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

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JUL 2 9 1992

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Glyphosate (Roundup); Review of 2-generation rat reproduction study; PP #0F03865, 2H05635 - Glyphosate in/on Wheat

Tox.Chem No.: 661A
MRID No.: 416215-01
DP Barcode No.: D176984, -85
Submission No.: S416044, -45

TO: Robert Taylor, PM #25
Fungicide-Herbicide Branch
Registration Division (H7505C)

FROM: William Dykstra, Ph.D., Toxicologist
Review Section I
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William Dykstra 7/23/92

for THRU: Roger Gardner, Section Head, Toxicologist
Review Section I
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ACTION REQUESTED: Monsanto Company has submitted a new 2-generation rat reproduction study with technical glyphosate in support of requested tolerances. Toxicology Branch-I (TB-I) has been requested to review the study as part of the tolerance petition.

CONCLUSIONS: Randomized groups of 30 male and 30 female Sprague-Dawley rats were continuously exposed by the diet to doses of 0, 2,000, 10,000, and 30,000 ppm of technical glyphosate for two consecutive generations.

The study is acceptable as core-guideline data. The NOEL is 10,000 ppm and the LEL is 30,000 ppm.

The reproductive NOEL is 30,000 ppm (HDT).

The systemic NOEL is 10,000 ppm and the LEL is 30,000 ppm. The systemic effects are increased incidences of soft stool, and decreased food consumption and body weight during growth.

The developmental NOEL is 10,000 ppm and the LEL is 30,000 ppm. The developmental effects are decreased pup body weight on lactation days 14 and 21.

There were no compound-related effects in survival of parents or pups, mating, fertility, gestation, viability and lactation indices, organ weights or in gross or microscopic findings.

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Reviewed By: William Dykstra, Ph.D. William Dykstra 7/23/92
Toxicology Branch I - IRS (H7509C)
for Secondary Reviewer: Roger Gardner, Section Head Pamela M. Hurley 7/23/92
Toxicology Branch I - IRS (H7509C) Roger Gardner 7/23/92

DATA EVALUATION REPORT

Study Type: 83-4; Two-Generation Rat Reproduction Study

Tox Chem. No.: 661A

MRID No.: 416215-01

Accession Number: N/A

Test Material: Glyphosate, Technical

Synonyms: Roundup

Study Number: MSL-10387

Sponsor: Monsanto Company

Testing Facility: Monsanto Agricultural Lab, EHL

Title of Report: Two Generation Reproduction Feeding Study with Glyphosate in Sprague-Dawley Rats

Author: M.S. Reyna

Report Issued: August 27, 1990

Conclusions: The study NOEL is 10,000 ppm and the LEL is 30,000 ppm.

The reproductive NOEL is 30,000 ppm (HDT).

The systemic NOEL is 10,000 ppm and the LEL is 30,000 ppm. The systemic effects are increased incidences of soft stool, and decreased food consumption and body weight during growth. Body weight gain during gestation and lactation are comparable between all treated groups and controls.

The developmental NOEL is 10,000 ppm and the LEL is 30,000 ppm. The developmental effects are decreased pup body weight and body weight gain on lactation days 14 and 21.

There were no compound-related effects in survival of parents or pups, mating, fertility, gestation, viability and lactation indices, organ weights or in gross or microscopic findings.

Classification: Core-Guideline

Special Review Criteria (40 CFR 154.7): N/A

Review:

Two-Generation Reproduction Feeding Study with Glyphosate in Sprague-Dawley Rats (Monsanto EHL, MSL-10387; August 27, 1990)

Quality Assurance: A Quality Assurance statement was signed by A.F. Uelner and dated August 22, 1990.

Test Material - Glyphosate; Lot No. XLI-203; 97.67% purity; White Powder.

Animals - 480 (240 male and 240 female Sprague-Dawley rats), approximately 7 weeks old, were used in the study. The weight range was 165.0 to 207.6 g for males and 135.6 to 162.7 g for females. Animals were housed individually and fed Purina Certified Rodent Chow #5002 and water ad libitum. Diets were prepared each week and analyzed for stability, homogeneity, and concentration periodically.

Sprague-Dawley rats were purchased from Charles River Breeding Labs, Portage, MI.

Methods - Randomized groups of 30 male and 30 female Sprague-Dawley rats (F0) were fed dietary levels of glyphosate at 0, 2,000, 10,000, and 30,000 ppm for 11 weeks, and then mated, to produce the F_1 generation. One male and one female were placed in male's cage for 7 days, unless copulatory evidence found sooner (copulatory plug or vaginal smear if unable to determine cage from which plug had fallen); if no evidence of mating had occurred after 7 days, the female was co-housed witha male having recorded copulatory activity (except for one female from the low-dose which was remated to an unproven male) for an additional 7 days, or until copulatory evidence was found; mating procedures for F_{1a} adults were the same as those for F_0 adults except it was modified to exclude sibling matings. Litters were culled to 8 pups on day 4 and weaned on day 21 of lactation. Following weaning, 30 F_1 rats sex/dose were randomly selected to continue as the second generation. Following approximately 14-week growth period, the F_1 rats were mated to product the F_2a and F_2b litters. All animals were maintained on their respective diets throughout pre-mating, mating, gestation, and lactation periods until sacrifice.

All rats were observed twice daily for toxic signs and mortality. Body weights were recorded weekly for both sexes and on days 0, 7, 14, and 21 of gestation and lactation in females. Food consumption was determined weekly for both sexes and during gestation and lactation in females.

Clinical examinations were performed on adults once a week. Examination of pups was performed at weighing. Pups were weighed on lactation day 0, 4 (pre- and post-cull), 14, and 21.

Scheduled sacrifice consisted of F_{1a} weanlings not selected for mating, F_{2a} and F_{2b} weanling pups and adult females which had littered, nonpregnant adult females and adult males. All F_0 and F_1 adults which died or were sacrificed in a moribund condition had a gross necopsy and selected tissues were saved. Pups found dead and culled pups had a gross necropsy, but no tissues were saved and no organs were weighed. Ovaries and testes with epididymides of F_0 and F_1 adults (unscheduled deaths and scheduled sacrifice) were weighed. The following organs were examined microscopically (F_0 and F_1 adults, both scheduled and unscheduled deaths): kidneys, ovaries, pituitary (F_1 only), prostate, seminal vesicle, skin/mammary gland, testes, epididymides, uterus/vagina, and gross lesions. All culled pups and those found dead during the postnatal period were given a gross necropsy (no organs weighed on tissues saved). The F_1 weanlings not selected for mating and all F_2a and F_2b weanlings received a gross necropsy. Kidneys from F_2b weanlings (1/sex/litter) were examined microscopically.

Adult body weights and food consumption were statistically analyzed by Dunnett's Multiple Comparison test (two-tailed). Terminal body weights, maternal body weights and food consumption during gestation and lactation, pup weight, precoital interval, gestation length, liter size, dead pups/litter, pup survival, and absolute and relative organ weights were evaluated by a decision-tree analysis procedure which, depending on the results for normality and homogeneity of variance (Bartlett's test), chose either parametric (Dunnett's test and linear regression) or nonparametric (Kruskall-Wallis, Jonchkeere's and/or Mann-Whitney tests) routines to detect differences and analyze for trends.

The uncorrected Chi-Square test was used for fertility indices and the incidence of microscopic lesions were analyzed by Fisher's Exact test with the Bonferroni Inequality Procedure. Statistical significance was $p < 0.05$ and $p < 0.01$.

Reproductive Indices:

$$\text{Male fertility index} = \frac{\text{No. females pregnant}}{\text{No. males mated}} \times 100$$

$$\text{Female fertility index} = \frac{\text{No. females pregnant}}{\text{Total No. females mated}} \times 100$$

$$\text{Gestation index} = \frac{\text{No. live litters born}}{\text{No. pregnancies}} \times 100$$

$$\text{Viability index} = \frac{\text{No. live pups at day 4 precull}}{\text{No. pups born alive}} \times 100$$

$$\text{Lactation index} = \frac{\text{No. pups alive at day 21}}{\text{No. pups alive on day 4 postcull}} \times 100$$

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Results

Analysis of Diets

Stability analyses at 2000 and 30,000 ppm varied from 89 to 111 percent for 2000 ppm and 82 to 107 percent for 30,000 ppm from days 0 (preparation) to day 35; whether stored at room temperature (up to 14 days or in a freezer (up to 35 days). The results of uniformity of mixing analyses at top, middle, and bottom for 2000 and 30,000 ppm averaged 1900 ± 52 and 28,000 ± 520, respectively.

Analysis for concentration during the study yielded the following results:

	Low	Mid	High
Target Conc. (ppm)	2000	10,000	30,000
Study Mean (ppm)	1900	9600	29,000
Std. Dev. (ppm)	120	530	1560
Study Average %	95.0	96.0	96.7

Toxic Signs

Compound-related toxic signs consisted of soft stools in high-dose males and females (both F_0 and F_1). There were no other compound-related clinical signs. In the F_0 adults at the high-dose, soft stools occurred in 30 males (457 occurrences) and 22 females (116 occurrences). In the F_1 adults at the high-dose, soft stools occurred in 30 males (698 occurrences) and 29 females (537 occurrences).

Mortality

There were no compound-related mortalities during the study. An F_0 females F2030 (mid-dose) died in the 6th week of the study before mating (12/7/88) with bladder, kidney, and vaginal lesions.

F_1 males M1068 (low dose) and M3074 (high-dose) died June 19, 1988 (week 21) (lymphosarcoma) and September 28, 1989 (kidney lesions), respectively. F1 female F1053 (low-dose) was sacrificed *in extremis* on September 18, 1989 with kidney necrosis and uterine lesions. Female F1058 (low-dose) died on September 10, 1989 with kidney and stomach lesions and had 9 dead normal pups contained in the uterus.

These deaths were not considered related to treatment.

Body Weight (Adults)

Body weights of high-dose male and female F_0 rats had statistically significant decreases (up to 8% decrease in both sexes) during the premating growth period. Similarly, F_1 high-dose male and female adults, though weighing less at weaning, continued to weigh up to 10 percent less than controls, which was also statistically significant. These body weight decreases in high-dose males and females are borderline biologically significant. The body weight of high-dose females remained lower than controls during gestation and lactation of F_1 and F_2a and F_2b litters, although by the end of lactation, high-dose body weights were comparable to controls.

Body weight of low- and mid-dose males and females were comparable to controls. The high-dose body weight findings are considered compound-related and may , in part, be due to the marginally decreased food consumption.

Food Consumption (Adults)

Food consumption was slightly lower in high-dose males and females than controls during most of the periods measured, which amounted to variations ranging from 1- 9%. This level of decreased food consumption is only marginally significant. The food consumption of mid- and low-dose groups were comparable to controls, except for mid-dose F_{1a} females, which were comparable to the high-dose. The decreased food consumption in the high-dose may be considered marginally compound-related and may be a result of unpalatability.

Tables of Body Weight and Food Consumption:

Observation and study week	Dose Group Control	Low	Mid	High
		F_0 males		
Mean body weight (g)				
0	187.9	188.1	188.1	188.0
14	528.3	528.9	518.1	488.5**
Mean weight gain (g)				
0 - 14	340.4	340.8	330.0	300.5**
Mean daily food consumption (g/day)				

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0 - 14	26.3	24.6	26.6	25.0
		F_0 females		
Mean body weight (g)				
0	150.5	160.5	150.2	150.3
11	276.7	272.6	273.0	253.8**
Mean weight gain (g)				
0 - 11	126.2	122.1	122.8	103.5**
Mean daily food consumption (g/day)				
0 - 11	16.7	17.8	17.1	16.4
		F_1 males		
Mean body weight (g)				
0	118.3	115.2	114.8	104.9**
14	537.9	541.9	520.3	483.0**
Mean weight gain (g)				
0 - 14	419.6	426.7	406.5	378.1**
Mean daily food consumption (g/day)				
0 - 14	27.3	27.1	26.0	25.8
		F_1 females		
Mean body weight (g)				

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0	99.8	96.7	97.1	88.8*
13	286.8	282.1	275.9	253.7**
Mean weight gain (g)				
0 - 13	187.0	186.4	178.8	164.9**
Mean daily food consumption (g/day)				
0 - 14	19.4	18.4	17.7*	17.3**

Observation and Study Time	Control	Low	Mid	High
		F_0 females		
Mean body weight (g)				
Day 0 of gestation	274	272	271	255**
Day 21 of gestation	398	392	395	374**
Day 0 of lactation	299	297	290	265*
Day 21 of lactation	313	313	319	316
Mean body weight gain (g)				
Days 0-21 of gestation	124	120	124	119*
Days 0-21 of lactation	14	16	29*	51*
Mean daily food consumption (g/day)				
Days 7-14 of gestation	21.0	20.2	21.4	20.4

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Observation and Study Time	Control	Low	Mid	High
		F_1 females (1st mating)		
Mean body weight (g)				
Day 0 of gestation	285	278	268*	251**
Day 21 of gestation	392	383	382	360**
Day 0 of lactation	299	285	296	277**
Day 21 of lactation	313	314	313	306
Mean body weight gain (g)				
Days 0-21 of gestation	107	105	114	109
Days 0-21 of lactation	14	29	17	29
Mean daily food consumption (g/day)				
Days 7-14 of gestation	20.8	21.3	22.3	21.9

Observation and Study Time	Control	Low	Mid	High
		F_1 females (2nd mating)		
Mean body weight (g)				
Day 0 of gestation	324	315	305*	281**
Day 21 of gestation	428	426	428	393**
Day 0 of lactation	342	340	333	312**
Day 21 of lactation	337	331	334	329

Mean body weight gain (g)

Days 0-21 of gestation	104	111	123	112
Days 0-21 of lactation	-5	-9	1	17

Mean daily food consumption (g/day)

Days 7-14 of gestation	22.7	22.4	23.1	21.8

* Statistically significantly different from control, $p<0.05$
** Statistically signiferently different from control, $p<0.01$

Mating and Fertility

F_0 - F_1 Generation

	Dose			
	Control	Low	Mid	High
Total Paired Females	30	30	29	30
(%) (Control)	--	100	97	100
Females w/Confirmed Copulation/Total Paired mean (%)	96.7	100	100	100
(%) (control)	--	103	103	103
Pregnant/Total Paired mean (%)	80.0	96.7	96.6	93.3
(%) (control)	--	121	121	117
Pregnant/Confirmed Copulation	82.0	96.7	96.6	93.3
(%) (control)	--	117	117	113
Precoital Length (Days)	3.50	3.40	3.07	3.74
(%) (control)	--	95	85	104
Gestational Length (Days)	22.20	22.22	22.50	22.25
(%) (control)	--	100	101	100
Males with Confirmed Copulation/Total Paired	86.7	93.3	93.1	90.0
(%) (control)	--	100	107	104

Males Impregnating Females/ Total Paired	70.0	90	89.7	83.3
(%) (control)	--	129	128	119
Males Impregnating Females/ Confirmed Copulation	80.8	96.4	96.3	92.8
(%) (control)	--	119	119	115

There were no compound-related effects in mating and fertility in the F_0 - F_1 generation.

Mating and Fertility

F_1a - F_2a Generation

	Dose			
	Control	Low	Mid	High
Total Paired Females	30	30	30	30
(%) (Control)	--	100	100	100
Females w/Confirmed Copulation/Total Paired	100	93.3	96.7	96.7
(%) (control)	--	93	97	97
Pregnant/Total Females	93.3	80.0	80.0	86.7
(%) (control)	--	86	86	93
Pregnant/Confirmed Copulation	93.3	85.7	82.8	89.7
(%) (control)	--	92	89	96
Precoital Length (Days)	2.84	3.12	3.60	3.16
(%) (control)	--	110	127	112
Gestational Length (Days)	22.4	22.5	22.6	22.5
(%) (control)	--	101	101	101
Males with Confirmed Copulation/Total Paired	93.3	86.7	83.3	83.3
(%) (control)	--	93	89	93
Males Impregnating Females/ Total Paired	90.0	73.3	76.7	80.0
(%) (control)	--	82	85	89
Males Impregnating Females/ Confirmed Copulation	96.4	84.6	92.0	96.4
(%) (control)	--	88	96	100

There were no compound-related effects in mating and fertility in the F_1a - F_2a.

Mating and Fertility

F_1a - F_2b Generation

	Dose			
	Control	Low	Mid	High
Total Paired Females	30	30	30	30
(%) (Control)	--	100	100	100
Females w/Confirmed Copulation/Total Paired	83.3	83.3	80.0	86.7
(%) (control)	--	100	96	104
Pregnant/Total Paired	53.3	70.0	63.3	63.3
(%) (control)	--	131	119	156
Pregnant/Confirmed Copulation	64.0	-84.0	79.2	96.2
(%) (control)	--	131	124	150
Precoital Length (Days)	3.68	3.20	3.06	2.45
(%) (control)	--	87	83	67
Gestational Length (Days)	22.4	22.5	22.3	22.5
(%) (control)	--	101	100	100
Males with Confirmed Copulation/Total Paired	70.0	69.6	70.0	80.0
(%) (control)	--	99	100	114
Males Impregnating Females/ Total Paired	46.7	58.8	60.0	76.7
(%) (control)	--	126	129	164
Males Impregnating Females/ Confirmed Copulation	68.7	85.0	85.7	96.8
(%) (control)	--	128	129	144

There were no compound-related effects in mating and fertility in treated rats in comparison to controls in the F_1a--F_2b generation.

Summary of Litter Weights

Mean Pup Weight (Day 21)

F_0 - F_1 Generation

Dose	Pup Body Weight (g)	Both Sexes
Control	51.96	(% Control)
Low	50.43	97

Mid	49.76	96
High	45.93**	88

F_1a - F_2a (Day 21)

Dose	Pup Body Weight (g)	Both Sexes
Control	53.34	(% Control)
Low	51.16	96
Mid	50.08*	94
High	45.00**	86

F_1a - F_2b (Day 21)

Dose	Pup Body Weight (g)	Both Sexes
Control	50.77	(% Control)
Low	51.83	102
Mid	50.95	100
High	43.44**	86

F_1a - F_2b (Day 14)

Dose	Pup Body Weight (g)	Both Sexes
Control	30.62	(% Control)
Low	31.27	102
Mid	31.94	104
High	28.82*	94

*p < 0.05. **p < 0.01.

Pup body weight of both sexes at each dose level were comparable to controls between days 0, 4 (pre- and post-cull), and usually 14. At days 14 and 21 in F_2b and day 21 in each of the other litters, the body weight of high-dose pups was significantly decreased (up to 14%) and body weight gain of high-dose pups was decreased from 15-20%. This finding may be compound-related or may be due to the ingestion of treated diet by the pups prior to and up to days 14 and 21.

The 6 percent decrease in body weight at the mid-dose in the second generation (F_1a -- F_2a) did not occur in the subsequent litter (F_2b) and is an equivocal result.

The NOEL for pup body weight and body weight gain is the mid-dose.

Litter Size (Day 0)

$F_0 - F_1$

Dose	Mean Number of Pups	Both Sexes
Control	13.3	(% Control)
Low	12.6	94
Mid	12.7	96
High	11.5	87

Mean dead pups per litter = 0.0, 0.2, 0.1, 0.1 for control, low, mid and high-dose groups, respectively.

$F_1a - F_2a$

Dose	Mean Number of Pups	Both Sexes
Control	12.0	(% Control)
Low	12.3	102
Mid	11.5	95
High	10.8	90

Mean dead pups per litter = 0.1, 0.3, 0.2, and 0.0 for control, low, mid, and high-dose groups, respectively.

$F_1a - F_2b$

Dose	Mean Number of Pups	Both Sexes
Control	11.9	(% Control)
Low	10.9	91
Mid	13.2	110
High	10.7	90

Mean dead pups per litter = 0.1, 0.2, 0.2, and 0.2, for control, low, mid, and high-dose groups, respectively.

There were no consistent, dose-related effects on litter size at Day 0 over the three generated litters. However, the slight (10-13%) decrease in mean number of pups at the high dose in the 1st two litters, since it was not statistically significant, is not considered compound-related. The NOEL for Day 0 litter size is the high-dose.

There were no compound-related effects in pup survival during lactation in treated pups in comparison to controls at any dose level at other measured intervals (days 0-4, 4-14, and 14-21).

Gross Pathology and Histopathology

There were no compound-related findings in gross necropsy or histopathology in examined treated rats in comparison to controls.

1. Body Weight (Terminal) and Organ Weights

Dose	F_0 Rats Mean Body Weight (g) Males	%	Females	%	F_1a Rats Mean Body Weight (g) Males	%	Females	%
Control	549.5		296.3		625.0		316.2	
Low	550.1	(100)	290.6	(98)	632.1	(101)	313.7	(99)
Mid	538.9	(98)	290.7	(98)	590.9	(96)	312.3	(99)
High	503.5**	(92)	285.9**	(90)	543.3**	(87)	284.7**	(90)

Dose	Ovaries (grams)	%	Ovaries (grams)	%
Control	0.1343		0.1579	
Low	0.1311	(98)	0.1437	(91)
Mid	0.1303	(97)	0.1504	(95)
High	0.1269	(94)	0.1587	(100)

Dose	Testes (grams)	%	Testes (grams)	%
Control	5.9959		6.6090	
Low	5.9019	(98)	6.3797	(97)
Mid	5.7836	(96)	6.4290	(97)
High	5.7906	(97)	6.3867	(97)

2. Relative Testicular/Body Weight

Dose	F_0 Rats		F_1a Rats	
Control	1.0949		1.0608	
Low	1.0087	(99)	1.0184	(96)
Mid	1.0070	(98)	1.0969	(103)
High	1.1684	(106)	1.1861**	(112)

The increased relative (to body) testicular weights of high dose F_0 and F_1a rats are considered due to the decreased terminal body weight, since the absolute weight of the testes were not affected by treatment. This finding is not a toxicological effect.

There were no compound-related gross or microscopic findings in adults or offspring.

In particular, the F_2b weanlings of 1/sex/litter were examined for kidney lesions. This was done since in an earlier (1981) reproduction study, the occurrence of renal tubular dilations in F_3b offspring were considered to be compound-related.

The findings of kidney lesions in F_2b offspring as reported are shown below:

	Sex							
	Males				Females			
Group	C	L	M	H	C	L	M	H
No. in Group	55	68	73	85	84	58	70	89
Kidneys								
No. Examined	15	0	0	23	6	0	0	23
Nephropathy	0			1	0			1
Tubular dilation	4			4	3			6
Fibrosis	1			0	0			1
Mineralization	0			0	0			1

The results show that the previous finding of dilated renal tubles in the earlier rat reproduction study was a spurious conclusion and that this finding is not compound-related, since it did not occur at doses up to 30,000 ppm.

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