

12-9-94

Primary Review by: Roger Gardner and Pam Hurley *Pamela M. Hurley* 12/9/94
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DATA EVALUATION RECORD
(Addendum of June 11, 1993)

Study Type: Multigeneration Reproduction
Guideline §83-4
Species: Rat

EPA Identification No.s: EPA Accession No. 258398, 258399
EPA Pesticide Chemical Code: 128501
Toxicology Chemical Code: 893C

Test Material: SC-0224 (19.2% purity); Lot # EHC-0355-25

Synonyms: Trimethylsulfonium carboxymethylaminomethylphosphonate;
sulfosate; Touchdown

Sponsor: Stauffer Chemical Co.

Study Number(s): T-11051

Testing Facility: Stauffer Chemical Co., Environmental Health
Center, Farmington, CN

Title of Report: SC-0224: Two-Generation Reproduction Study in
Rats

Author(s): J. L. Minor, J. R. Downs, et al.

Report Issued: April 19, 1984

Conclusions: Sulfosate was administered in the diet to groups of 20 male and 30 female Sprague-Dawley rats through two matings in each of two successive generations. Dose levels were 0, 150, 800, or 2000 ppm. The NOEL for systemic effects is 150 ppm and the LEL is 800 ppm based on consistent decreases in absolute and sometimes relative organ weights in both generations (thymus, heart, kidney and liver) at 800 and 2000 ppm and decreases in body weights and body weight gains during the pre-mating period at 2000 ppm. The NOEL for reproductive/developmental effects is 150 ppm and the LOEL is 800 ppm based on decreased litter size in the F_{0a} and F_{1b} litters at 2000 ppm and on decreased mean pup weights during lactation in the second litters at 800 ppm and in all litters at 2000 ppm.

Core Classification: Guideline

Discussion:

Systemic Toxicity: The decreases in body weight and body weight gain appear to be related to a palatability problem since food efficiency did not appear to be affected. However, although the food efficiency was not statistically significantly affected at any time point, it was quite a bit less than the controls at several time points. The NOEL was set at 150 ppm because the decreases in organ weights were consistent across both generations. The point discussed in the first Data Evaluation Record concerning platelet counts is probably not biologically significant because it was not consistent across generations.

Reproductive/Developmental Toxicity: The statistically significant decreases in pup weights at the 800 ppm level were borderline biologically significant because at no time were either the body weights or body weight gains less than 90% of the control values and because the effect was not apparent in all litters.

Investigators' Conclusions: The investigators summarized their conclusions as follows:

The principal effects attributed to SC-0224 were reductions in body weights and feed intakes at 800 and 2000 ppm. Reductions in body weight became progressively more apparent throughout the study, initially appearing as a significant reduction for P0 males after five weeks and at both 800 and 2000 ppm for P0 females during reproductive phases. Body weights for P1 males at 800 and 2000 ppm and females at 2000 ppm were significantly reduced throughout their study period. Reductions in feed intakes generally accompanied the reductions in body weights. Pup weights were significantly reduced after lactational day 7 at 2000 ppm for all litters and for both second litters at 800 ppm. Both the slight reductions in litter size at 2000 ppm and the reductions in pup weights at 800 and 2000 ppm appeared to be secondary to the health of the dams. There was no evidence of altered intrauterine development, increased stillborns, or pup anomalies.

Based on reduced feed intakes and body weights in both parents and pups observed at 800 and 2000 ppm, the no-effect level was 150 ppm SC-0224 in the diet, corresponding to an approximately (sic) daily intake of 7.5 mg/kg/day.

Previous reviews (Document Nos. 005173 and 005690) also described decreases in body weight, feed consumption and organ weights in adult males and females of the P0 and P1 generation. Selected data are summarized in Tables 1 and 2 below to supplement the previous conclusions regarding these endpoints. Table 3 summarizes body weight, feed consumption and efficiency data for P0 and P1 females during gestation, Table 4 summarizes body weight, feed consumption and efficiency data for P0 and P1 females during lactation, Table 5 summarizes the litter size data and Table 6 summarizes the pup weight data mentioned in the investigators' conclusions above. Also provided are copies of

the fertility and reproductive behavior and pup survival and developmental indices tables taken directly from the report.

Table 1: Selected body weight, feed consumption, and feed efficiency means from report tables 5-10 and 23-28.

Observation	Dose level (ppm)			
	0	150	800	2000
F ₀ Generation Males - pre mating				
Body weight (g) on day				
0	143	141	144	141
118	543	551	537	488**
Body weight gain (g)				
Day 0-118	400	410	393	347
Feed consumption (g/day)				
Day 8	16	16	15	13**
29	22	18**	17**	18**
62	23	23	19**	16**
91	22	23	23	14**
118	20	18**	19	16**
Feed efficiency ⁺				
Day 8	62	55	56	60
29	36	37	32	36
118	14	6	9	4
F ₀ Generation Females - pre mating				
Body weight (g) on day				
0	122	122	122	120
118	280	280	273	263*
Body weight gain (g)				
Day 0-118	158	162	151	143
Feed consumption (g/day)				
Day 8	12	12	11	11
29	14	11**	10**	13
62	17	16	13**	12**
118	16	14	15	14
Feed efficiency ⁺				
Day 8	37	36	36	40
29	19	19	16	20
62	15	17	4	4

* Significantly different from control, $p \leq 0.05$, two tailed.

** Significantly different from control, $p \leq 0.01$, two tailed.

⁺ According to the report, feed efficiency was calculated as $100 \times \text{interval body weight change} \div \text{interval days} \div \text{daily feed intake}$.

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Table 1: Selected body weight, feed consumption, and feed efficiency means from report tables 7-10 and 23-28.

Observation	Dose level (ppm)			
	0	150	800	2000
F ₁ Generation Males - pre mating				
Body weight (g) on day				
0	181	171	164**	128**
62	508	503	451**	380**
Body weight gain (g)				
Day 0-62	327	332	287	252
Feed consumption (g/day)				
Day 5	17	17	14**	10**
27	19	19	17**	15**
62	19	19	18	16**
Feed efficiency ⁺				
Day 6	53	55	56	52
27	29	30	29	28
62	15	16	15	18
F ₁ Generation Females - pre mating				
Body weight (g) on day				
0	138	137	132	121**
62	277	271	249**	234**
Body weight gain (g)				
Day 0-62	139	134	117	113
Feed consumption (g/day)				
Day 7	12	12	11*	10**
28	13	13	12*	11*
62	14	13	12*	11*
Feed efficiency ⁺				
Day 7	31	30	30	35
28	16	14	17	15
62	10	8	10	8

* Significantly different from control, $p \leq 0.05$, two tailed.

** Significantly different from control, $p \leq 0.01$, two tailed.

⁺ According to the report, feed efficiency was calculated as
 $100 \times \text{interval body weight change} / \text{interval days} \times \text{daily feed intake}$.

Table 2: Selected absolute organ weights (g) from Tables 15, 16, 33 and 34 of the original report.

Organ	Dose level (ppm)			
	0	150	800	2000
F ₀ Generation Males				
Whole body	634.303	634.956	605.508	533.490**
Heart	1.637	1.694	1.609	1.500
Kidney				
Left	1.501	1.488	1.486	1.436
Right	1.535	1.560	1.479	1.444
Liver	14.727	15.475	14.007	12.583
Spleen	0.855	0.831	0.840	0.824
Thymus	0.500	0.524	0.446	0.339***
F ₁ Generation Males				
Whole body	648.511	634.630	584.991**	476.453**
Heart	1.727	1.738	1.542**	1.402*** ^a
Kidney				
Left	1.608	1.597	1.467	1.296***
Right	1.651	1.620	1.471**	1.308**
Liver	14.086	14.159	12.235**	9.822**
Spleen	0.828	0.863	0.745	0.672**
Thymus	0.466	0.461	0.420*	0.332**
F ₀ Generation Females				
Whole body	309.304	309.410	299.583	282.189**
Heart	1.209	1.164	1.081*** ^a	1.026**
Kidney				
Left	0.944	0.937	0.937	0.869**
Right	0.952	0.947	0.922	0.900
Liver	7.873	7.802	7.454	7.384
F ₁ Generation Females				
Whole body	331.341	323.829	295.506**	269.477**
Heart	1.234	1.164	1.118**	1.067**
Kidney				
Left	1.031	1.008	1.008	0.851**
Right	1.089	1.019	0.973**	0.882**
Liver	7.912	7.518	7.341* ^a	6.904*** ^a

* Significantly different from control, $p \leq 0.05$, two tailed.

** Significantly different from control, $p \leq 0.01$, two tailed.

^aThese organ weights were also statistically significantly decreased when expressed as relative organ weights.

Table 3: Selected female body weight, feed consumption, and feed efficiency means during gestation from report tables 41, 43, 45, 47, 49 and 51.

Observation	Dose level (ppm)			
	0	150	800	2000
F _{0a} Generation				
Body weight (g) on gestation day 0	245	256	250	236
20	312	348*	311	322
Body weight gain (g) gestation day 0-20	67	92	61	86
Feed consumption (g/day) gestation day 6	16	16	14**	13**
13	17	17	14**	14**
20	8	11*	9	13**
Feed efficiency* gestation day 6	29	29	29	27
13	27	25	25	45
20	-56	42	18	46
F _{0b} Generation				
Body weight (g) on gestation day 0	303	288	272	265*
20	404	408	380	361**
Body weight gain (g) gestation day 0-20	101	120	108	96
Feed consumption (g/day) gestation day 6	16	17	16	14**
13	17	17	16	14**
20	16	16	14*	15
Feed efficiency* gestation day 6	29	26	27	26
13	25	24	23	21
20	56	58	57	50

* Significantly different from control, $p \leq 0.05$, two tailed.

** Significantly different from control, $p \leq 0.01$, two tailed.

+ According to the report, feed efficiency was calculated as $100 \times \text{interval body weight change} / \text{interval days} \times \text{daily feed intake}$.

Table 3: Selected female body weight, feed consumption, and feed efficiency means during gestation from report tables 41 - 52.

Observation	Dose level (ppm)			
	0	150	800	2000
F _{1a} Generation				
Body weight (g) on gestation day 0	268	261	247*	230**
20	386	373	349**	320**
Body weight gain (g) gestation day 0-20	118	112	102	90
Feed consumption (g/day) gestation day 6	14	14	13	13
13	17	16	16	15
20	16	16	14*	14**
Feed efficiency* gestation day 6	33	32	33	32
13	22	23	21	20
20	56	54	53	45
F _{1b} Generation				
Body weight (g) on gestation day 0	316	304	280**	269**
20	432	418	385**	362**
Body weight gain (g) gestation day 0-20	116	114	105	93
Feed consumption (g/day) gestation day 6	18	17	16	16
13	17	18	16	16
20	16	16	15	16
Feed efficiency* gestation day 6	24	24	21	25
13	20	18	19	18
20	60	56	56	45

* Significantly different from control, $p \leq 0.05$, two tailed.

** Significantly different from control, $p \leq 0.01$, two tailed.

* According to the report, feed efficiency was calculated as $100 \times \text{interval body weight change} / \text{interval days} \times \text{daily feed intake}$.

Table 4: Selected female body weight, feed consumption, and feed efficiency means during lactation from report tables 57 - 68.

Observation	Dose level (ppm)			
	0	150	800	2000
F _{0a} Generation				
Body weight (g) on				
lactation day 0	264	288**	261	252
21	283	286	275	260**
Body weight gain (g)				
lactation day 0-21	19	-2	14	16
Feed consumption (g/day)				
lactation day 7	34	35	29*	24**
14	41	45	36**	27**
21	53	56	49	36**
Feed efficiency ⁺				
lactation day 7	8	3	-8	6
14	1	3	3	0
21	-3	-5	-1	2
F _{0b} Generation				
Body weight (g) on				
lactation day 0	323	326	305	293**
21	313	316	303	289**
Body weight gain (g)				
lactation day 0-21	-10	-10	-2	-4
Feed consumption (g/day)				
lactation day 7	30	31	27	25*
14	39	39	34*	29*
21	47	49	45	35*
Feed efficiency ⁺				
lactation day 7	6	3	7	?
14	2	1	3	1
21	-6	-3	-1	-1

* Significantly different from control, $p \leq 0.05$, two tailed.

** Significantly different from control, $p \leq 0.01$, two tailed.

⁺ According to the report, feed efficiency was calculated as
 $100 \times \text{interval body weight change} / \text{interval days} \times \text{daily feed intake}$.

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Table 4: Selected female body weight, feed consumption, and feed efficiency means during lactation from report tables 42, 44, 46, 48, 50 and 52.

Observation	Dose level (ppm)			
	0	150	800	2000
F _{1a} Generation				
Body weight (g) on				
lactation day 0	314	314	280**	263**
21	301	286	275**	247**
Body weight gain (g)				
lactation day 0-21	-13	-28	-5	-16
Feed consumption (g/day)				
lactation day 7	31	33	28	21**
14	41	39	36*	28**
21	57	55	50*	39**
Feed efficiency*				
lactation day 7	1	0	1	4
14	1	-3	1	2
21	-2	-5	0	-6
F _{1b} Generation				
Body weight (g) on				
lactation day 0	342	339	306**	294**
21	325	316	298**	289**
Body weight gain (g)				
lactation day 0-21	-17	-23	-8	-5
Feed consumption (g/day)				
lactation day 7	27	30	27	24**
14	38	38	34**	29**
21	53	50	47*	40**
Feed efficiency*				
lactation day 7	-5	3	3	-4
14	0	0	2	-1
21	3	3	-2	0

* Significantly different from control, $p \leq 0.05$, two tailed.

** Significantly different from control, $p \leq 0.01$, two tailed.

+ According to the report, feed efficiency was calculated as
 $100 \times \text{interval body weight change} \div \text{interval days} \div \text{daily feed intake}$.

Table 5: Summary of Mean Litter Sizes

Observation and study time	Control	Dose Levels		
		Low	Mid	High
F ₁ Generation				
<u>Litter A</u>				
Day 0	11.9	12.6	11.7	10.6*
Day 4 pre-cull	12.0	12.2	11.4	10.4*
Day 4 post-cull	12.0	12.2	11.4	10.4*
Day 7	11.9	12.2	11.3	10.8
Day 14	11.9	12.2	11.3	10.8
Day 21	11.9	12.2	11.3	10.6*
<u>Litter B</u>				
Day 0	11.9	12.9	11.8	11.3
Day 4 pre-cull ^a	11.8	12.6	11.8	11.2
Day 7	7.8	7.7	7.4	7.6
Day 14	7.8	7.7	7.4	7.6
Day 21	7.7	7.7	7.4	7.6
F ₂ Generation				
<u>Litter A</u>				
Day 0	11.2	12.6	10.6	10.3
Day 4 pre-cull	10.8	12.3	10.7	10.7
Day 4 post-cull	10.8	12.3	10.7	10.7
Day 7	11.2	12.6	10.7	10.7
Day 14	11.2	12.6	10.7	10.7
Day 21	11.2	12.6	10.7	10.7
<u>Litter B</u>				
Day 0	13.9	12.2*	12.4	10.3**
Day 4 pre-cull ^a	13.5	12.3	12.2	10.2**
Day 7	7.9	7.8	7.6	7.6
Day 14	7.9	7.8	7.6	7.6
Day 21	7.9	7.8	7.6	7.5

* Statistically significantly different from control, $p < 0.05$.

** Statistically significantly different from control, $p < 0.01$.

^aBoth B litters were culled to 8 pups at day 4, however, the mean litter sizes were not given (assumed 8).

Table 6: Mean Pup Weights During Lactation

Observation and Study Time	Contr.	Dose Levels		
		Low	Mid	High
F ₁ Generation				
<u>Litter A</u>				
Mean pup weight (day 0)	5.6	5.8	5.6	5.7
Mean pup weight (day 4 pre-cull)	9.5	9.8	10.0	8.1**
Mean pup weight (day 7)	14.2	14.5	14.2	11.8**
Mean pup weight (day 14)	26.8	27.6	25.7	20.3**
Mean pup weight (day 21)	42.7	44.7	41.6	30.9**
Weight gain: days 1 - 21	37.1	38.9	36.0	25.2 ^a
<u>Litter B</u>				
Mean pup weight (day 0)	6.3	5.8*	5.8*	5.9*
Mean pup weight (day 4 pre-cull)	10.7	9.7*	9.9	9.3**
Mean pup weight (day 7)	17.7	16.7	16.3*	14.8
Mean pup weight (day 14)	35.3	34.5	32.0**	27.6**
Mean pup weight (day 21)	56.3	55.5	51.3**	41.6**
Weight gain: days 1 - 21	50.0	49.7	45.5	35.7
F ₂ Generation				
<u>Litter A</u>				
Mean pup weight (day 0)	5.9	6.0	5.7	5.8
Mean pup weight (day 4 pre-cull)	10.0	9.5	9.9	9.3
Mean pup weight (day 7)	15.4	14.2	14.5	12.9**
Mean pup weight (day 14)	29.1	26.7	26.9	21.7**
Mean pup weight (day 21)	48.2	43.1*	43.9	33.0**
Weight gain: days 1 - 21	42.3	37.1	38.2	27.2
<u>Litter B</u>				
Mean pup weight (day 0)	5.7	6.1*	5.7	6.1
Mean pup weight (day 4 pre-cull)	10.0	10.5	9.7	10.3
Mean pup weight (day 7)	16.8	17.5	15.9	15.9
Mean pup weight (day 14)	34.3	35.4	32.0*	29.0**
Mean pup weight (day 21)	56.7	58.4	52.2**	44.4**
Weight gain: days 1 - 21	51.0	52.3	46.5	38.3

* Statistically significantly different from control, $p < 0.05$.

** Statistically significantly different from control, $p < 0.01$.

^aPup weight gain was calculated by EPA toxicologist (statistical significance was not calculated).

Substantive Review

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