12-13-91

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

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DEC 13 1991

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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Glyphosate - EPA Registration No. 524-308 - 2-Year Chronic Feeding/Oncogenicity Study in Rats with Technical Glyphosate.

Caswell No.: 661A
HED Project No.: 0-2037
MRID No.: 416438-01

FROM: William Dykstra, Ph. D.
Review Section I
Toxicology Branch I
Health Effects Division (H7509C)

William Dykstra 12/4/91

THRU: Roger Gardner, Section Head
Review Section I
Toxicology Branch I
Health Effects Division (H7509C)

Roger Gardner 12-4-91 KB 12/9/91

TO: Robert J. Taylor, Product Manager 25
Registration Division (H7507C)

and

Lois Rossi, PM 74
Reregistration Branch
Special Review and Reregistration Division (H7508C)

Recommendations and Conclusions

1. On June 26, 1991, the results of the subject study were presented to the Health Effects Division's (HED) Carcinogenicity Peer Review Committee (see Attached Peer Review Document). Special consideration was given to the incidences of pancreatic islet cell tumors in males, thyroid C-cell tumors in male and female rats, and hepatocellular tumors in male rats.

2. The Committee classified glyphosate into Group E (evidence of noncarcinogenicity in humans) based on a lack of convincing evidence of carcinogenicity in adequate studies in two species.

1

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3. With respect to non-neoplastic lesions, the NOEL is considered to be the lowest dose tested (2000 ppm). The LEL is the mid dose of 8000 ppm, and the effect is a statistically and toxicologically significant increase in the incidence of inflammation of squamous mucosa in the stomach of female rats.

   At 20,000 ppm, there were additional significant effects as follows: inflammation of squamous cell mucosa in the stomach of females, decreased body weight gain of females, cataracts of the lens of the eyes in males, increased male liver weight relative to body weight at 12 months, increased male absolute liver weight, increased male liver weight relative to brain weight at terminal sacrifice, an increased incidence of pancreatic acinar cells with atrophy in males, an increase in urinary specific gravity at 6 months in males, and a significant decrease in urinary pH in males at 6, 18 and 24 months in males.

4. A copy of the HED Peer Review document and the Data Evaluation Record for the 2-year chronic feeding/oncogenicity study are attached. The feeding study is classified as Core Guideline.

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OCT 30 1991

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: SECOND Peer Review of Glyphosate

CAS No. 1071-83-6
EPA Chem. Code 417300
40 CFR 180.364
TOX Chem. No.: 661A
Reg Group: List A (6B)

FROM: William Dykstra, Ph.D. William Dykstra
Toxicology Branch I (IRS)
Health Effects Division (H7509C)

and

George Z. Ghali, Ph.D. G. Ghali 8/22/91
Science Analysis and Coordination Branch
Health Effects Division (H7509C)

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

and

Lois Rossi, Chief
Reregistration Branch
Special Review and Reregistration Division (H7508W)

The Health Effects Division Carcinogenicity Peer Review Committee convened on June 26, 1991 to discuss and evaluate the weight of the evidence on Glyphosate with particular emphasis on its carcinogenic potential. The Committee concluded that Glyphosate should be classified as a Group E (evidence of non-carcinogenicity for humans), based upon lack of convincing carcinogenicity evidence in adequate studies in two animal species.

It should be emphasized, however, that designation of an agent in Group E is based on the available evidence at the time of evaluation and should not be interpreted as a definitive conclusion that the agent will not be a carcinogen under any circumstances.

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A. Individual in Attendance

1. Peer Review Committee (Signature indicates concurrence with the peer review unless otherwise stated.)

Penny Fenner-Crisp	Penelope A. Fenner-Crisp
William L. Burnam	
Karl Baetcke	
Marcia Van Gemert	Marcia van Gemert
Esther Rinde	
Hugh Pettigrew	
Marion Copley	
Lucas Brennecke	
George Ghali	

2. Peer Review Members in Absentia (Committee members who were unable to attend the discussion; signature indicates concurrence with the overall conclusions of the Committee.)

Reto Engler	
Richard Hill	—
John Quest	
Kerry Dearfield	
Yin-Tak Woo	
Jean Parker	— NON CONCUR
William Sette	
Robert Beliles	DO NOT CONCUR
Julie Du	

3. Scientific Reviewers (Committee or noncommittee members responsible for data presentation; signature indicates technical accuracy of panel report.)

William Dykstra	
Roger Gardner	9-5-91

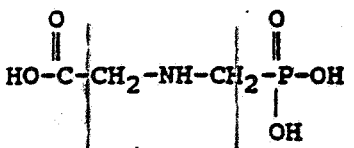
B. Background Information

Glyphosate is the isopropylamine (IPA) or sodium salt of N-(phosphonomethyl) glycine, marketed under the trade names of Roundup, Rodeo, Shackle, and Polado. Glyphosate is a wide spectrum plant growth regulator herbicide which is used to control grasses, sedges, and broadleaf weeds. It acts by the inhibition of amino acid synthesis.

Tolerances established for glyphosate and its aminomethyl phosphonic acid (AMPA) metabolite in 40 CFR 180.364 include the following:

IPA salt of glyphosate: soybeans, cotton, corn, sorghum, wheat, rice, vegetables, citrus fruits, pome fruits, stone fruits, tropical fruits, pastures, and alfalfa.

Sodium salt of glyphosate: sugarcane.



Glyphosate

On February 11, 1985, the carcinogenic potential of glyphosate was first considered by a panel (then called the Toxicology Branch Ad Hoc Committee) comprised of members of the Toxicology Branch of the Hazard Evaluation Division. The Committee, in a consensus review dated March 4, 1985, classified glyphosate as a Group C carcinogen based on an increased incidence of renal tubular adenomas in male mice. According to the consensus review, the tumor is rare, it occurred in a dose-related manner, and the incidence was outside the reported historical control range. The Committee also concluded that dose levels tested in a 26-month rat feeding study were not adequate for the assessment of glyphosate's carcinogenic potential in this species.

The kidney slides from the long-term mouse feeding study were subsequently reexamined, and one pathologist diagnosed an additional kidney tumor in control males. These findings were presented to the FIFRA Scientific Advisory Panel (SAP) which proposed that glyphosate be classified into Group D (inadequate animal evidence of carcinogenic potential). The SAP, in their meeting of February 11-12, 1986 (report dated February 24, 1986), concluded that, after adjusting for the greater survival in the high-dose mice compared to concurrent controls, no statistically significant pairwise differences existed, although the trend was significant. The SAP further noted that, although comparison of

these findings to historical control incidences yielded a statistically significant result, this finding did not override the lack of pairwise significance of comparisons to concurrent controls.

The SAP determined that the carcinogenic potential of glyphosate could not be determined from existing data and proposed that rat and/or mouse studies be repeated in order to clarify these equivocal findings.

HED deferred a decision on the repeat of an additional mouse oncogenicity study until the 1990 rat feeding study had been evaluated by the Peer Review Committee.

C. Material Evaluated

The material available for review consisted of a document prepared by Dr. William Dykstra summarizing major scientific and regulatory issues and relevant toxicology information, data evaluation records of a combined chronic toxicity/carcinogenicity study in rats and a carcinogenicity study in mice, the FIFRA Scientific Advisory Panel report dated Feb 24, 1986, a review of historical control data on mouse kidney tumors, a toxicology one-liner for the glyphosate data base and an OPP peer review report entitled "Consensus Review of Glyphosate" dated March 4, 1985.

D. Evaluation of Carcinogenicity Data

1. **Lankas, G. P. December 23, 1981. A Lifetime Study of Glyphosate in Rats. Unpublished report No. 77-2062 prepared by BioDynamics, Inc. EPA Acc. Nos. 247617 - 247621. MRID 00093879.**

a. Experimental Design

The lifetime feeding study in Sprague-Dawley rats at 50/sex/dose was conducted at dietary concentrations of glyphosate of 0, 30, 100, and 300 ppm. These concentrations were adjusted during the course of the study so that actual doses of 0, 3, 10, and 31 mg/kg/day in males and 0, 3, 11, and 34 mg/kg/day in female rats were maintained.

b. Discussion of Tumor Data

An increase in the incidence of interstitial cell tumors of the testes was observed in male rats. Because of the absence of a dose-response relationship, the lack of preneoplastic changes, the wide variability in the spontaneous incidence of this tumor, the similarity in incidences between the high-dose

group and the historical controls, and lack of any evidence of genotoxicity, it was concluded by the previous Peer Review Committee that the observed incidence did not reflect a carcinogenic response.

Additionally, there was the question of possible thyroid carcinomas in high-dose females. After a review of the slides by a consulting pathologist, and a reassessment of all relevant data, including the fact that no effect of treatment on tumor latency or the combined incidences of adenoma and carcinoma was apparent, the earlier Peer Review Committee concluded that the data did not demonstrate a carcinogenic response in the thyroid.

c. Nonneoplastic Lesions and Adequacy of Dosing Considerations

No effect of treatment on the incidence of nonneoplastic lesions was noted. No effects of treatment on survival, body weight gain, clinical pathology, or findings at necropsy were noted. Therefore, there is no evidence that the highest dose tested was adequate to evaluate the carcinogenic potential of glyphosate.

2. **Stout, L. D. and Ruecker, F. A. (1990). Chronic Study of glyphosate Administered in Feed to Albino Rats. Laboratory Project No. MSL-10495; Sept. 26, 1990. MRID No. 416438-01; Historical Controls; MRID No. 417287-00.**

a. Experimental Design

This chronic toxicity/carcinogenicity study in the rat was submitted to the Agency as a replacement study for the 26-month 1981 chronic toxicity/carcinogenicity study in the rat. In this study, randomized groups of 60 male and 60 female young (8 weeks old) Sprague-Dawley rats were fed dietary levels of 0, 2000, 8000, or 20,000 ppm or the equivalent of 0, 100, 400, and 1000 mg/kg/day of technical glyphosate for 2 years. At 12 months, 10 animals/sex/group were sacrificed.

b. Discussion of Tumor Data

Age-adjusted, statistical analyses of the tumor data are presented. The most frequently observed tumors in this study were pancreatic islet cell adenomas in males, thyroid C-cell adenomas and/or carcinomas in males and females, and hepatocellular adenomas and carcinomas in males. The following is a discussion of each type of tumor.

i. Pancreas (Tables 1 - 3)

Low-dose and high-dose males had a statistically significant increased incidence of pancreatic islet cell adenomas.

Table 1: 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	20,000
Carcinomas	1/43[a]	0/45	0/49	0/48
(%)	(2)	(0)	(0)	(0)
p =	0.159	0.409(n)	0.467(n)	0.472(n)
Adenomas	1/43	8/45	5/49	7/48[b]
(%)	(2)	(18)	(10)	(15)
p =	0.170	0.018*	0.135	0.042*
Adenomas/carcinomas	2/43	8/45	5/49	7/48
(%)	(5)	(18)	(10)	(15)
p =	0.241	0.052	0.275	0.108
Hyperplasia only	2/43	0/45	3/49	2/48[c]
(%)	(5)	(0)	(6)	(4)
p =	0.323	0.236	0.526	0.649

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

[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.

[d] $p \leq 0.05$; Fisher's Exact test with Bonferoni correction.

Note:

Significance of trend denoted at Control. Significance of pair-wise comparison with control denoted at Dose level. If then $p < 0.05$.

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Historical control data on the incidence of pancreatic islet cell adenomas from Monsanto's EHL are shown in Table 2 below.

Table 2: EHL 87122 - Historical Control Information for Histopathological Findings (All Deaths)

Terminal Necropsy Study	Months of Date	Study Length (Months)	No. Observed	No. Affected	% Affected
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

Committee's interpretation: Although the incidences of the pancreatic islet cell adenomas at the low-, mid- and high-dose groups exceeded the historical control range of 1.8 to 8.5 percent in male rats, there was no statistically significant positive dose-related trend in the occurrence of these tumors in males, no progression to carcinoma, and the incidence of hyperplasia was not dose-related. Therefore, the pancreatic islet cell tumors were not considered to be compound-related. It was also noted that the incidence of this lesion in the concurrent control for males was at the low end of the historical control range. The Committee concluded that the apparent statistical significance of the pairwise comparisons of the treated male groups with the concurrent control might have been attributable to this factor and not to actual carcinogenic response.

The incidences of islet cell pancreatic tumors in the earlier rat study (Bio/dynamics Project No. 77-2062) are shown in Table 3. The incidence of pancreatic islet cell tumors for the two studies does not show a dose-related increase in adenomas or adenoma/carcinoma combined and is within the range of open literature control data for male Sprague-Dawley rats (0 to 17%) for unadjusted data.

Table 3: Incidence of Pancreatic Islet Cell Tumors in Male Sprague-Dawley Rats Given Diets Containing Glyphosate for 26 Months (first rat feeding study).

Tumors	Dose (mg/kg/day) 0	3	10	30
Hyperplasia	3/50	2/49	1/50	0/50
(%)	(6)	(4)	(2)	(0)
Adenomas	0/50	5/49	2/50	2/50
(%)	(0)	(10)	(4)	(4)
Carcinomas	0/50	0/49	0/50	1/50
(%)	(0)	(0)	(0)	(2)
Adenoma/carcinoma	0/50	5/49	2/50	3/50
(%)	(0)	(10)	(4)	(6)

ii. Thyroid (Tables 4 - 6)

C-cell adenomas were slightly increased in male and female mid- and high-dose groups as shown in Tables 4 and 5. Historical control ranges for the thyroid tumors in Sprague-Dawley rats were reported as shown in Table 6.

Committee's interpretation: Although C-cell adenomas slightly exceeded the historical control range for both sexes, there was no statistically significant trend or pairwise comparison with controls in males. In females, the incidence of C-cell adenomas was not statistically significant in the pairwise comparison with controls but had a statistically significant positive dose-related trend. However, there was no progression to carcinoma in a dose-related manner, and no significant dose-related increase in severity of grade or incidence of hyperplasia in either sex. Therefore, the C-cell adenomas in males and females are not considered compound-related.

Table 4: Glyphosate - Sprague-Dawley Male Rats, Thyroid C-Cell Tumor Rates* and Cochran-Armitage Trend and Fisher's Exact Test Results (p values).

Tumors	Dose (ppm) 0	2000	8000	20 000
Carcinomas	0/54	2/55[a]	0/58	1/58
(%)	(0)	(4)	(0)	(2)
p =	0.452	0.252	1.000	0.518
Adenomas	2/54[b]	4/55	8/58	7/58
(%)	(4)	(7)	(14)	(12)
p =	0.069	0.348	0.060	0.099
Adenoma/carcinoma	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	1/55	5/58[c]	4/58
(%)	(7)	(2)	(9)	(7)
p =	0.312	0.176	0.546	0.601

[a] First carcinoma observed at week 93 at 8000 ppm.

[b] First adenoma observed at week 54 at 0 ppm.

[c] First hyperplasia observed at week 54 at 8000 ppm.

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

Note: Significance of trend denoted at Control. Significance of pair-wise comparison with control denoted at Dose level. If then $p < 0.05$.

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

	Dose (ppm)			
Tumors	0	2000	8000	20,000
Carcinomas	0/57	0/60	1/59[a]	0/55
(%)	(0)	(0)	(2)	(0)
p =	0.445	1.000	0.509	1.000
Adenomas	2/57	2/60	6/59[b]	6/55
(%)	(4)	(3)	(10)	(11)
p =	0.031*	0.671(n)	0.147	0.124
Adenoma/carcinoma	2/57	2/60	7/59	6/55
(%)	(4)	(3)	(12)	(11)
p =	0.033*	0.671(n)	0.090	0.124
Hyperplasia only	10/57[c]	5/60	7/59	4/55
(%)	(18)	(8)	(12)	(7)
p =	0.113	0.112	0.274	0.086(n)

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[a] First carcinoma observed at week 93 at 8000 ppm.

[b] First adenoma observed at week 72 at 0 ppm.

[c] First hyperplasia observed at week 54 at 8000 ppm.

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

(n) Negative change from control.

Note: Significance of trend denoted at Control. Significance of pair-wise comparison with control denoted at Dose level. If then $p < 0.05$.

Table 6: Historical Control Data for the Incidence of Thyroid C-Cell Tumors in Sprague-Dawley Strain Rats.

Tumor	Range (%) Males	Females
Carcinomas	0.0 - 5.2	0.0 - 2.9
Adenomas	1.8 - 10.6	3.3 - 10.0
Hyperplasia	4.3 - 20.0	4.3 - 16.9

iii. Liver (Table 7)

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. The reported historical control incidence of hepatocellular carcinomas ranged from 0 to 6.7%, and that for hepatocellular adenomas ranged from 1.4 to 18.3%. There were no dose-related increases in the incidences of other hepatocellular lesions.

Table 7: Glyphosate - Sprague-Dawley Male Rats, Hepatocellular Tumor Rates* and Cochran-Armitage Trend and Fisher's Exact Test Results (p values).

Tumors	Dose (ppm) 0	2000	8000	20,000
Carcinomas	3/44	2/45	1/49	2/48[a]
(%)	(7)	(4)	(2)	(4)
p =	0.324	0.489(n)	0.269(n)	0.458(n)
Adenomas	2/44	2/45	3/49	7/48[b]
(%)	(5)	(4)	(6)	(15)
p =	0.016*	0.683(n)	0.551	0.101
Adenoma/carcinoma	5/44	4/45	4/49	9/48
(%)	(11)	(9)	(8)	(19)
p =	0.073	0.486(n)	0.431(n)	0.245
Hyperplasia only	0/44	0/45	1/49[c]	0/48
(%)	(0)	(0)	(2)	(0)
p =	0.462	1.000	0.527	1.000

[a] First carcinoma observed at week 85 at 20,000 ppm.

[b] First adenoma observed at week 88 at 20,000 ppm.

[c] First hyperplasia observed at week 89 at 8000 ppm.

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

Note: Significance of trend denoted at Control. Significance of pair-wise comparison with control denoted at Dose level. If then $p < 0.05$.

Committee's interpretation: Despite the slight dose-related increase in hepatocellular adenomas in males, this increase was not significant in the pair-wise comparison with controls and was within the historical control range. Furthermore, there was no progression from adenoma to carcinoma and incidences of hyperplasia were not compound-related. Therefore, the slightly increased occurrence of hepatocellular adenomas in males is not considered compound-related.

c. Nonneoplastic lesions

There were no compound-related nonneoplastic lesions.

d. Adequacy of Dosing for Assessment of Carcinogenic Potential

The HDT was 20,000 ppm which is the limit dose for carcinogenicity testing in rats. However, it appears that animals could have tolerated higher doses.

3. **Hogan, G. K. (1983). A chronic feeding study of glyphosate in mice. Unpublished report prepared by Bio/Dynamics Inc., dated July 21, 1983. Report No. 77-2061. EPA Acc. Nos. 251007 - 251009, and 251014.**

a. Experimental Design

Groups of 50 male and 50 female CD-1 mice were administered glyphosate in the diet at concentrations of 1000, 5000, or 30,000 ppm for 18 months.

b. Discussion of Tumor Data

Glyphosate produced an equivocal carcinogenic response in males characterized by an incidence of renal tubular neoplasms of 1/49, 0/49, 1/50, and 3/50 in the control, low-, mid-, and high-dose groups, respectively. No kidney tumors were found in females. Historical control data from 16 studies terminated between 1978 and 1982 provided by the testing laboratory indicated that the incidence of this type of tumor was found in 2/19 control groups (1/54 and 2/60, or a total of 3/1286).

The Toxicology Branch Ad Hoc Oncogenicity Peer Review Committee, in their meeting of February 11, 1985, tentatively classified glyphosate as a "Class C" carcinogen (report dated March 4, 1985). The kidney slides were reexamined by a consulting pathologist, and data were submitted indicating that an additional kidney tumor had been found in control males (the incidence in the control group was originally reported as 0/49 before the reexamination of the slides).

The Agency then requested that additional kidney sections from the mouse study be prepared and examined. The resultant microslides were examined by a number of pathologists. These examinations revealed no additional tumors, but confirmed the presence of the tumors identified in the original study report. The tumor in the control kidney was not present in any of the additional sections.

Because of the equivocal nature of the findings, the Toxicology Branch Ad Hoc Oncogenicity Peer Review Committee asked the expert assistance of the FIFRA Scientific Advisory Panel (SAP) in determining the proper Weight-of-the-Evidence classification of the study. After reviewing all the available evidence, the SAP, in their meeting of February 11-12, 1986, proposed that glyphosate be classified as "Class D," or having "inadequate animal evidence of oncogenicity." The principal reason for this assessment by SAP was their determination that, after adjusting for the greater survival in the high-dose mice compared to concurrent controls, no statistically significant pairwise differences existed, although the trend was significant. The SAP further noted that, although comparison of these findings to historical control incidences yielded a statistically significant result, this finding did not override the lack of pairwise significance of comparisons to concurrent controls.

The SAP determined that the carcinogenic potential of glyphosate could not be determined from existing data and proposed that rat and/or mouse studies be repeated in order to clarify these equivocal findings.

Committee's interpretation: In their meeting of June 26, 1991, the Health Effects Carcinogenicity Peer Review Committee concluded that despite the fact that the incidence of renal tubular neoplasm in the high dose males exceeded that of historical controls, the biological significance of the findings was questionable because of: a) lack of significance in pairwise comparison with concurrent controls, b) there was no concurrent increase in non-neoplastic renal tubular lesions in male mice (e.g. tubular necrosis/regeneration, hyperplasia, hypertrophy ..etc), c) the examination of multiple sections of kidneys from all groups resulted in no additional neoplasms; this fact is particularly important since not only were the original sections closely scrutinized by more than one pathologist, but additional sections as well, and d) increased incidence in high dose group was very small compared to control considering the very high concentration which produced highly significant reduction in body weight gain in males. Furthermore, the increased incidence of chronic interstitial nephritis in males is not relevant to the tubular neoplasms. There was actually a decrease in renal tubular epithelial changes (basophilia and hyperplasia) in males, and although there was a dose-related increase in these changes in female mice, no tubular neoplasms were observed in females.

c. Nonneoplastic lesions:

Other nonneoplastic changes noted in high-dose male mice included centrilobular hypertrophy and necrosis of hepatocytes, chronic interstitial nephritis, and proximal tubule epithelial cell basophilia and hypertrophy in the kidneys of females. The no-observable-effect level (NOEL) for nonneoplastic chronic effects was the mid-dose level, 5000 ppm.

d. Adequacy of Dosing for Assessment of Carcinogenic Potential

Glyphosate was tested in this study at levels higher than the limit dose. Body weight gain in males of the high dose was 13, 17 and 27% less than the controls at 3, 12 and 24 months respectively. The decrease in body weight gains was statistically significant ($p < 0.01$). This effect was less obvious in females. The doses tested were considered adequate for the carcinogenic potential assessment of glyphosate.

E. Additional Toxicology Data on Glyphosate

1. Metabolism

When Sprague-Dawley rats were given a single oral dose of C-14 glyphosate, 30 to 36 percent of orally administered glyphosate was absorbed.

Data showed that less than 0.27 percent of the dose was expired as CO_2 within 24 hours. Glyphosate, per se, was the highest radiolabeled material found in the urine and feces. The minimum level of glyphosate extracted from urine and feces was 97.5 percent. Amino methyl phosphonic acid (AMPA) was found in the excreta of animals at levels of 0.2 to 0.3 percent and 0.2 to 0.4 percent in urine and feces, respectively. No detectable AMPA metabolite was found in intravenously dosed rats and high dose, orally dosed rats. There were no other metabolites of glyphosate found.

Based on analysis of radioactivity in urine and feces and using the "sigma-minus" plotting method, males and females had alpha half-lives of 2.11 and 7.52 hours and 5.00 to 6.44 hours, respectively. The beta half-lives of males and females in these groups ranged from 69.0 to 181 hours for males and 79.9 to 337 hours for females.

Less than 1 percent of the absorbed dose remains in tissues and organs, primarily bone. Repeated dosing with glyphosate

does not significantly change the metabolism, distribution, or excretion of glyphosate.

N-Nitrosoglyphosate (NNG)

The Agency has determined that carcinogenicity testing of nitroso contaminants will normally be required only in those cases in which the level of nitroso compounds exceeds 1.0 ppm [see "Pesticide Contaminated with N-nitroso Compounds, proposed policy 45 FR 42854 (June 25, 1980)"]. The levels of NNG in technical glyphosate have been examined by HED. The overall NNG content in individual samples of technical glyphosate analyzed at production plants is shown below:

[redacted]

The overall data show that 92.6 percent of the individual glyphosate samples analyzed contain less than 1.0 ppm (1000 ppb) of NNG. TB concluded that the NNG content of glyphosate technical is not toxicologically significant.

2. Mutagenicity

Glyphosate has been tested in several mutagenicity assays and found to be negative in each of the three categories recommended for evaluating genotoxic potential. The acceptable studies include the following: Salmonella assay, both with and without S-9, up to toxicity or 5000 ug/plate, in vivo cytogenetic assay in rat bone marrow up to 1000 mg/kg, mammalian gene HGPRT mutation assay in CHO cells in vitro both with and without S-9 up to toxic levels (10 mg/mL) and rec assay with B. subtilis up to 2000 ug/disk.

Unacceptable studies which were also negative included DNA repair in rat hepatocytes between 0.0000135 and 0.125 mg/ml, and a dominant lethal assay in mice up to 2000 mg/kg.

3. Developmental and Reproductive Toxicity

In rats, doses up to 3500 mg/kg/day showed no evidence of malformations. Evidence of developmental toxicity in the form of unossified sternebrae and decreased fetal body weight was noted in fetuses from the high dose (3500 mg/kg/day). This dose was also toxic to dams as evidenced by weight gain

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deficits, altered physical appearance, and mortality during treatment. The developmental and maternal toxic NOEL for this study was 1000 mg/kg/day.

In rabbits, doses up to 350 mg/kg/day showed no evidence of malformations. The highest dose tested was toxic to does as evidenced by altered physical appearance and mortality. No treatment-related developmental effects were noted. The NOEL for maternal toxicity is 175 mg/kg/day and the NOEL for developmental toxicity is 350 mg/kg/day.

In a three-generation reproduction study in the rat, the only toxicologically significant finding was focal renal tubular dilation in the kidneys of male pups from the F_{3b} generation of high-dose dams (30 mg/kg/day). The NOEL for this effect was 10 mg/kg/day. No effects on fertility, reproductive, or other study parameters were noted.

4. Structure - Activity Relationships

Currently there are no structurally related pesticides registered by the Agency which resemble glyphosate. A nonregistered pesticide, sulfosate, has been reviewed for carcinogenic potential in mice and rats and reported to be negative.

5. Acute, Subchronic and Chronic Feeding/ Oncogenicity Data

Glyphosate is not considered to be toxic to mammals (rat oral LD_{50} of 4320 mg/kg (both sexes), and a dermal LD_{50} greater than 7940 mg/kg in rabbits).

A 1-year chronic feeding study in dogs at 6/sex/dose was conducted using doses of 0, 20, 100, and 500 mg/kg/day, administered by capsule. The NOEL for the study was 500 mg/kg/day (HDT).

F. Weight of the Evidence Considerations

The Committee considered the following findings to be of significance regarding the weight-of-the-evidence determination of the carcinogenic potential of glyphosate.

1. Glyphosate was associated with increased incidences of pancreatic islet cell adenomas in male Sprague Dawley rats at all treatment levels in comparison to the concurrent control group (Table 1). Although the low- (18%), mid- (10%) and high-dose group (15%) incidences exceeded the 1.8 to 8.5% range of historical controls from Monsanto's EHL data base, the pancreatic islet cell adenomas were not considered

compound-related for the following reasons: a) there was no statistically significant positive dose-related trend in the occurrence of these tumors or in the incidence of hyperplasia in males over the wide range of dosing (2000 to 20000 ppm), and b) there was no progression to carcinoma. Tertiary evidence from the open literature cited by the registrant showed a range of 0 to 17% for pancreatic islet cell adenomas in Sprague-Dawley male rats for unadjusted data. The incidence of pancreatic islet cell tumors for the two rat studies does not show a dose-related increase in adenomas or adenoma/carcinoma combined and is within the range of open literature control data for male Sprague-Dawley rats (0 to 17%) for unadjusted data.

No increased incidence of these tumors was observed in female rats in comparision to concurrent controls.

2. C-cell adenomas were slightly increased in male and female mid- and high-dose groups in the rat (Tables 4 and 5). Although C-cell adenomas slightly exceeded the historical control range for both sexes, there was no statistically significant trend or pairwise comparison with controls in males. In females, the incidence of C-cell adenomas was not statistically significant in the pairwise comparison with controls but had a statistically significant positive dose-related trend. However, there was no progression to carcinoma in a dose-related manner, and no significant dose-related increase in severity of grade or incidence of hyperplasia in either sex. Therefore, the C-cell adenomas in males and females are not considered compound-related.

3. There was a slight dose-related increase in hepatocellular adenomas in male rats (Table 7), but the incidence was within the range of historical controls from Monsanto's EHL. This increase was not significant in the pair-wise comparison with controls and there was no progression from adenoma to carcinoma. The incidence of hyperplasia was not compound-related. There were no dose-related increases in the incidences of other hepatocellular lesions. Therefore, the increased incidence of hepatocellular adenomas in males was not considered compound-related.

4. Glyphosate produced an equivocal carcinogenic response in male mice characterized by an incidence of renal tubular neoplasms of 1/49, 0/49, 1/50, and 3/50 in the control, low-, mid-, and high-dose groups, respectively. No kidney tumors were found in females. Historical control data from 16 studies terminated between 1978 and 1982 provided by the testing laboratory indicated that the incidence of this type of tumor was found in 2/19 control groups (1/54 and 2/60, or a total of 3/1286).

Despite the fact that the incidence of renal tubular neoplasm in the high dose males exceeded that of historical controls, the biological significance of the findings was questionable because of: a) lack of significance in pairwise comparison with concurrent controls, b) there was no concurrent increase in non-neoplastic renal tubular lesions in male mice (e.g. tubular necrosis/regeneration, hyperplasia, hypertrophy ..etc), c) the examination of multiple sections of kidneys from all groups resulted in no additional neoplasms; this fact is particularly important since not only were the original sections closely scrutinized by more than one pathologist, but additional sections as well, and d) increased incidence in high dose group was very small compared to control considering the very high concentration which produced highly significant reduction in body weight gain in males. Furthermore, the increased incidence of chronic interstitial nephritis in males is not relevant to the tubular neoplasms. There was actually a decrease in renal tubular epithelial changes (basophilia and hyperplasia) in males, and although there was a dose-related increase in these changes in female mice, no tubular neoplasms were observed in females. Overall, the Peer Review Committee did not feel that this lesion was compound-related.

5. Glyphosate was tested up to the limit dose in the rat, and up to levels higher than the limit dose in mice.

6. There was no evidence of genotoxicity for glyphosate.

7. Currently there are no structurally related pesticides registered by the Agency which resemble glyphosate. A nonregistered pesticide, sulfosate, has been reviewed for carcinogenic potential in mice and rats and was reported to be negative.

G. Classification:

Considering criteria contained in EPA Guidelines (FR 51:33992-34003, 1986] for classifying a carcinogen, the Committee concluded that Glyphosate should be classified as a Group E (evidence of non-carcinogenicity for humans), based on lack of convincing carcinogenicity evidence in adequate studies in two animal species.

It should be emphasized, however, that designation of an agent in Group E is based on the available evidence at the time of evaluation and should not be interpreted as a definitive conclusion that the agent will not be a carcinogen under any circumstances.

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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

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: List 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.

ACKERMAN (EPL)

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, 12, 18, and 24 months for hematology and clinical analysis from 10/sex/ group animals. The CHECKED (X) parameters were examined.

a. Hematology

X	Hematocrit (HCT)*	X	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.

		Incidence (%)			
Organ/Lesion	Dose Sex (ppm):	0	2000	8000	20,000
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	~~116~~ 105	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)

Dose (mg/kg/day)	% Incidence Males 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

Sex/Lesion	Incidence (%) 0 ppm	2000 ppm	8000 ppm	20,000 ppm	Monsanto's EHL Historical Control 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

008897

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 incidance 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 008897

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 nonneoplastic 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