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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

JUN 24 1993

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: **Sulfuryl Fluoride. ID# 078003.** Evaluation of a Neurotoxicity Study on Short-Term Inhalation Exposure of Rats, Performed According to a Modified Protocol for Guideline 81-8.

Tox. Chem. No.: 816A
PC No.: 078003
Submission No.: S441354
DP Barcode No.: D191640

FROM: Linnea J. Hansen, Ph.D.
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THRU: Marion P. Copley, D.V.M., D.A.B.T.
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CONCLUSIONS:

In the attached DER, TB-I has reviewed the short-term neurotoxicity study of sulfuryl fluoride in rats (MRID 427720-01). TB-I agreed with the study authors' conclusion that there were no apparent neurotoxic effects in rats exposed for 2 consecutive days (6 hrs/day by inhalation) at doses up to 300 ppm. Parameters examined included functional observational battery, motor activity and the electrophysiological parameters affected in the 13-week inhalation study in rats (flash-evoked potential, sensory-evoked potential and auditory brainstem response to click; reviewed in HED Doc. no. 9479). Microscopic neuropathology was not examined based on lack of effects in a 2-week rat inhalation study at 100 or 300 ppm (study not reviewed by TB-I).

NOEL: ≥ **300 PPM**
LEL: > **300 PPM** (no neurotoxicity or general clinical effects were observed at any dose tested).

Classification: **Core-Minimum**

1

This study appeared to have been properly conducted and is considered acceptable for regulatory purposes. Although it does not strictly meet Guideline 81-8 requirements, it satisfies the data requirement for this study as modified by agreement between the Agency and DowElanco and provides a NOEL for short-term inhalation exposure to sulfuryl fluoride. The protocol modifications are discussed in greater detail in the DER.

ACTION REQUESTED:

DowElanco submitted for evaluation a study entitled "Sulfuryl Fluoride: Electrodiagnostic, FOB and Motor Activity Evaluation of Nervous System Effects from Short-Term Exposure". This study was performed as required by a Data Call-In for additional neurotoxicity testing for sulfuryl fluoride (memo from L. Hansen to L. Rossi, dated 7-31-92) with protocol modifications to Guideline 81-8 as agreed upon by the Agency and DowElanco during a conference call on 1-27-93. The intent of this study was to provide an acceptable NOEL for short-term inhalation exposure to sulfuryl fluoride as might be expected for applicators following reentry into fumigated/aerated structures. The protocol modifications were intended to obtain a reasonable NOEL and to minimize unnecessary tests (eg. where results of previously conducted studies indicated that no effects would be expected).

010363

GUIDELINE: 81-8

Primary Review: Linnea J. Hansen, Ph.D. Linnea J Hansen 6/21/93
Review Section IV, Tox. Branch I
Secondary Review: Marion P. Copley, D.V.M., D.A.B.T.
Review Section IV, Tox. Branch I
Marion P. Copley 6/21/93

DATA EVALUATION RECORD

STUDY TYPE: Short-Term Neurotoxicity TOX. CHEM. NO.: 816A
Species: Rat
Guideline: 81-8 (Specially Designed Study)

MRID NO.: 427720-01 PC NO.: 078003

TEST MATERIAL: Sulfuryl Fluoride

SYNONYMS: Vikane®/CAS No. 2699-79-8

SPONSOR: DowElanco, 9002 Purdue Rd., Indianapolis, Indiana 46268-1189

STUDY DOC. NO.: K-016399-045, -045D, -045E, -045F, -045G

TESTING FACILITY: The Toxicology Research Laboratory, Health and Environmental Sciences, Dow Chemical Company, Midland, MI 48674

TITLE OF REPORT: Sulfuryl Fluoride: Electrodiagnostic, FOB and Motor Activity Evaluation of Nervous System Effects from Short-Term Exposure

AUTHORS: R.R. Albee, P.J. Spencer and G.J. Bradley

REPORT ISSUED: May 3, 1993

CONCLUSIONS:

Doses administered: 0, 100 or 300 ppm sulfuryl fluoride, by inhalation to female Fischer 344 rats for 2 consecutive days, 6 hrs exposure/day.

NOEL: ≥ 300 ppm
LEL: > 300 ppm (no treatment-related effects on electrophysiological, functional or motor activity parameters were observed in this study).

Classification: Core-minimum

This study appeared to have been properly conducted and is considered acceptable for regulatory purposes. It was conducted in order to provide sufficient information to

determine a NOEL for short-term inhalation exposure to sulfuryl fluoride and was performed according to a modified protocol as agreed upon by the Agency and DowElanco.

A signed quality assurance statement was present.

A. MATERIALS

Test Compound:	sulfuryl fluoride, technical	
	Purity:	99.8% (w/w)
	Description:	odorless, colorless gas
	Lot No.:	WP 920619-953
	Contaminants:	air and water
Vehicle:	none (air)	
Test Animal:	Species:	rat
	Strain:	Fischer-344 (females only)
	Source:	Charles River Laboratories, Inc., Kingston, NY
	Age:	approx. 10 weeks at start of study
	Weight:	133.5 - 162.7 g

B. STUDY DESIGN

1. Modifications to 81-8 Neurotoxicity Testing Protocol: This study was performed according to a modified protocol for Guideline 81-8 as agreed upon by DowElanco and the Agency in order to obtain a NOEL for short-term inhalation exposure to sulfuryl fluoride. Neurotoxicity was the most sensitive endpoint in a 13-week inhalation study in rats (NOEL = 30 ppm; disturbances in electrophysiological parameters observed at 100 ppm; MRID 408399-02; reviewed in HED Doc. no. 9479). The following modifications were incorporated into the study design:

   a. Female rats only were tested due to the number of parameters to be examined and since they appeared to be slightly more sensitive in the 13-week study.

   b. Two doses were selected, 100 and 300 ppm, based on results from previously conducted 2-week and 13-week inhalation studies in rats (see B-2 below). Achievement of toxicity at high dose was not required.

   c. A 2-day exposure was performed to approximate repeated short-term exposure as might be expected for applicators following reentry after aeration.

   d. Only those electrodiagnostic parameters affected in the 13-week rat study were tested.

e. Histology was not required because no microscopic neuropathology was observed in the 2-week rat study at doses up to 600 ppm.

f. The Agency agreed that motor activity (MA) may be tested on the day following exposure, rather than the same day, due to logistical problems with completion of all required parameters. The functional observational battery (FOB) and electrophysiological parameters (EP) were to be assessed as soon after termination of exposure as possible.

2. Rationale for Dose Selection

Doses were chosen based on results of previously conducted 2-week and 13-week inhalation studies in rats [data summarized in Dow Study Report ID No. TOXOV; "Sulfuryl Fluoride (SO_2F_2) Toxicological Overview", dated 7-1-92]. In the 2-week study (not reviewed by TB-I), mild kidney lesions were observed at 300 ppm; at 600 ppm sulfuryl fluoride caused kidney lesions, respiratory effects and mortality. No neurohistopathology was observed at any dose. The study NOEL was 100 ppm, but neurological functional or electrophysiological parameters were not examined.

Kidney lesions were also observed at 300 ppm in the 13-week study, along with respiratory effects, fluorosis of teeth, excess salivation and degenerative microscopic changes in the brain (single animal). Effects on electrophysiological parameters (increased latency of flash-evoked potential and somatosensory evoked response in females; auditory brain stem response in males) were noted at 100 ppm. The study NOEL was 30 ppm.

Based on the available information and the intent of this study, doses of 100 and 300 ppm were tested. It was anticipated that these doses would provide adequate information to determine a NOEL for short-term inhalation exposure to sulfuryl fluoride.

3. Animal Assignment

Following a minimum 1-week acclimatization period, animals were randomly assigned to the following test groups as shown in Table 1:

Test Group	Dose Level (ppm)	Number Assigned (female only)
Control	0	12
Low Dose	100	12
High Dose	300	12

of variance. Reactivity to handling was tested statistically using a test of proportions (Bruning and Kintz, 1977). Other FOB parameters were analyzed qualitatively. Statistical analysis is summarized in the table in Appendix 1.

The Fmax test for homogeneity of variance was performed (Bruning and Kintz, 1977). Outliers were removed one at a time when departure from homoscedasticity was considered too extreme by the Study Director. In this study 4 correlation values from the 100 ppm and 3 values from the 300 ppm pre-exposure FEP-V low-intensity, mid-latency groups were removed. One value from the post-exposure FEP-V low intensity, mid latency group was also removed. ANOVA was conducted post hoc for treatment effects on post-exposure correlation data for this parameter.

C. METHODS AND RESULTS:

1. Functional Observational Battery (FOB)

An FOB was conducted preexposure and between 0.7 and 1.4 hrs post-exposure (body weights taken between 0.4 - 0.6 hrs post-exposure). The following parameters were examined:

a. body weight
b. cage-side observations (abnormal movements or behavior, ease of removal)
c. hand-held observations (general appearance, palpebral closure, pupil size, lacrimation, salivation, abnormalities of skin or haircoat, perineal staining, muscle tone, extensor-thrust response, abnormal movements eg. tremors, convulsions, abnormal respiration and reactivity to handling)
d. open-field observations (responsiveness to noise, touch or tail pinch, abnormal behavior, activity level, gait and urine/fecal quantities)
e. hind- and forelimb grip performance
f. hindlimb landing food splay.

Results - Representative FOB parameters measured before and after exposure are presented below in Table 2:

TABLE 2: FUNCTIONAL OBSERVATIONAL BATTERY[1]

	0 PPM		100 PPM		300 PPM	
PARAMETER	Pre-exp.	Post-exp.	Pre-exp.	Post-exp.	Pre-exp.	Post-exp.
Body wt., g	145.9	142.8	145.9	143.7	143.5	139.7
Hindlimb grip, g grip/g body wt.	1.51	1.67	1.48	1.61	1.60	1.71
Forelimb grip, g grip/g body wt.	1.28	1.97	1.40	1.89	1.46	1.94
Foot splay, cm	3.03	3.14	2.92	3.2	2.64	2.93
(Values below expressed as number of animals per dose group with observation)						
Resistance to removal min.	6	2	5	3	2	1
mod.	0	0	1	0	0	0
Reaction to handling, min.	1	5	1	6	2	2
mod.	11	2	11	1	10	0
Reaction to sharp noise, min.	1	2	0	0	0	1
mod.	9	10	11	11	9	9
pron.	2	0	1	1	3	2
Reaction to tail pinch, min.	0	0	0	1	0	1
mod.	12	12	12	11	12	11
Urination, none	3	0	0	1	2	1
min.	7	9	9	9	7	10
mod.	2	3	3	2	3	9
Defecation, none	9	3	7	6	5	6
min.	3	6	5	3	6	6
mod.	0	3	0	2	1	1
pron.	0	0	0	1	0	1

1 Data taken from Tables II-2 to II-7; all parameters reflect results from 12 animals per dose group tested over a four-day period

Mortality: There was no mortality during the study.

Functional Observations: There were no statistically significant, treatment-related effects observed among functional parameters following exposure to sulfuryl fluoride at 100 or 300 ppm. Rats exposed to 300 ppm showed diminished reaction to handling which was not statistically significant and probably reflected animals becoming accustomed to handling. All animals showed normal gait, coordination, behavior, respiration, muscle tone, extensor thrust, pupil size, salivation, lacrimation, palpebral closure (open) and response to touch. No treatment-related general clinical observations (including appearance of eyes, feces, urine, skin, fur or other general observations) were observed.

Measurements of front or hind limb strength and landing foot splay showed no treatment-related differences. Mean body weights were also unaffected by treatment: in each group including controls, mean body weights were slightly lower following exposure (<3%), which probably reflected the withholding of food during exposures.

2. Electrodiagnostics

Surgery: Rats were implanted with epidural electrodes (somatosensory, visual cortex, cerebellar and reference electrodes) 3 weeks before exposure. Animals were anesthetized by methoxyflurane inhalation and maintained under anesthesia by isoflurane. Stereotactic instruments were used to place 4 epidural electrodes (7 mm stainless steel set screws) into the skull, held in place with dental acrylic.

Collection of Data: A Nicolet Pathfinder II electrodiagnostic system (Nicolet Biomedical Instruments, Madison, WI) was used. The following data were collected prior to exposure and between 1.5 - 4.4 hrs post-exposure:

a. Flash evoked potential (FEP-V from visual cortex and FEP-C from cerebellum). Strobe flashes of 0.1 and 0.6 cd-s/m^2 at a rate of 0.7 flashes/sec were used. Early latency reflects visual cortex input and early complex processing; mid-latency reflects complex cortical-cortical and cortical-subcortical processing.
b. Auditory brainstem response to clicks (ABR-C). Clicks of 75 dB at a rate of 29.1 clicks/sec were used and response was recorded from the electrode over the cerebellum. Reflects processing from accoustic nerve to upper brainstem.
c. Somatosensory evoked potentials (SEP-S from sensory cerebral cortex and SEP-C from cerebellar vermis). Electrical stimuli of 3 mA, 50μsec at a rate of 1.7 pulses per second were used. Stimuli were delivered from the ventrolateral caudal nerves at base of the tail. SEP-S reflects somatosensory input pathway, brainstem, thalamus and first cortical neuron. SEP-C reflects complex cortical and cortical-subcortical processing.

Body temperature was recorded from a rectal thermometer prior to and after collection of electrodiagnostic data.

Analysis of Data: Waveforms were digitally filtered to emphasize particular frequency components. Waveforms from individual animals were averaged to give a composite waveform for pre- and post-exposure data. Composites were compared to a template for each parameter made by making an average waveform of all pre-exposure responses.

Results - Summarized representative results of the electrodiagnostic tests are presented below in Table 3:

TABLE 3: ELECTROPHYSIOLOGICAL TESTING RESULTS (POST-EXPOSURE ONLY)[1]

FLASH EVOKED POTENTIAL (FEP_V)						
	LOW INTENSITY			MEDIUM INTENSITY		
EARLY-LATENCY (35.1 - 95.1 msec)	LATENCY[2]	CORRELATION[3]	POWER[4]	LATENCY	CORRELATION	POWER
0 PPM	-3.57	0.65	26.8	-1.17	0.50	36.3
100 PPM	-4.10	0.64	28.6	-0.90	0.50	38.7
300 PPM	-4.10	0.67	28.5	-1.15	0.52	37.2
MID-LATENCY (94.8 - 282.0 msec)	LATENCY	CORRELATION	POWER	LATENCY	CORRELATION	POWER
0 PPM	-2.10	0.98	114.2	1.00	0.98	136.3
100 PPM	-5.90	0.94	110.9	-1.10	0.96	140.9
300 PPM	-4.30	0.96	90.5	-2.30	0.97	137.1

SENSORY EVOKED POTENTIAL (SEP)						
	CEREBELLUM (SEP_C)			SENSORY CORTEX (SEP_S)		
EARLY-LATENCY (4.0 - 25.0 msec)	LATENCY	CORRELATION	POWER	LATENCY	CORRELATION	POWER
0 PPM	-0.29	0.84**	18.1	-0.01	0.90	11.7
100 PPM	-0.33	0.92	19.6	-0.24	0.90	15.3
300 PPM	-0.17	0.93	17.4	-0.06	0.90	15.0
LONG-LATENCY (25.1 - 70.0 msec)	LATENCY	CORRELATION	POWER	LATENCY	CORRELATION	POWER
0 PPM	1.23	0.98	37.9	0.17	0.97	71.0
100 PPM	0.43	0.98	38.6	-0.20	0.95	89.2
300 PPM	1.23	0.99	37.9	-0.43	0.97	83.9

AUDITORY BRAINSTEM RESPONSE (ABR_C)				
(1.13 - 5.0 msec)	LATENCY	CORRELATION	POWER	
0 PPM	-0.01	0.93	2.52	
100 PPM	0.01	0.93	2.79	
300 PPM	0.01	0.95	2.82	

1 Data taken from Tables IV-5, IV-6, IV-9 and IV-10 of study
2 Latency difference in msec between individual waveform and template waveform for defined data window
3 Optimized cross correlation (R) between individual waveform and template waveform for defined data window
4 Standard deviation of voltage (μV) across defined data window
** Statistically significant differences by treatment x time for treated animals

Composite waveforms for each parameter are presented in Appendix 2. There were no apparent treatment-related effects observed among animals exposed to 100 or 300 ppm sulfuryl fluoride for 2 days. SEP-C waveforms were statistically significant (repeated ANOVA $\alpha < 0.02$) when analyzed treatment x time, representing a greater degree of correlation with the composite waveform. This was not considered a toxicologically significant effect since it did not represent a deleterious change. Cerebellar FEP waveforms were not analyzed statistically. Body temperature was measured prior to and after ED testing and it was not affected by exposure to sufluryl fluoride.

3. Motor Activity

Motor activity was assessed prior to exposure and at 18 - 19 hrs post-exposure rather than on the same day for logistical reasons. Animals were placed in visually separated motor activity chambers in a quiet, dimly lit room. Infrared photobeams in the chambers were calibrated prior to each testing session. Motor activity (no. beam breaks) was measured for each animal in 48 minute sessions. Activity was monitored using a DEC PDP11/83 microcomputer with SKED-11 Software System and Micro/RSX Operating System. Data was analyzed both as total activity per session and as activity per epoch (each session consisted of six, 8 minute epochs).

Results - Total motor activity and activity by epoch (pre- and post-exposure) is presented below in Table 4:

TABLE 4; MOTOR ACTIVITY (BEAM BREAKS/48 MINUTE SESSION OR BREAKS/8-MIN EPOCHS)[1]

	0 PPM		100 PPM		300 PPM	
	Pre-exp	Post-exp	Pre-exp	Post-exp	Pre-exp	Post-exp
Total Beam Breaks	12.51	9.76	12.51	10.67	12.22	10.44
Breaks by Epoch:						
1 (0-8 min)	7.53	6.52	7.44	7.79	7.34	7.65
2 (9-16 min)	6.12	4.83	6.17	4.27	6.09	4.91
3 (17-24 min)	5.02	3.19	4.93	2.87	5.74	2.85
4 (25-32 min)	3.56	2.16	3.63	1.96	3.79	1.36
5 (33-40 min)	3.48	1.49	2.21	1.83	1.59	1.16
6 (41-48 min)	0.67	0.59	2.07	0.83	0.63	0.83

1 Data taken from Tables III-1 to III-3 of study

There were no apparent treatment-related effects on motor activity in rats tested up to 300 ppm for either total activity or during 8-minute epochs. Activity decreased with

time for all dose groups as animals became accustomed to the chamber.

D. DISCUSSION:

TB-I agreed with the Study Authors that there were no apparent treatment-related neurotoxic effects (or effects on other general clinical observations made in this study) following 2-day inhalation exposure to sulfuryl fluoride at 100 or 300 ppm. Testing was not repeated at later times (eg. 7 and 14 days post-exposure) because of the absence of effects within 18 hrs of exposure. Sensitivity of the motor activity testing may have been reduced because testing was not performed until 18 hrs post-exposure, but was considered acceptable by TB-I since it was performed within 24 hrs of termination of exposure, no FOB effects were noted immediately following exposure and since there was no evidence of MA effects in a chronic inhalation study interim testing at 3 months at doses up to 80 ppm (study in progress; results to-date summarized in the sulfuryl fluoride toxicity overview document mentioned previously). Electrophysiological parameters affected at 100 ppm in the 13-week rat study (slowing of SEPs, FEPs and ABR) were not affected after 2-days' exposure at 100 or 300 ppm. Concentrations of sulfuryl fluoride which cause neurotoxic effects when administered subchronically therefore do not appear to cause observable neurotoxic effects when exposure is short-term. A NOEL of 300 ppm was therefore established in this study for short-term inhalation exposure to sulfuryl fluoride.

NOEL: $\geq$ 300 ppm
LEL: > 300 ppm (no treatment-related effects observed at any dose)

Classification: Core-Minimum

VIKANE (Sulfuryl fluoride) Tol Petition 610363

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