue abscess that resulted in inanition. These deaths were not considered treatment-related.

No treatment-related clinical signs of toxicity were observed among surviving animals of either sex.

2. Functional Observational Battery

An abbreviated qualitative functional observational battery was conducted at weeks 4, 8 and 12 to assess more carefully any effects of exposure to sulfuryl fluoride on the following neurobehavioral parameters:

Autonomic functions, including lacrimation, salivation, pupil size, respiration, urine staining, fecal staining and/or diarrhea;

Sensorimotor responses to tail pinch and touch (startle response not assessed because the auditory brainstem response of CD-1 mice is often observed to be poor);

Gait and sensorimotor coordination including gait, pattern and intensity, visual placing;

Clinical observations including convulsions, tremors, skin and haircoat condition, muscle tone, vocalization.

Results - No treatment-related effects on the above neurobehavioral parameters were observed.

3. Body Weights

Body weights were measured weekly including during

acclimatization and at sacrifice.

Results - Representative mean body weights and total body weight gain during the study are shown below in Table 2:

TABLE 2: REPRESENTATIVE MEAN BODY WEIGHTS AND TOTAL WEIGHT GAIN, GRAMS[1,2]

		0 PPM	10 PPM	30 PPM	100 PPM
DAY 1	M	33.1	32.4	32.4	32.8
	F	24.9	24.2	24.9	24.1
DAY 18	M	34.9	34.8	34.3	33.6
	F	26.7	27.2	27.9	25.3
DAY 39	M	38.0	37.1	37.1	34.7* (-9)
	F	28.9	28.9	29.7	27.0 (-7)
DAY 53	M	38.4	37.2	37.6	35.4 (-8)
	F	29.6	29.7	30.4	27.5 (-6)
DAY 74	M	39.2	38.3	38.3	35.5* (-9)
	F	29.8	30.7	30.2	27.6* (-7)
DAY 93	M	39.6	38.8	38.9	35.3* (-11)
	F	30.3	30.7	31.2	27.6* (-9)
TOTAL WT. GAIN[3]	M	6.5	6.4	6.5	2.5 (-61)
	F	5.4	6.5	6.3	3.5 (-35)

1 Data taken from Tables 14 and 15 of study report
2 Numbers in parentheses represent % change compared to controls
3 Weight gain calculated by reviewer; data not analyzed statistically
* $p \leq 0.05$ ** $p \leq 0.01$

Statistically significant reductions in mean body weights were observed in both sexes at 100 ppm (-11%, males and -9%, females at termination). Significant reductions were observed beginning on Day 39 in males and Day 25 in females and were sustained throughout most of the weekly measurements thereafter (not significant in males, day 46 and 53 measurements; in females, day 39, 53 and 60 measurements). Cumulative body weight gain in males and females was also reduced at 100 ppm (-61% and -35% less than controls, respectively). TB-I agreed with the study authors that this reduction was related to treatment.

4. Food Consumption

Food consumption was not determined.

5. Blood was collected for hematology immediately before sacrifice from 10 animals/sex/dose. The CHECKED (X) parameters were examined.

a. Hematology

X		X	
X	Hematocrit (HCT)*	X	Leukocyte differential count*
X	Hemoglobin (HGB)*		Mean corpuscular HGB (MCH)
X	Leukocyte count (WBC)*		Mean corpusc. HGB conc.(MCHC)
X	Erythrocyte count (RBC)*		Mean corpusc. volume (MCV)
X	Platelet count*		Reticulocyte count
	Blood clotting measurements (Thromboplastin time) (Clotting time) (Prothrombin time)		

* Required for subchronic and chronic studies

Results - No treatment-related effects on hematologic parameters were observed.

b. Clinical Chemistry was analyzed from blood collected from 10 rats/sex/group from the orbital plexus immediately prior to sacrifice. The CHECKED (X) parameters were determined.

X	Electrolytes:	X	Other:
X	Calcium*	X	Albumin*
	Chloride*	X	Blood creatinine*
X	Fluoride+	X	Blood urea nitrogen*
	Magnesium	X	Cholesterol*
X	Phosphorus*	X	Globulins
	Potassium*	X	Glucose*
	Sodium*	X	Total bilirubin
	Enzymes	X	Total serum protein (TP)*
X	Alkaline phosphatase (ALK)	X	Triglycerides
	Cholinesterase (ChE)		Serum protein electrophores
	Creatinine phosphokinase*		Direct bilirubin
	Lactic acid dehydrogenase (LDH)	X	A/G ratio
X	Serum alanine aminotransferase (SGPT)*		
X	Serum aspartate aminotransferase (SGOT)*		
	Gamma glutamyl transferase (GGT)		

* Required for chronic studies
+ Fluoride ion only analyzed in the 4 animals/sex/dose used for whole-body perfusion

Results - Selected clinical chemistry parameters are shown below in Table 3:

TABLE 3: SELECTED CLINICAL CHEMISTRY PARAMETERS[1]

	Sulfuryl fluoride concentration			
Sex/Parameter	0 ppm	10 ppm	30 ppm	100 ppm
MALES				
Fluoride, ppm	0.107	0.112	0.156	0.259*
Triglyceride, mg/dl	91	83	89	143*
Alk. phos., mu/ml	43	42	47	57*
FEMALES				
Fluoride, ppm	0.090	0.088	0.132*	0.233*
Triglyceride, mg/dl	76	63	81	69
Alk. phos., mu/ml	45	52	49	58

1 Data extracted from Tables 20 through 24 of study report
* $p \leq 0.05$

Sulfuryl fluoride caused a dose-related increase in the serum fluoride levels of males and females at 30 and 100 ppm. The increases were statistically significant in males and females at 100 ppm (approximately 250% increase in both sexes) but only in females at 30 ppm (approximately 50% increase in both sexes). It is noted, however, that mean fluoride levels represent only a sample of 4 animals/sex/dose. Statistically significant elevations in serum triglyceride (+33%) and alkaline phosphatase (+46%) were observed at 100 ppm in males only; TB-I did not consider these to be biologically significant. A significant portion of the increase in triglycerides was due largely to one male with a high level. There was also no corresponding microscopic pathology observed in the liver.

7. Sacrifice and Pathology

Ten animals/sex/dose of the main study group that died or were sacrificed on schedule were subject to gross pathological examination and the CHECKED (X) tissues were collected for histological examination. Sacrifice was performed under methoxyflurane anesthesia. Eyes were examined in situ using a glass slide technique under fluorescent light. Lungs were infused with fixative to restore their approximate inspiratory volume and nasal cavities flushed with fixative via the pharyngeal duct for rapid fixation. Except for nasal tissues, trachea, lungs, brain, thyroid, heart, liver, kidneys, salivary glands and testes, only control and high dose tissues were examined. The (XX) organs, in addition, were weighed.

Perfusion for Neurohistopathology and Processing of Tissues: The satellite groups of 4 mice/sex/exposure group

were anesthetized with CO_2 on the day following the last exposure, blood collected for fluoride analysis, eyes examined in situ using a glass-slide technique with fluorescent light and perfused in situ with neutral phosphate buffered 1.5% glutaraldehyde/4% formaldehyde. A total of 3 sections were examined from the brain of each animal. These sections included the following regions of the brain: corpus callosum, caudate putamen, globus pallidus, optic chiasm, cortex (parietal, frontal, temporal), lateral ventricles, hippocampus, thalamus, hypothalamus, third ventricle, cerebellum, inferior colliculus, V nerve, pyramidal tract, nucleus trapezoid body. Slides of nervous system tissues were processed for hematoxylin and eosin staining; special stains were not used because previous studies in rats exposed to sulfuryl fluoride did not demonstrate an advantage in identifying lesions (microvacuolation) sometimes associated with sulfuryl fluoride exposure.

X		X		X	
Digestive system		Cardiovasc./Hemat.		Neurologic	
X	Tongue	X	Aorta*	XX	Brain*+
X	Salivary glands*	XX	Heart*	X	Periph. nerve*#
X	Esophagus*	X	Bone marrow*	X	Spinal cord (3 levels)*#
X	Stomach*	X	Lymph nodes*	X	Pituitary*
X	Duodenum*	X	Spleen		Eyes (optic n.)*#
X	Jejunum*	X	Thymus*	Glandular	
X	Ileum*	Urogenital		X	Adrenal gland*
X	Cecum*	XX	Kidneys*+	X	Lacrimal gland#
X	Colon*	X	Urinary bladder*	X	Mammary gland*#
X	Rectum*	XX	Testes*+	X	Parathyroids*++
XX	Liver *+	X	Epididymides	X	Thyroids*++
X	Gall bladder*	X	Prostate	Other	
X	Pancreas*	X	Seminal vesicle	X	Bone*#
Respiratory		X	Ovaries*+		Skeletal muscle*#
X	Trachea*	X	Uterus*	X	Skin*#
X	Lung*			X	All gross lesions and masses*
X	Nose^			X	Coagulating gland
	Pharynx^				
X	Larynx^				

* Required for subchronic and chronic studies.
^ Required for chronic inhalation.
# In subchronic studies, examined only if indicated by signs of toxicity or target organ involvement.
+ Organ weight required in subchronic and chronic studies.

a. Organ weight - Selected mean organ weight data are presented below in Table 4:

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TABLE 4: SELECTED MEAN ABSOLUTE (GRAMS) AND RELATIVE (% BODY WT) ORGAN WEIGHTS[1]

SEX/ORGAN:		0 PPM	10 PPM	30 PPM	100 PPM
MALES (N)		(10)	(10)	(10)	(9)
Brain	Abs	0.502	0.493	0.479	0.471*
	Rel	1.294	1.321	1.288	1.377
Liver	Abs	2.212	2.146	2.163	1.861*
	Rel	5.682	5.770	5.779	5.411
Kidney	Abs	0.625	0.614	0.638	0.490*
	Rel	1.604	1.645	1.703	1.427
Heart	Abs	0.170	0.166	0.164	0.147*
	Rel	0.436	0.444	0.439	0.428
FEMALES (N)		(9)	(9)	(10)	(10)
Brain	Abs	0.511	0.504	0.504	0.482*
	Rel	1.721	1.619	1.647	1.760
Liver	Abs	1.621	1.650	1.673	1.477*
	Rel	5.460	5.300	5.463	5.373
Kidney	Abs	0.385	0.406	0.407	0.371
	Rel	1.297	1.303	1.330	1.350
Heart	Abs	0.134	0.141	0.139	0.125*
	Rel	0.451	0.453	0.454	0.454

1 Data taken from Tables 26 and 27 of study report
* $p \leq 0.05$

Statistically significant reductions in liver, kidney and heart absolute weights at 100 ppm in both sexes were related to reduced body weight and relative organ weights showed no significant differences compared to controls. Except for absolute kidney weight in males, which was reduced by 22% compared to controls, decreases were less than 10%. No corresponding microscopic pathology was observed in these organs.

Absolute brain weight was also statistically significantly reduced at 100 ppm in both males and females (6% less than controls), but the relative brain weights were not affected.

b. Gross Observations - No treatment-related grossly visible effects were observed.

c. Microscopic Pathology - Selected histopathologic observations are shown below in Table 5. Findings from the 4

perfused animals/sex/dose are listed separately:

TABLE 5: SELECTED HISTOPATHOLOGICAL OBSERVATIONS[1]

	PPM			
SEX/OBSERVATION	0	10	30	100
MALES: (No. examined)	(10)	(10)	(10)	(10)
Brain				
Caudate putamen vacuol., focal, v.sl. to sl.	0	0	0	9
External capsule vacuol., focal, v.sl. to sl.	0	0	0	9
Salivary glands				
Decr. salivary material, v.sl.	1	0	1	10
Thyroid gland				
Follicular hypertrophy, v.sl.	0	0	0	9
PERFUSED MALES: (No. examined)	(4)	(4)	(4)	(4)
Cerebrum				
Caudate putamen, vacuol., focal, v.sl. to sl.	0	0	0	3
Ext. capsule vacuol., focal, v.sl. to sl.	0	0	0	4
Thalamus/hypothalamus				
Ext. capsule vacuol., focal, v.sl. to sl.	0	0	0	4
FEMALES: (No. examined)	(10)	(10)	(10)	(10)
Brain				
Caudate putamen vacuol., focal, v.sl. to sl.	0	0	0	8
External capsule vacuol., focal, v.sl. to sl.	0	0	0	10
Salivary glands				
Decr. salivary material, v.sl.	1	0	0	0
Thyroid gland				
Follicular hypertrophy, v.sl.	0	0	0	6
PERFUSED FEMALES: (No. examined)	(4)	(4)	(4)	(4)
Cerebrum				
Caudate putamen, vacuol., focal, v.sl. to sl.	0	0	0	3
Ext. capsule vacuol., focal, v.sl. to sl.	0	0	0	4
Thalamus/hypothalamus				
Ext. capsule vacuol., focal, v.sl. to sl.	0	0	0	3

1 Data extracted from Tables 29 and 30 of the study report.

Mild effects were observed at 100 ppm in the caudate putamen and external capsule, which showed very slight to slight vacuolization, in all animals except the male that died. In some cases the study pathologist noted involvement of the amygdaloid region. The lesion was not associated with inflammatory or degenerative lesions and was generally more prominent in female mice. Despite the low degree of severity, this is considered treatment-related due to the complete lack of this observation in all control, low- or mid-dose animals and observation of similar brain lesions in other species exposed to sulfuryl fluoride (see Discussion). Increased thyroid follicular cell hypertrophy (v. slight) was also observed only at 100 ppm in males and females; severity was greater in males. The study authors considered the reduced secretory material in salivary glands of the high-dose

males to be related to the body weight effects.

D. DISCUSSION

This 13-week inhalation study was conducted as a range-finding study for an 18-month inhalation oncogenicity study in mice (MRID 43354903; currently in review). The main target organs of sulfuryl fluoride in the mouse following subchronic inhalation exposure to 100 ppm sulfuryl fluoride are brain and thyroid. Male and female mice showed reduced body weight/body weight gain, vacuolation of the caudate putamen/external capsule and thyroid follicular cell hypertrophy. Although the severity of the brain and thyroid microscopic lesions was slight, TB-I agreed with the study authors that they are related to treatment. The toxicologic significance of the reduced secretory material in the salivary glands of males is unclear, but is possibly secondary to body weight effects as suggested by the study authors. In the absence of toxicity at 30 ppm, the increase in serum fluoride is not used to determine systemic toxicity LOEL/NOEL, but a separate LOEL/NOEL is provided.

Similar brain lesions were observed in the 18-month mouse oncogenicity study and the 1-year dog study (MRID 43354901; currently in review) and previously reviewed studies (eg. 90-day rat neurotoxicity study, MRID 40839902/HED doc. no. 009479; 13-week dog study, MRID 43356601/HED doc. no. 009506; rat 2-generation reproduction study, MRID 41279801/HED doc. no. 009479). The rat neurotoxicity NOEL is 30 ppm (based on electrophysiological disturbances) and therefore neurotoxicity effects are observed at similar exposure concentrations in both rat and mouse. The toxicity endpoint for subchronic/chronic exposure risk assessment will be determined following completion of review of submitted data.

Classification: Core-Minimum

Study deficiencies: Details of non-exposure housing conditions not provided, some hematology and clinical chemistry parameters not evaluated, food consumption not measured, some organs (thyroid, adrenals, lung) not weighed. The lack of this information is not considered sufficient to affect the conclusions of this study.