10-17-91

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

008711

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

OCT 17 1991

MEMORANDUM

SUBJECT: Review of Rangefinding Toxicological Studies for Different Isomer Mixtures of Sulfluramid ([redacted])

TO: Phil Hutton/Michael Mendelsohn, PM-18
Registration Division (H-7505C)

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DP BARCODE NO.: D164368
CASWELL NO.: 454E
SUBMISSION NO.: S396021
HED PROJECT NO: 1-1257
MRID NO.: 418699-00 (Cover letter and Summary Report);
418699-01 (Rangefinding Study with Sulfluramid [redacted])
418699-02 (Rangefinding Study with Sulfluramid [redacted])
418699-03 (Rangefinding Study with Sulfluramid [redacted])
418699-04 (Rangefinding Study with Sulfluramid [redacted])

ACTION REQUESTED

To review rangefinding toxicological studies for different Sulfluramid isomeric [redacted] mixtures [redacted] fed in the diet of rats for a period of 28 days.

BACKGROUND

Sulfluramid is used as an indoor bait product against ants and roaches. It can be produced with different ratios of [redacted] isomers. Four rangefinding toxicological studies in rats fed with various sulfluramid isomeric ratios for a period of 28 days were conducted to compare the toxicities of these isomeric mixtures. The results of these rangefinding studies will be used as the basis for the selection of the appropriate test material for a subchronic toxicity study.

MANUFACTURING PROCESS INFORMATION IS NOT INCLUDED

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SUMMARY OF THE FOUR RANGEFINDING STUDIES SUBMITTED

Study Design

Four studies consisted of five treated dose groups of five male and five female Sprague-Dawley rats. Each group was fed with 30, 60, 120, 240, and 480 ppm in the diet with sulfluramid [redacted] respectively, for a period of 28 days. Two concurrent control groups of 5 males and 5 females each received untreated diet only. One of the control groups was compared with Sulfluramid [redacted] and [redacted] treated groups and the other control was compared with the [redacted] and [redacted] Sulfluramid treated groups.

Test Compounds

Composition of the four test compounds used in the four rangefinding studies were as follows:

- o Sulfluramid [redacted] (MRD-89-513). A pale yellow paste. Analysis showed that it consisted of [redacted] isomers.
- o Sulfluramid [redacted] (MRD-89-512). A white powder/crystal. Analysis indicated that it consisted of [redacted] isomers.
- o Sulfluramid [redacted] (MRD-89-468). A white powder. Analysis indicated that it consisted of [redacted] isomers plus [redacted]
- o Sulfluramid [redacted] (MRD-89-467). A white powder/crystal. Analysis indicated that it consisted of [redacted] isomers.

Results of the Rangefinding Studies

a. Mortality (Appendix S-A)

Administration of the various sulfluramid isomer ratios in the diet up to 120 ppm for a period of 28 days did not result in any deaths. Based on the results of the mortality data (see Appendix S-A) Sulfluramid [redacted] appears to be more toxic than the other sulfluramid isomer ratios. Sulfluramid [redacted] is more toxic to the males than to the females. There was an increase in deaths with increasing dosages and length of dietary administration of sulfluramid, regardless of its isomer ratios.

b. Clinical Signs

Emaciation and hyperactivity were observed in rats fed at high doses with all four sulfluramid isomer ratios. Tremors and red oral discharge were noted in rats fed with sulfluramid [redacted]. Urine stain was only observed in rats fed with sulfluramid [redacted] and [redacted] In general, symptoms of toxicity increased with increasing dose and they were more prevalent in Sulfluramid [redacted] and [redacted] treated rats.

MANUFACTURING PROCESS INFORMATION IS NOT INCLUDED

c. Body Weight, Percent Body Weight Gain, and Food Consumption Values (Appendices S-C and S-D).

Body weight and food consumption values derived from the individual studies and percent body weight gains (calculated by this reviewer) are presented in Appendices S-C and S-D.

Treatment-related body weight and food consumption reductions were observed in 240 and 480 ppm males and in 120, 240, and 480 ppm females as compared to their respective controls. The effects of body weight and food consumption reductions were more pronounced in the females than in the males. Sulfluramid [redacted] did not appreciably affect the 480 ppm male body weights but Sulfluramid [redacted] affected the 240 ppm male body weights more severely than the other Sulfluramid isomers given at the same dose level.

d. Testis and Epididymis Weights

The relative testis and epididymis weights of the treated groups were comparable to their respective controls and no treatment-related effects were evident.

e. Gross Abnormalities (Appendix S-E)

Thickened liver was observed in treated rats up to 240 ppm dose level, but none was observed in the 480 ppm dose level. The largest incidences of thickened liver were observed in the 60, 120, and 240 ppm dose groups. It is noted that thickened liver was only observed in male rats treated with Sulfluramid [redacted] and Sulfluramid [redacted] Except for rats treated with Sulfluramid [redacted] discolored liver was confined to the 240 and 480 ppm dose groups.

Undescended testes were observed in the 240 ppm and 480 ppm dose groups treated with the various Sulfluramid isomer ratios.

f. Microscopic Abnormalities (Appendix S-F)

As indicated in the individual DERs for the rangefinding study reports, serious discrepancies in the reporting of the histopathological data were noted in these study reports:

- Study with Sulfluramid [redacted] (MRID#418699-01). There is some concern why grossly abnormal livers of the intermediate dose groups (30, 60, and 120 ppm) observed during necropsy were not histopathologically evaluated. It was noted on p. 14 of the study report that "grossly abnormal livers in the 120 and 240 ppm dose groups were to be microscopically evaluated...", however, Table 21 (p. 102 of the study report) indicates that grossly abnormal livers of the lower dose groups were not microscopically evaluated.

- Study with Sulfluramid [redacted] (MRID#418699-02). Although on p. 14 of the study report it was noted that grossly abnormal livers in the 120 and 240 ppm dose groups were to be microscopically evaluated, the investigators failed to evaluate grossly abnormal livers of the 120 ppm and other lower dose livers observed during necropsy.

- Study with Sulfluramid [redacted] (MRID#418699-04). It was noted on p. 20 of the study report that no rats of the 480 ppm dose group exhibited hepatocellular hypertrophy, while on table 18 (p. 99 of the study report) it was stated that no 480 ppm rat livers were examined histopathologically because all rats died prior to necropsy.

Because of the discrepancies noted above, only tentative conclusions can be made on the results of histopathological findings as follows:

- It appears that the liver is the target organ for all the various Sulfluramid isomer ratios tested. Liver abnormalities were observed in the 60, 120, 240, and 480 ppm dose groups. Because livers of the 30, 60, 120 ppm Sulfluramid [redacted] and [redacted] the 30 ppm Sulfluramid [redacted] the 30 and 60 ppm Sulfluramid [redacted] dose groups were not histopathologically evaluated and since only a limited number of the other available livers were evaluated, definitive conclusions can not be made.

- Microscopic testis and epididymis abnormalities were noted in one of the three 240 ppm Sulfluramid [redacted] rats evaluated.

CONCLUSIONS AND RECOMMENDATIONS

Based on the mortality data, variability among the various sulfluramids was noted. Sulfluramid [redacted] appears to be more toxic than the other sulfluramid isomeric mixtures, while Sulfluramid [redacted] and Sulfluramid [redacted] exhibited sex variability.

In general, clinical signs increased with increasing dose and they were generally more prevalent in sulfluramid [redacted] and [redacted] treated rats than in rats treated with the other two test articles. Slight variability in the distribution of certain clinical signs was also noted.

Generally, the effects of body weight and food consumption reductions were more pronounced in the females than in the males. Sulfluramid [redacted] did not appreciably affect the 480 ppm male body weights while Sulfluramid [redacted] affected the 240 ppm male body weights more severely than the other Sulfluramid isomeric mixtures given at the same dose level. Treatment-related body weight and food consumption reductions were observed in the 240 and 480 ppm males and in the 120, 240, and 480 ppm females as compared to their respective controls.

Variable distribution of liver gross abnormalities was noted in rats treated with different sulfluramids and at different dose levels.

The histopathological data as presented in these study reports could not be adequately evaluated because:

- o Grossly abnormal livers observed in the various dose groups were not histopathologically evaluated.
- o An inadequate number of rat livers was histopathologically evaluated, even when specimens were available.
- o Contradictory statements on the incidence of hepatocellular hypertrophy between the text and data presented in the tables were noted.

Because of the discrepancies of the histopathological data noted above, only tentative conclusions can be made.

It appears that the liver is the target organ for all the various Sulfluramid isomeric mixtures tested.

Based on body weight and food consumption data presented in all four study reports, the NOELs and LOELs for the different sulfluramid isomeric mixtures tested are the same. The NOEL is 120 ppm for the males and 60 ppm for the females. Accordingly, the LOEL is 240 ppm for the males and 120 ppm for the females. However, based on all the data presented in the four studies that were submitted, there appear to be some differences in toxicity among the various Sulfluramid isomeric mixtures that were tested. Furthermore, since the number of animals used in each dose group were too small, the definitive NOEL and LOEL for the different sulfluramid isomeric mixtures can not be determined.

Because the numbers of animals were too small to establish definitive NOELs and LOELs, and also because of the concerns indicated above (particularly in respect to the discrepancies noted in the histopathological data and why clinical signs and gross observation data were not included in the summary conclusion), Toxicology Branch II can not determine the comparative toxicity and toxicological profiles of the various Sulfluramid isomeric mixtures tested. Based on the results of these rangefinding studies that were submitted, it is also not possible for this Agency to make a determination as to which Sulfluramid isomeric mixture among the four tested that would be the most appropriate and representative test material for use in subchronic or other toxicity studies.

DISCREPANCIES

- In the discussions of the bridging toxicological data (letter dated May 7, 1991; MRID#418699-00), the investigators did not include the results of clinical and gross observations, and the organ weight data.

- Study with Sulfluramid [redacted] (MRID#418699-01). There are some concerns why grossly abnormal livers of the intermediate dose groups (30, 60, and 120 ppm) observed during necropsy were not histopathologically evaluated. It was noted on p. 14 of the study report that "grossly abnormal livers in the 120 and 240 ppm dose groups were to be microscopically evaluated...", however, Table 21 (p. 102 of the study report) indicates that grossly abnormal livers of the lower dose groups were not microscopically evaluated.

- Study with Sulfluramid [redacted] (MRID#418699-02). Although on p.14 of the study report it was noted that grossly abnormal livers in the 120 and 240 ppm dose groups were to be microscopically evaluated, the investigators failed to evaluate grossly abnormal livers of the 120 ppm and other lower dose livers observed during necropsy. On p. 19 of the study report it was noted that " The testes and epididymides collected from the 240 and 480 ppm dose groups were all normal". However, in Table 20 (p. 100 of the study report) it was noted that no testes and epididymides were examined.

- Study with Sulfluramid [redacted] (MRID#418699-04). It was noted on p. 20 of the study report that no rats of the 480 ppm dose group exhibited hepatocellular hypertrophy, while on table 18 (p. 99 of the study report) it was noted that no 480 ppm rat livers were examined histopathologically because all rats died prior to necropsy.

MANUFACTURING PROCESS INFORMATION IS NOT INCLUDED

APPENDIX S-A: Summary Rat Mortalities

Dose Group/Compound	Week 1	Week 2	Week 3	Week 4
	M/F	M/F	M/F	M/F
Control I	0/0	0/0	0/0	0/0
Control II	0/0	0/0	0/0	0/0
30 ppm Dose Group				
Sulfluramid [redacted]	0/0	0/0	0/0	0/0
Sulfluramid [redacted]	0/0	0/0	0/0	0/0
Sulfluramid [redacted]	0/0	0/0	0/0	0/0
Sulfluramid [redacted]	0/0	0/0	0/0	0/0
60 ppm Dose Group				
Sulfluramid [redacted]	0/0	0/0	0/0	0/0
Sulfluramid [redacted]	0/0	0/0	0/0	0/0
Sulfluramid [redacted]	0/0	0/0	0/0	0/0
Sulfluramid [redacted]	0/0	0/0	0/0	0/0
120 ppm Dose Group				
Sulfluramid [redacted]	0/0	0/0	0/0	0/0
Sulfluramid [redacted]	0/0	0/0	0/0	0/0
Sulfluramid [redacted]	0/0	0/0	0/0	0/0
Sulfluramid [redacted]	0/0	0/0	0/0	0/0
240 ppm Dose Group				
Sulfluramid [redacted]	0/0	0/0	0/0	3/0
Sulfluramid [redacted]	0/0	0/0	0/0	1/0
Sulfluramid [redacted]	0/0	0/1	1/2	2/2
Sulfluramid [redacted]	0/0	0/0	1/2	2/2
480 ppm Dose Group				
Sulfluramid [redacted]	0/0	1/0	3/0	5/3
Sulfluramid [redacted]	0/0	0/1	2/3	5/5
Sulfluramid [redacted]	0/0	2/3	3/4	5/5
Sulfluramid [redacted]	0/0	1/1	1/4	2/5

M/F = Males/Females.

MANUFACTURING PROCESS INFORMATION IS NOT INCLUDED

APPENDIX S-B
Summary Treatment-related Clinical Signs

Clinical Signs	0ppm	30ppm	60ppm	120ppm	240ppm	480ppm
	M/F	M/F	M/F	M/F	M/F	M/F
Sulfluramid [redacted]						
Emaciation	0/0	0/0	0/0	0/0	4/5	3/5
Hyperactivity	0/0	0/0	0/0	0/0	1/0	3/0
Tremors	0/0	0/0	0/0	0/0	0/0	0/0
Urine Stain	0/0	0/0	0/0	0/0	0/0	0/0
Oral Discharge/red	0/0	0/0	0/0	0/0	0/0	0/0
Sulfluramid [redacted]						
Emaciation	0/0	0/0	0/0	0/4	1/4	5/5
Hyperactivity	0/0	0/0	0/0	0/0	2/0	2/1
Tremors	0/0	0/0	0/0	0/0	1/0	1/1
Urine Stain	0/0	0/0	0/0	0/0	0/0	0/0
Oral Discharge/red	0/0	0/0	0/0	0/0	3/0	4/2
Sulfluramid [redacted]						
Emaciation	0/0	0/0	0/2	0/2	2/3	5/5
Hyperactivity	0/0	0/0	0/0	0/0	1/1	1/3
Tremors	0/0	0/0	0/0	0/0	2/0	2/0
Urine Stain	0/0	0/0	0/0	0/0	2/3	0/3
Oral Discharge/red	0/0	0/0	0/0	0/0	3/3	4/3
Sulfluramid [redacted]						
Emaciation	0/0	0/0	0/0	0/1	3/4	3/5
Hyperactivity	0/0	0/0	0/1	1/1	2/0	1/1
Tremors	0/0	0/0	0/0	1/1	1/0	0/1
Urine Stain	0/0	0/0	0/0	0/0	3/2	0/3
Oral Discharge/red	0/0	0/0	0/0	0/0	4/3	0/3

M/F= Males/Females

APPENDIX S-C
Summary Mean Body Weights (gm) on Day 0, 14, and 28 of Study and Percent Body Weight Gains For the Different Test Compounds (Derived from Individual Studies and values were rounded off)

	0 ppm	30 ppm	60 pm	120 pm	240 ppm	480 ppm
	M/F	M/F	M/F	M/F	M/F	M/F
Sulfluramid [redacted]						
Day 0	244/184	246/186	244/182	242/185	243/182	242/180
Day 14	329/227	339/234	329/227	324/209	289/192	237/156
Day 28	404/264	419/250	396/253	386/223	263/209	234/131
% BW_b Gain	66/44	70/34	62/39	60/21	16/15	-4/-27
Sulfluramid [redacted]						
Day 0	244/184	242/182	242/179	245/182	245/186	246/182
Day 14	329/227	329/216	335/211	328/203	317/186	257/147
Day 28	404/264	389/244	409/232	380/217	388/185	196/ a
% BW_b Gain	66/44	61/34	69/30	55/19	58/-0.5	-20/ a
Sulfluramid [redacted]						
Day 0	242/180	243/182	244/183	244/181	244/180	242/180
Day 14	337/223	335/217	339/211	331/205	301/173	261/135
Day 28	415/257	413/241	41/231	401/219	382/174	222/ a
% BW_b Gain	71/43	70/32	68/26	65/21	57/-3	-8/ a
Sulfluramid [redacted]						
Day 0	242/180	244/180	242/177	244/182	245/180	240/177
Day 14	337/223	343/217	341/209	331/201	316/171	307/141
Day 28	415/257	419/247	420/233	397/215	390/185	379/ a
% BW_b Gain	71/43	72/37	74/32	63/18	59/3	58/ a

M/F= Males/Females; Sulfl. = Sulfluramid.; a = all rats died;
b = Percent Body Weight Gain at day 28; BW = Body Weight.

MANUFACTURING PROCESS INFORMATION IS NOT INCLUDED

APPENDIX S-D
Summary Mean Weekly Food Consumption (gm) on Day 7, 14, and 28 of Study For the Different Test Compounds (values rounded off)

Day of Study	0 ppm	30 ppm	60 pm	120 pm	240 ppm	480 ppm
	M/F	M/F	M/F	M/F	M/F	M/F
Sulfluramid [redacted]						
Day 7	189/136	198/140	190/137	196/133	174/117	156/78
Day 14	190/147	203/138	191/146	189/116	151/102	86/70
Day 28	192/151	206/131	189/134	183/111	96/96	66/61
Sulfluramid [redacted]						
Day 7	189/136	187/132	186/128	190/119	184/107	174/82
Day 14	190/147	187/132	194/130	193/118	180/95	126/61
Day 28	192/151	176/135	192/145	177/108	178/87	94/ a
Sulfluramid [redacted]						
Day 7	187/134	188/136	194/130	190/122	179/101	153/79
Day 14	191/137	194/139	200/130	195/121	168/88	128/51
Day 28	195/138	193/134	200/120	192/105	149/70	74/a
Sulfluramid [redacted]						
Day 7	187/134	200/132	194/131	182/123	183/97	179/76
Day 14	191/137	203/141	198/129	190/115	186/88	193/60
Day 28	195/138	201/141	203/131	186/112	190/83	187/ a

M/F= Males/Females; Sulfl. = Sulfluramid.; a = all rats died.

MANUFACTURING PROCESS INFORMATION IS NOT INCLUDED

APPENDIX S-E: Pertinent Gross Findings During Necropsy in Rats

	0ppm	30ppm	60ppm	120ppm	240ppm	480ppm
	M/F	M/F	M/F	M/F	M/F	M/F
Sulfluramid [redacted]						
Thickened Liver	1/0	3/0	1/0	3/0	1/0	0/0
Discolored Liver	0/0	0/0	0/0	0/0	2/0	2/1
Vasc. Brain	0/0	0/0	0/0	0/0	0/0	0/0
Undesc. Testes	0/-	0/-	0/-	0/-	1/-	3/-
Urine Stain	0/0	0/0	0/0	0/0	0/0	0/0
Sulfluramid [redacted]						
Thickened Liver	1/0	2/0	3/0	4/0	4/0	0/0
Discolored Liver	0/0	0/0	0/0	0/0	1/0	1/0
Vasc. Brain	0/0	0/0	0/0	0/0	0/0	0/0
Undesc. Testes	0/-	0/-	0/-	0/-	1/-	5/-
Urine Stain	0/0	0/0	0/0	0/0	1/0	4/5
Sulfluramid [redacted]						
Thickened Liver	0/1	0/0	2/1	2/2	2/1	0/0
Discolored Liver	0/0	0/0	0/0	0/0	2/0	0/0
Vasc. Brain	0/0	0/0	0/0	0/0	0/0	0/0
Undesc. Testes	0/-	0/-	0/-	0/-	2/-	4/-
Urine Stain	0/0	0/0	0/0	0/0	2/1	4/4
Dark Ingesta[b]	0/0	0/0	0/0	0/0	1/2	3/3
Sulfluramid [redacted]						
Thickened Liver	0/1	0/0	0/1	1/1	1/0	0/0
Discolored Liver	0/1	0/0	0/1	1/1	1/0	0/0
Vasc. Brain	0/0	0/0	0/0	0/0	0/2	2/4
Undesc. Testes	0/-	0/-	0/-	0/-	1/-	1/-
Urine Stain	0/0	0/0	0/0	0/0	3/1	1/2
Dark Ingesta[b]	0/0	0/0	0/0	0/0	2/0	1/1

M/F= Males/Females; b = Dark ingesta not observed in rats treated with Sulfluramid [redacted] and Sulfluramid [redacted] ne = not evaluated; Undesc. = Undescended; Vasc. = Vascularized.

APPENDIX S-F: Pertinent Histopathological Findings in Males

TISSUES	0	30	60	120	240	480
	F/T	F/T	F/T	F/T	F/T	F/T
Sulfluramid [redacted]						
# of Rat Livers Examined	0/1	ne	ne	ne	2/2	2/2
Liver Hypertrophy	0/1	ne	ne	ne	2/2	2/2
Liver Multifocal Necrosis	0/1	ne	ne	ne	0/2	1/2
Liver Vacuolation	0/1	ne	ne	ne	1/2	0/2
Epididymis	0/5	ne	ne	ne	0/2	0/1
Testis	0/5	ne	ne	ne	0/2	0/1
Sulfluramid [redacted]						
# of Rat Livers Examined	0/1	ne	ne	ne	5/5	1/1
Liver Hypertrophy	0/1	ne	ne	ne	5/5	1/1
Liver Multifocal Necrosis	0/1	ne	ne	ne	1/5	1/1
Liver Vacuolation	0/0	ne	ne	ne	0/0	0/0
Multi. Mono. Infil./Liver	0/1	ne	ne	ne	1/5	0/1
Epididymis	0/5	ne	ne	ne	0/4	0/0
Testis	0/5	ne	ne	ne	0/4	0/0
Sulfluramid [redacted]						
# of Rat Livers Examined	0/1	ne	2/2	2/2	3/3	ne[a]
Liver hypertrophy	0/1	ne	2/2	2/2	3/3	ne[a]
Liver Multifocal Necrosis	0/1	ne	0/0	0/2	1/3	ne[a]
Liver Vacuolation	0/0	ne	0/0	0/0	0/0	0/0
Multi. Mono. Infil./Liver	0/1	ne	1/2	1/2	1/3	ne[a]
Epididymis	0/5	0/5	0/5	0/5	0/3	ne[a]
Testis	0/5	0/5	0/5	0/5	0/3	ne[a]
Sulfluramid [redacted]						
# of Rat Livers Examined	0/1	ne	ne	0/1	0/1	ne[a]
Liver Hypertrophy	0/1	ne	ne	1/1	1/1	ne[a]
Liver Multifocal Necrosis	0/0	ne	ne	0/0	0/0	ne[a]
Liver Vacuolation	0/0	ne	ne	0/0	0/0	ne[a]
Multi. Mono. Infil./Liver	0/0	ne	ne	0/0	0/0	ne[a]
Epididymis	0/5	0/5	0/5	0/5	1/3	0/3
Testis	0/5	0/5	0/5	0/5	1/3	0/3

a= All died; F/T= Total Number of findings//Total Numbers Examined;
ne = Not evaluated

MANUFACTURING PROCESS INFORMATION IS NOT INCLUDED