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

008390

JUN 3 1991

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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Glyphosate; 2-Year Combined Chronic Toxicity/ Carcinogenicity Study in Sprague-Dawley Rats - List A Pesticide for Reregistration

Caswell No.: 661A
Project No.: 0-2037
Case No.: 103601
Submission No.: S384281
MRID No.: 416438-01
(Volume 1-6)

FROM: William Dykstra, Ph.D. William Dykstra 5/14/91
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Review Section I
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Health Effects Division (H7509C) KB 5/30/91

Requested Action

Review new 2-year chronic toxicity/carcinogenicity study in rats with glyphosate.

Conclusion and Recommendation

1. Due to the high incidences of pancreatic islet cell tumors in each of the treated male groups (2000, 8000, and 20,000 ppm) in comparison to concurrent controls, Toxicology Branch I has recommended that the carcinogenic potential of glyphosate be addressed by the Peer Review Committee. The approximate date on which this issue will be considered is mid-June 1991.

2. The study is acceptable as core-guideline data. A Data Evaluation Report of the study is attached.

The NOEL is the mid-dose of 8000 ppm and the LEL is the high-dose of 20,000 ppm. At the LEL, the effects were decreased body weight and body weight gain in females, cataracts in males, decreased urinary pH in males, increased relative liver weight (to body) at 12 months, and increased absolute and relative liver weight (to brain) at 24 months in males.

Attachment

008390

Reviewed By: William Dykstra, Ph.D. William Dykstra 5/14/91
Section I, Toxicology Branch I - IRS (H7509C)
for Secondary Reviewer: Roger Gardner, Section Head Pamela M. Hurley 5/14/91
Section I, Toxicology Branch I - IRS (H7509C)

DATA EVALUATION REPORT

Study Type: 83-5 - Combined Chronic Toxicity/Carcinogenicity - Rats

TOX Chem No.: 661A

Accession No.: N/A

MRID No.: 416438-01 (Volumes 1-6)

Test Material: Glyphosate, technical; 96.5% purity; Lot XLH-264

Synonym: Roundup

This is the Stout and Ruecker (1990) study discussed in Section 4.5.3 of EPA's carcinogenicity assessment.

Study No.: MSL-10495

Sponsor: Monsanto Company
St. Louis, MO

Testing Facility: Monsanto Environmental Health Laboratory
St. Louis, MO

Title of Report: Chronic Study of Glyphosate Administered in Feed to Albino Rats.

Authors: L.D. Stout and F.A. Ruecker

Report Issued: September 26, 1990

Conclusions: Glyphosate was fed to randomized groups of 60/sex/dose Sprague-Dawley rats at doses of 0, 2000, 8000 and 20,000 ppm.

The NOEL for systemic effects is 8000 ppm (the mid-dose). At 20,000 ppm (LEL, HDT), the effects were decreased body weight and body weight gain in females, cataracts in males, decreased urinary pH in males, increased relative liver weight (to body) at 12 months, and increased absolute and relative liver weight (to brain) at 24 months in males.

Due to the high incidence of pancreatic islet cell adenomas in each of the treated male groups in comparison to concurrent controls, Toxicology Branch I (TB-I) has recommended that the carcinogenic potential of glyphosate be addressed by the Peer Review Committee.

Classification: Core-Guideline

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

A. Materials:

1. Test Compound - Glyphosate technical; Description: White powder; Batch No.: XLH-264; Purity: 96.5 percent; Contaminants: L'st in CBI appendix.

2. Test Animals - Species: Albino rat; Strain: Sprague-Dawley; Age: 8 weeks; Weight: Males 284 g, Females 221 g; Source: Charles River Breeding Laboratory, Portage, MI

B. Study Design:

1. Animal Assignment - Animals were assigned randomly to the following test groups:

Test Group	Dose in Diet (ppm)	Main Study 24 Months Male	Main Study 24 Months Female	Interim Sac. 12 Months Male	Interim Sac. 12 Months Female	Total Number of Animals Male	Total Number of Animals Female
Control	0	50	50	10	10	60	60
Low (LDT)	2000	50	50	10	10	60	60
Mid (MDT)	8000	50	50	10	10	60	60
High (HDT)	20,000	50	50	10	10	60	60

2. Diet Preparation - Diet was prepared weekly and stored at room temperature. Samples of treated food were analyzed for stability and concentration routinely.

Results - With respect to stability, diets sampled at the low and high concentrations after 7 and 14 days of open container storage at room temperature averaged 94 percent of day 0. Diet analyses for concentration showed all reported values, except one, to be within 20 percent of nominal levels. Homogeneity analyses of the 2000 and 20,000 ppm diets showed the coefficient of variation to be less than 5%. The following results, summarized in the report, are of dietary concentrations during the study.

	Test Groups T-1	T-2	T-3
Target Exposure (ppm)	2000	8000	20,000
Study Mean Concen. (ppm)	1900	7600	19,000
Standard Deviation (ppm)	140	440	1030
Study Average (% Target)	95	95	95

3. Animals received food (Purina Rodent Chow #5002) and water ad libitum.

4. Statistics - The following statistical procedures were used to detect statistically significant differences between treated animals and their respective controls.

a. Dunnett's Multiple Comparison Test (two-tailed) - In-life body weights, cumulative body weight changes, food consumption, absolute leukocyte counts, reticulocyte counts, urine pH, urine specific gravity, and clinical chemistry data obtained at months 6, 12, and 18 using the KDA clinical analyzer.

b. Fisher's Exact Test (one-tailed) - Incidence of selected ocular lesions.

c. Fisher's Exact Test (one-tailed) with Bonferroni Inequality Procedure (to adjust for false positives resulting from multiple comparisons) - The incidences of nonneoplastic microscopic lesions were tested at the $p \leq 0.01$ level. The incidences of neoplastic microscopic lesions were tested at $p \leq 0.05$ and ≤ 0.01 levels.

d. Mortality Data - Analyzed by SAS (Statistical Analysis System, SAS Institute, Cary, North Carolina) lifetable procedure which includes determination of the Generalized Wilcoxin and Generalized Savage statistics.

e. Peto Analysis - Inspection of the histopathologic data was used to select lesions for statistical analysis by the prevalence methods of Peto, et al. 1980.

5. Quality assurance was performed and signed by Arthur Uelner on September 12, 1990.

C. Methods and Results:

1. Observations - Animals were inspected twice daily for signs of toxicity and mortality and clinical examinations were performed once weekly.

Results

There were no compound-related toxic or clinical signs during the study. The incidences and types of observations were noted with similar occurrence and frequency between control and treated rats of both sexes.

Mortality (Survival) - There was no compound-related effect on survival. As presented in the report, survival was comparable between control and treated rats of both sexes.

Group/ Period	6 Months	12 Months	18 Months	Term
	Percent Survival			
MN	98	90	73	29
M1	98	90	76	38
M2	100	98	84	34
M3	100	96	84	34
FN	100	94	76	44
F1	100	100	80	44
F2	100	98	70	34
F3	96	90	76	36

2. Body Weight - They were weighed once weekly for 13 weeks, then monthly for remainder of study.

Results - There were no statistically significant decreases in body weight or body weight gain in males during the study. In high-dose females, body weight decreases were statistically significant starting on day 51 throughout month 20. The mean body weight of high-dose females was decreased by 3 percent at day 51, 14 percent at month 20, and 3 percent of control at month 24. By month 20, body weight gain was decreased by 23 percent in high-dose females in comparison to controls. Therefore, the NOEL for decreased body weight and body weight gain is the mid-dose of 8000 ppm. Body weights of the groups of female rats are shown below.

Females: Mean Body Weight (Grams)

Study Week	1	7	13	81	104
Dose (ppm)					
0	220.9	296.8	326.0	543.2	488.2
2000	220.7	220.9	327.9	523.4	535.6
8000	220.8	299.4	329.1	540.0	542.6
20,000	220.8	287.7*	314.0*	470.6**	471.4
% B.W. Gain (High-Dose Animals)	0	-11.9%	-11.4%	-22.7%	-6.4%

*p < 0.5, **p < 0.01

3. Food Consumption and Compound Intake - Consumption was determined and mean daily diet consumption was calculated. Efficiency and compound intake were calculated from the consumption and body weight gain data.

Results

Food Consumption - There were no statistically significant decreases in food consumption in either treated sex in comparison to controls during the study.

Study averages for consumption of test material (mg glyphosate/kilogram body weight/day), based on the target concentrations, were approximately 89, 362, and 940 in males and 113, 457, and 1183 in females for the low-, mid-, and high-dose groups, respectively.

4. Ophthalmalogical examinations were performed at pretest and twice prior to terminal sacrifice on all animals by Dr. Cecil Moore and Dr. Lionel Rubin.

Results - Both Dr. Moore and Dr. Rubin found statistically significant increases in cataracts and lens abnormalities in high-dose male rats in comparison to controls at terminal sacrifice. The results are shown below as presented in the report.

	MOORE			RUBIN		
Group	Animals Examined	Animals With Lens Abnormalities[a]	% Animals With Lens Abnormalities[a]	Animals Examined	Animals With Lens Abnormalities[b]	% Animals With Lens Abnormalities[b]
MN	15	0	0	14	1	7
M1	22	1	5	22	2	9
M2	18	3	17	17	3	18
M3	20	5*	25	19	8*	42
FN	23	0	0	23	1	4
F1	24	0	0	24	1	4
F2	17	1	6	17	1	6
F3	19	2	11	19	3	16

[a]Unilateral and bilateral cataracts (all types) or Y-suture opacities
[b]Unilateral and bilateral complete, diffuse posterior subcapsular, anterior polar or sutural cataracts
*$p < 0.05$ and > 0.01 (Fisher's Exact Test without Bonferoni Inequality, one-tailed)

Historical control data for lens disorders and cataracts diagnosed by Dr. Moore from Monsanto's EHL historical data base or control groups of studies are shown below.

EHL Historical Control Incidences of Pertinent Lens Abnormalities (Includes Unilateral and Bilateral Cataracts (all types, including Sutural) as Determined by Dr. Moore in CD Rats)

		Males			Females		
Study	Exam Date	No. Observed	No. Affected	% Affected	No. Observed	No. Affected	% Affected
1	07/83	37	0	0	38	0	0
2	02/85	22	3	14	17	2	12
3	09/85	30	10	33	24	6	25
4	11/85	17	2	12	25	3	12
5	04/86	11	1	9	16	1	6
6	09/88	12	2	17	29	1	3

The mean prevalence for males is 14.2 percent with a range of 0 to 33 percent. Dr. Rubin's evaluation showed the high-dose males to be beyond the range of EHL historical controls.

Both Dr. Moore and Dr. Rubin concluded that the occurrence of cataracts in the high-dose group may be compound-related.

Histopathological evaluation by an EHL pathologist of terminally sacrificed male rats showed the following cataract incidences: control, 2/14; low-dose, 3/19; mid-dose, 3/17; and high-dose, 5/17. There were no statistically significant differences.

For all animals on study, the EHL incidence of cataracts was control, 4/60; low-dose, 6/60; mid-dose, 5/60; and high-dose, 8/60. Again, there were no statistically significant differences.

EPL pathologist Dr. Larry Ackerman also examined all slides of eyes of all male rats on study. Dr. Ackerman's results are summarized below.

Group	Animals Examined	Animals With Lens Abnormalities[a]	% Animals With Lens Abnormalities[a]
MN	60	3	5
M1	60	4	7
M2	60	4	7
M3	60	8	13
FN	60	0	0
F1	60	0	0
F2	60	2	3
F3	60	2	3

[a]Unilateral and bilateral basophilic degeneration of major cataracts.

There are no significant differences in Dr. Ackerman's findings.

In summary, based on the ophthalmic examinations, the NOEL for cataracts and degenerative lens changes is the mid-dose level of 8000 ppm.

5. Blood was collected before treatment and at 6, 2, 18, and 24 months for hematology and clinical analysis from 10/sex/ group animals. The CHECKED (X) parameters were examined.

a. Hematology

X		X	
X	Hematocrit (HCT)*		Total plasma protein (TP)
X	Hemoglobin (HGB)*	X	Leukocyte differential count
X	Leukocyte count (WBC)*	X	Mean corpuscular HGB (MCH)
X	Erythrocyte count (RBC)*	X	Mean corpuscular HGB conc. (MCHC)
X	Platelet count*	X	Mean corpuscular volume (MCV)
X	Reticulocytes		

*Recommended by Subdivision F (October 1982) guidelines for chronic studies.

Results - There were no compound-related hematological findings or changes that were considered toxicologically significant. Most of the statistically significant changes observed were usually small in magnitude, and were not consistent or dose-related.

b. Clinical Chemistry

X	Electrolytes:	X	Other:
X	Calcium*	X	Albumin*
X	Chloride*	X	Blood creatinine*
	Magnesium*	X	Blood urea nitrogen*
X	Phosphorus*	X	Cholesterol*
X	Potassium*	X	Globulins
X	Sodium*	X	Glucose*
	Enzymes:	X	Total bilirubin*
X	Alkaline phosphatase	X	Direct bilirubin
	Cholinesterase	X	Total protein
	Creatinine phosphokinase*		Triglycerides
	Lactic acid dehydrogenase		
X	Serum alanine aminotransferase (also SGPT)*		
X	Serum aspartate aminotransferase (also SGOT)*		

*Recommended by Subdivision F (October 1982) guidelines for chronic studies.

Results - There were no compound-related clinical chemistry findings or changes that were considered toxicologically significant. Most of the statistically significant changes were small and were not consistent or dose-related. At 24 months, there was a statistically significant increase in alkaline phosphatase in high-dose females (187% of control values) in comparison to controls. This is due to animal number F3053 which had a value of 490 IU/L. When this animal is not counted, the high-dose group is no longer statistically significant. Evaluation of the histopathological results of F3053 showed the following tumors: pheochromocytoma, adenocarcinoma (metastatic to the lung) of mammary gland, as well as a mammary gland adenoma, adenofibroma, and fibroma. Other nonneoplastic lesions were also present in the liver, heart, and kidneys.

6. Urinalysis - Urine was collected from fasted animals at 6, 12, 18, and 24 months on 10 sex/group of fasted animals. The CHECKED (X) parameters were examined.

X	Appearance*	X	Glucose*
X	Volume	X	Ketones*
	Specific gravity*	X	Bilirubin*

*Recommended by Subdivision F (October 1982) guidelines for chronic studies.

X	pH	X	Blood*
X	Sediment (miroscopic)*		Nitrate
X	Protein*	X	Urobilinogen

*Recommended by Subdivision F (October 1982) guidelines for chronic studies.

Results - A statistically significant increase in urine specific gravity (1.043 in controls vs. 1.061* ($p < 0.05$) in high-dose) and decrease in urine pH (6.9 in controls vs. 6.0 at high-dose) was observed in high-dose males at 6 months. Additionally, high-dose males showed statistically significantly decreased urinary pH at the 18- and 24-month sampling periods. The authors stated that this may have been related to the renal excretion of glyphosate which is a weak acid. However, since female rats did not display this finding, this explanation is not totally valid.

18 Months	pH
Control	6.8
High-Dose	5.8**
24 Months	
Control	6.4
High-Dose	5.7*

*$p < 0.05$
**$p < 0.01$

The NOEL for urinalysis is 8000 ppm.

7. Sacrifice and Pathology - All animals that died and that were sacrificed on schedule were subject to gross pathological examination and the CHECKED (X) tissues were collected for histological examination. The (XX) organs in addition were weighed.

X	Digestive System	X	Cardiovasc./Hemat.	X	Neurologic
	Tongue	X	Aorta*	XX	Brain*
X	Salivary glands*	X	Heart*	X	Periph. nerve*
X	Esophagus*	X	Bone marrow*	X	Spinal cord (3 levels)*
X	Stomach*	X	Lymph nodes*		

*Recommended by Subdivision F (October 1982) guidelines for chronic studies.

X	Duodenum*	X	Spleen*	X	Pituitary*
X	Jejunum*	X	Thymus*	X	Eyes (optic n.)*
X	Ileum*		Urogenital		Glandular
X	Cecum*	XX	Kidneys*	X	Adrenals*
X	Colon*	X	Urinary bladder*		Lacrimal gland
X	Rectum*	XX	Testes*	X	Mammary gland*
XX	Liver*	XX	Epididymides	X	Parathyroids*
	Gallbladder*	XX	Prostate	X	Thyroids*
X	Pancreas*	X	Seminal vesicle		Other
	Respiratory	X	Ovaries	X	Bone*
X	Trachea*	X	Uterus*	X	Skeletal
	muscle*				
X	Lung*			X	Skin
X	Nasal turbinates			X	All gross lesions all masses
				X	Harderian gland

*Recommended by Subdivision F (October 1982) guidelines for chronic studies.

Results

a. Organ Weight

12 Months - Relative to body weight, liver weight was statistically significantly increased in high-dose males.

Dose	Relative Weight Liver (%)	Percent Controls
Control	2.4082	
Low	2.5166	104
Mid	2.5269	105
High	2.7122*	113

*$p < 0.05$

Terminal Sacrifice - High dose males had statistically significantly increased absolute liver weight and liver weight relative to brain weight in comparison to controls.

Absolute Liver Weight (g)			Percent Liver Weight Relative to Brain Weight		
Dose		% Control	Dose		% Control
Control	16.5051		Control	707.2950	
Low	17.9773	109	Low	783.4629	111
Mid	17.8834	107	Mid	753.2652	106
High	18.6139*	113	High	805.0906*	114

*p < 0.05

The NOEL for organ weights is 8000 ppm.

b. Gross Pathology - There were no compound-related gross necropsy findings at the interim sacrifice, terminal sacrifice, or in animals dying on study.

c. Microscopic Pathology - (Age-adjusted, statistical analyses by statisticians of SACB are attached.)

1) Nonneoplastic - Mid-level females had a statistically significant increased incidence of inflammation of the gastric squamous mucosa. The findings for both sexes, as presented in the report, is shown below.

		Number of Lesions/Number Examined Incidence (%)			
Organ/Lesion	Sex	Dose (ppm): 0	2000	8000	20000
Stomach Inflammation Squam. Mucosa	M	2/58 (3)	3/58 (5)	5/59 (8)	7/59 (12)
	F	0/59 (0)	3/60 (5)	9/60* (15)	6/59 (10)

p ≤ 0.01; Fisher Exact Test with Bonferroni Inequality.

There was no increase in severity of the grade of the lesion with dose in either sex.

Historical control data from EHL are provided below.

Stomach	Inflammation, Squamous mucosa	Female	1	02/85	23	60	2 3.3
			2	10/85	24	70	3 4.3
			3	06/88	24	60	0 0.0
			4	09/88	24	59	1 1.7
			5	01/89	24	60	8 13.3
			6	03/89	24	58	5 8.6

Since the lesion is not dose-related, was not increased in severity with dose, is within the range of historical controls, at the high-dose, and occurred in only two (one mid-dose female (F2014) and one high-dose male (M3002)) terminally sacrificed animals (Note: this means that the lesion occurred a total of 33 incidences in rats which did not reach terminal sacrifice), the lesion is not considered compound-related.

2) Neoplastic

1. Pancreas - Low-dose males had a statistically significant incidence of pancreatic islet cell adenomas. The incidences of both sexes are shown below.

Organ/Lesion	Sex	Dose (ppm): 0	2000	8000	20,000
		Incidence (%)			
PANCREAS (Islet Cell)					
Hyperplasia	M[a]	2/58 (3) NS	0/57 (0)	4/60 (7)	2/59 (3)
	F[a]	4/60 (7)	1/60 (2)	1/60 (2)	0/59 (0)
Adenoma	M[a]	1/58 (2) NS	8/57* (14)	5/60 (8)	7/59 (12)
	F[a]	5/60 (8) NS	1/60 (2)	4/60 (7)	0/59 (0)
Carcinoma	M[a]	1/58 (2) NS	0/57 (0)	0/60 (0)	0/59 (0)

[a]All deaths considered
*$p \leq 0.05$; Fisher Exact Test with Bonferroni Inequality
NS = Not significant; Peto Test ($p \leq 0.05$)
NA = Peto Test not performed

Organ/Lesion	Sex	Incidence (%) Dose (ppm): 0	2000	8000	20,000
	F[a]	0/60 (0) NA	0/60 (0)	0/60 (0)	0/59 (0)
Adenoma, Carcinoma Combined	M[a]	2/58 (3) NS	8/57 (14)	5/60 (8)	7/59 (12)
	F[a]	5/60 (8) NS	1/60 (2)	4/60 (7)	0/59 (0)

[a]All deaths considered
*$p \leq 0.05$; Fisher Exact Test with Bonferroni Inequality
NS = Not significant; Peto Test ($p \leq 0.05$)
NA = Peto Test not performed

Historical control data from Monsanto's EHL are shown below.

EHL 87122 - Historical Control Information for Histopathological Findings (All Deaths)

Organ	Lesion	Sex	Study	Terminal Necropsy Date	Months of Study	No. Observed	No. Affected	% Affected
Pancreas	Islet Cell Adenoma	Male	1	07/83	24	68	2	2.9
			2	02/85	23	59	5	8.5
			3	10/85	24	69	4	5.8
			4	06/85	24	57	1	1.8
			5	09/88	24	60	5	8.3
			6	01/89	24	60	3	5.0
			7	03/89	24	59	3	5.1

It can be seen from the study results that the incidences of the pancreatic islet cell adenomas at the low- and high-dose group exceed the historical control range of 1.8 to 8.5 percent. However, there is no dose-response relationship in the occurrence of these tumors in males, no progression to carcinoma, and the incidence of hyperplasia is not dose-related.

In a 1981 Lifetime (26 Months) Feeding Study in Rats with Glyphosate (Bio/dynamics Project No. 77-2062), the incidences of islet cell pancreatic tumors were as follows:

Dose (mg/kg/day)	Sex	0	3	10	30
Hyperplasia	M	3/58 (6)	2/49 (4)	1/50 (2)	0/50 (0)
	F	2/50 (4)	1/50 (2)	0/50 (0)	0/50 (0)
Adenoma	M	0/50 (0)	5/49 (10)	2/50 (4)	2/50 (4)
	F	2/50 (4)	1/50 (2)	1/50 (2)	0/50 (0)
Carcinoma	M	0/50 (0)	0/50 (0)	0/50 (0)	1/50 (2)
	F	0/50 (0)	1/50 (2)	1/50 (2)	1/50 (2)
Adenoma/Carcinoma Combined	M	0/50 (0)	5/50 (10)	2/50 (4)	3/50 (6)
	F	2/50 (4)	2/50 (4)	2/50 (4)	1/50 (2)

These finding were not considered compound-related effects in this study; the combined incidence of pancreatic islet cell adenoma and carcinoma in males was 0, 10, 4, and 6 in the control, low-, mid-, and high-dose groups, respectively. In females, the combined incidence was 4, 4, 4, and 2 in control, low-, mid-, and high-dose groups, respectively. Shown below are the 1981 and 1990 studies combined.

Pancreatic Islet Cell Tumors

			% Incidence Males				
Dose (mg/kg/day)	0	3	10	30	90	360	940
No. Examined	118	49	50	50	57	60	59
Hyperplasia	5	2	1	0	0	7	3
%	(4)	(4)	(2)	(0)	(0)	(12)	(5)
Adenoma	1	5	2	2	8	5	7
%	(1)	(10)	(4)	(4)	(14)	(8)	(12)

	% Incidence						
	Males						
Dose (mg/kg/day)	0	3	10	30	90	360	940
Carcinoma	1	0	0	1	0	0	0
%	(1)	(0)	(0)	(2)	(0)	(0)	(0)
Adenoma/Carcinoma Combined	2	5	2	3	8	5	7
%	(2)	(10)	(4)	(6)	(14)	(8)	(12)

The incidence of pancreatic islet cell tumors for the two studies does not show a dose-related increase in adenoma/carcinoma combined and is within the range of open literature control data for male Sprague-Dawley rats (0 to 17%).

Open literature information (data attached) provided by Monsanto from other laboratories shows a prevalence up to 17.0 percent in untreated Sprague-Dawley rats.

Due to the high incidence of islet cell pancreatic adenomas in each male treated group, in comparison to concurrent controls, TB-I recommends that the HED Peer Review Committee review the oncogenic potential of glyphosate with respect to this tumor type.

2. Thyroid - C-cell adenomas were slightly increased in male and female mid- and high-dose groups as shown below.

Thyroid C-Cell Lesions

	Incidence (%)				Monsanto's EHL Historical Control
Sex/Lesion	0 ppm	2000 ppm	8000 ppm	20,000 ppm	Range %
			Males		
Hyperplasia	5/60 (8.3)	1/58 (1.7)	6/58 (10.3)	5/60 (8.3)	4.3 - 20
Adenoma	2/60 (3.3)	4/58 (6.9)	8/58 (13.8)	7/60 (11.7)	1.8 - 10.6
Carcinoma	0/60 (0)	2/58 (3.4)	0/58 (0)	1/60 (1.7)	0 - 5.2

Thyroid C-Cell Lesions

Sex/Lesion	Incidence (%) 0 ppm	2000 ppm	8000 ppm	20,000 ppm	Monsanto's EHL Historical Control Range %
		Females			
Hyperplasia	10/60 (16.7)	5/60 (8.3)	9/60 (15)	5/60 (8.3)	4.3 - 16.9
Adenoma	2/60 (3.3)	2/60 (3.3)	6/60 (10)	6/60 (10)	3.3 - 10
Carcinoma	0/60 (0)	0/60 (0)	1/60 (1.7)	0/60 (0)	0 - 2.9

Since there was no dose-response in adenomas in either sex, no progression to carcinoma in a dose-related manner, no significant dose-related increase in severity of grade or incidence in hyperplasia, and in light of historical controls adenomas, the C-cell adenomas in males and females are not considered compound related.

3. Liver

Males - There was a slight dose-related increase in hepatocellular adenomas in males but the incidence was within the range of historical controls from Monsanto's EHL.

Hepatocellular Neoplasms in Males

Lesion	Incidence (%)[a] 0 ppm	2000 ppm	8000 ppm	20,000 ppm	Monsanto's EHL Historical Control Range
Adenoma	2/60 (3.3)	2/60 (3.3)	3/60 (5.8)	7/60 (11.7)	1.4 - 18.3
Carcinoma	3/60 (5)	2/60 (3.3)	1/60 (1.7)	2/60 (3.3)	0 - 6.7

Nonneoplastic liver lesions are shown below.

Hepatocellular Lesions in Males

Lesion	Incidence (%) 0 ppm	2000 ppm	8000 ppm	20000 ppm	Monsanto's EHL Historical Control Range
Hyperplasia	0/60	0/60	1/60 (1.7)	1/60 (1.7)	Not Available[a]
Focus of Cell Alteration	23/60 (38)	20/60 (33)	29/60 (48)	27/60 (45)	13.3 - 45.6
Centrilobular Necrosis	4/60 (6.7)	5/60 (8.3)	3/60 (5.0)	4/60 (6.7)	Not Available

[a]Could not be determined because hyperplasia and hypertrophy were combined for some studies in historical control data base.

As can be seen from the hepatocellular tumor data, the historical controls, and the non-neoplastic liver lesions data, there is no progression from adenoma to carcinoma and the nonneoplastic lesions (hyperplasia, centrilobular necrosis, and focus of cell alteration) do not show a compound-related effect. Therefore, the slightly increased occurrence of hepatocellular adenomas in males is not considered compound-related.

Attachment

R:62826:Dykstra:C.Disk:KEVRIC:04/26/91:aw:EK:CL
R:62894:Dykstra:C.Disk:KEVRIC:05/10/91:aw

008390

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

008390

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

Subject. Glyphosate, Qualitative Risk Assessment -
2-Year Sprague-Dawley Rat Dietary Study

Caswell no.66A

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The qualitative risk assessment of glyphosate was based upon a 2-year dietary study of Sprague-Dawley rats.

The attached tables present in tabular form, the results of the statistical analysis of data from the dietary study of Sprague-Dawley rats (MSL 10495, R.D.no. 1014, Project no. 0-2037).

The sponsor of the study was Monsanto Agricultural Company The study was completed and issued in September, 1990.

Table 1. Glyphosate - Sprague-Dawley Rat Study, Male Mortality Rates+ and Cox or Generalized K/W Test Results++

	Weeks					
Dose (ppm)	1-26	27-53	54[a]	54-78	79-105[b]	Total
0	1/60	4/58[c]	10/54	8/44	22/36	35/49(71)
2000	1/60	4/59	10/55	7/45	19/38	31/50(62)
8000	0/60	1/60	10/59	7/49	25/42	33/50(66)
20000	0/60	2/60	10/58	6/48	25/42	33/50(66)

+ Number of animals that died during interval/Number of animals alive at the beginning of the interval.

++ Thomas, D.G., Breslow, N. and Gart, J.J. - Trend and Homogeneity Analysis of Proportions and Life Table Data, version 2.0.

( ) Percent

a Interim sacrifice at week 54.
b Final sacrifice at week 105.
c excludes an accidental death - one animal at week 53.

Note: Time intervals were selected for display purposes only.
Significance of trend denoted at Control.
Significance of pair-wise comparison with control denoted at Dose level.
If * then $p<.05$ and if ** then $p<.01$.

Table 2. Glyphosate - Sprague-Dawley Rat Study, Female Mortality Rates[+] and Cox or Generalized K/W Test Results[++]

	Weeks					
Dose (ppm)	1-26	27-53	54[a]	54-78	79-105[b]	Total
0	0/60	3/60	10/57	9/47	16/38	28/50(56)
2000	0/60	0/60	10/60	10/50	18/40	28/50(56)
8000	0/60	1/60	10/59	14/49	18/35	33/50(66)
20000	2/60	3/58	10/55	7/45	20/38	32/50(64)

[+] Number of animals that died during interval/Number of animals alive at the beginning of the interval.

[++] Thomas, D.G., Breslow, N. and Gart, J.J. - Trend and Homogeneity Analysis of Proportions and Life Table Data, version 2.0.

( ) percent

[a] Interim sacrifice at week 54.
[b] Final sacrifice at week 105.

Note: Time intervals were selected for display purposes only.
Significance of trend denoted at Control.
Significance of pair-wise comparison with control denoted at Dose level.
If * then $p<.05$ and if ** then $p<.01$.

Table 3. Glyphosate - Sprague-Dawley Male Rats, Hepatocellular Tumor Rates+ and Cochran-Armitage Trend Test and Fisher's Exact Test Results (p values)

	Dose (ppm)			
Tumors	0	2000	8000	20000
Carcinomas (%)	3/44 (7)	2/45 (4)	1/49 (2)	2[a]/48 (4)
p=	0.324	0.489(n)	0.269(n)	0.458(n)
Adenomas (%)	2/44 (5)	2/45 (4)	3/49 (6)	7/48 (15)
p=	0.016*	0.683(n)	0.551	0.101
Both (%)	5/44 (11)	4/45 (9)	4/49 (8)	9/48 (19)
p=	0.073	0.486(n)	0.431(n)	0.245
Hyperplasia only (%)	0/44 (0)	0/45 (0)	1[c]/49 (2)	0/48 (0)
p=	0.462	1.000	0.527	1.000

+ Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 55.

(n) negative change from control

[a] First carcinoma observed at week 85, dose 20000 ppm.
[b] First adenoma observed at week 88, dose 20000 ppm.
[c] hyperplasia observed at week 89, dose 8000 ppm.

Note: Significance of trend denoted at Control.
Significance of pair-wise comparison with control denoted at Dose level.
If * then $p<.05$ and if ** then $p<.01$.

Table 4. Glyphosate - Sprague-Dawley Male Rats, Pancreatic Islet Cell Tumor Rates[+] and Cochran-Armitage Trend Test and Fisher's Exact Test Results (p values)

	Dose (ppm)			
Tumors	0	2000	8000	20000
Carcinomas	1[a]/43	0/45	0/49	0/48
(%)	(2)	(0)	(0)	(0)
p=	0.159	0.489(n)	0.467(n)	0.472(n)
Adenomas	1/43	8/45	5/49	7[b]/48
(%)	(2)	(18)	(10)	(15)
p=	0.170	0.018*	0.135	0.042*
Both	2/43	8/45	5/49	7/48
(%)	(5)	(18)	(10)	(15)
p=	0.241	0.052	0.275	0.108
Hyperplasia	2/43	0/45	3/49	2[c]/48
only (%)	(5)	(0)	(6)	(4)
p=	0.323	0.236(n)	0.562	0.649(n)

[+] Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacificed before week 55.

(n) negative change form control

[a] First carcinoma observed at week 105, dose 0 ppm.
[b] First adenoma observed at week 81, dose 20000 ppm.
[c] First hyperplasia observed at week 91, dose 20000 ppm.

Note: Significance of trend denoted at Control.
Significance of pair-wise comparison with control denoted at Dose level.
If * then p<.05 and if ** then p<.01.

Table 5. Glyphosate - Sprague-Dawley Male Rats, Thyroid C-Cell Tumor Rates+ and Cochran-Armitage Trend Test and Fisher's Exact Test Results (p values)

	Dose(ppm)			
Tumors	0	2000	8000	20000
Carcinomas	0/54	2[a]/55	0/58	1/58
(%)	(0)	(4)	(0)	(2)
p=	0.452	0.252	1.000	0.518
Adenoma	2[b]/54	4/55	8/58	7/58
(%)	(4)	(7)	(14)	(12)
p=	0.069	0.348	0.060	0.099
Both	2/54	6/55	8/58	8/58
(%)	(4)	(11)	(14)	(14)
p=	0.077	0.141	0.060	0.060
Hyperplasia only (%)	4/54 (7)	1/55 (2)	5[c]/58 (9)	4/58 (7)
p=	0.312	0.176(n)	0.546	0.601

+ Number of tumor bearing animals/Number of animals examined, excluding those that died before week 54.

(n) negative change from control

[a] first carcinoma observed at week 86, dose 2000 ppm.
[b] first adenoma observed at week 54, dose 0 ppm.
[c] first hyperplasia observed at week 54, dose 8000 ppm.

Note: Significance of trend denoted at Control.
Significance of pair-wise comparison with control denoted at Dose level.
If * then $p<.05$ and if ** then $p<.01$.

Table 6. Glyphosate - Sprague-Dawley Female Rats, Thyroid C-Cell Tumor Rates[+] and Cochran-Armitage Trend Test and Fisher's Exact Test Results (p values)

	Dose(ppm)			
Tumors	0	2000	8000	20000
Carcinomas	0/57	0/60	1[a]/59	0/55
(%)	(0)	(0)	(2)	(0)
p=	0.445	1.000	0.509	1.000
Adenomas	2/57	2/60	6[b]/59	6/55
(%)	(4)	(3)	(10)	(11)
p=	0.031*	0.671(n)	0.147	0.124
Both	2/57	2/60	7/59	6/55
(%)	(4)	(3)	(12)	(11)
p=	0.033*	0.671(n)	0.090	0.124
Hyperplasia	10[c]/57	5/60	7/59	4/55
only (%)	(18)	(8)	(12)	(7)
p=	0.113	0.112(n)	0.274(n)	0.086(n)

[+] Number of tumor bearing animals/Number of animals examined, excluding those that died before 54 weeks.

(n) negative change from control

[a] First carcinoma observed at week 93, dose 8000 ppm.
[b] First adenoma observed at week 72, dose 8000 ppm.
[c] First hyperplasia observed at week 54, dose 0 ppm.

Note: Significance of trend denoted at Control.
Significance of pair-wise comparison with control denoted at Dose level.
If * then $p<.05$ and if ** then $p<.01$.

APPENDIX 1

Historical Control Information For Individual Studies
Conducted In CD Rats

GLYPHOSATE

Page_____ is not included in this copy.

Pages 29 through 40 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

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____ A draft product label.

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The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.