Glyphosate/Tox

Caswell file

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Reviewable Glyphosate

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

MEMORANDUM APR 3 1985

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Glyphosate; ~~EPA~~ Reg.#: 524-308; mouse oncogenicity study
Caswell #: 661A
Accession #: 251007-014

TO: Robert Taylor
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4/1/85

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Conclusions:

1. Glyphosate was oncogenic in male mice causing renal tubule adenomas, a rare tumor, in a dose-related manner. The study is acceptable as core-minimum data.

2. The information on the oncogenicity of glyphosate was evaluated by a Toxicology Branch AD Hoc Committee which concluded that this was an oncogenic response. A copy of the consensus report of the committee is attached.

Review:

1. A chronic feeding study of Glyphosate in mice (Biodynamics # BDN-77-420; Project No. 77-2061; 7/21/83).

Test Material:

Glyphosate technical, purity = 99.7%; fine, white clumped powder; lot number, NB178260813; NB178261017.

Groups of 50 male and 50 female randomized CD-1 mice, individually caged, were administered diets containing 0, 1000, 5000, and 30,000 ppm of test material for 24 months.

Parameters evaluated were toxic signs, mortality, body weight, food consumption, water consumption and hematology at 12, 18 and 24 months.

All animals were necropsied and selected organs were weighed. Tissues were stained in H and E and examined microscopically.

Statistical analyses of the data were performed.

Results:

No treatment-related toxic signs were noted during the study. Mortality was low during the first 18 months of the study as shown in the table below as reported:

Cumulative Mortality

DOSE	Males			Females		
(ppm)	12 Mo	18 Mo	24 Mo	12 Mo	18 Mo	24 Mo
0	9	12	30	3	15	30
1,000	9	19	34	4	16	38
5,000	7	14	33	1	8	23
30,000	4	11	24	5	13	27

Body weight was consistently decreased for males and to a lesser extent, females at the 30,000 ppm dosage level during the study at several sampling intervals. Changes in body weight at the low- and mid-dose group were variable and not dose-related.

Food consumption showed no compound-related or dose-related effect. Hematological values although significant in some instances did not show a consistent dose-related response.

Necropsy did not show treatement-related lesions. There was good correlation between gross and microscopic findings. The relative and absolute weight of the testes and ovaries were increased in high dose males and females, but no histopathological finding was present as a underlying factor.

Renal tubule adenomas occurred in male mice in the following manner as reported:

Dose (ppm)	0	1,000	5,000	30,000
Number examined	49	49	50	50
Renal tubule adenoma	0	0	1	3

They occurred in male mice 4029, 4032 and 4041 of the high-dose, and male 3023 of the mid-dose group and all were unilateral.

These tumors are rare, dose related and considered compound-related. These tumors were present at terminal kill.

Other neoplasmas were considered unrelated to treatment. No effect on latency was noted.

Significant trends and significant high-dose effects were observed in non-neoplastic lesions. The lesions considered treatment-related were hepatocyte hypertrophy, central lobular hepatocyte necrosis and chronic interstitial nephritis in high-dose males and proximal tubule epithelial basophilia and hypertrophy in high-dose females.

The table below shows the incidence of these lesions as reported:

	Control	Low	Mid	High	Linear Trend
Central lobular hepatocyte hypertrophy					
- males	9/49	5/50	3/50	17/50	b
- females	3/49	5/50	5/50	1/49	
Central lobular hepatocyte necrosis					
- males	0/49	2/50	2/50	10/50[a]	b
- females	2/49	1/50	4/49	2/49	
Chronic interstitial nephritis					
- males	5/49	2/49	7/50	12/50	b
- females	4/50	8/50	2/50	4/50	
Proximal tubule epithelial basophilia and hypertrophy					
- males	15/49	10/49	15/50	7/50	
- females	0/50	2/50	4/50	9/50[a]	a

[a]Statistically significant increase compared to control ($p \leq 0.01$) using the Chi-Square test (uncorrected for continuity).

[b]Statistically significant linear trend ($p \leq 0.01$) using the Cochran-Armitage test.

Conclusion:

Glyphosate was oncogenic in male mice producing a dose-related increased in renal tubule adenomas, a rare tumor. Dose-related non-neoplastic lesions occurred in both sexes. The NOEL for systemic effects was 5000 ppm. At the LEL, 30,000 ppm, there were increased hepatocyte hypertrophy, hepatocyte necrosis and interstitial nephritis in male mice and an increased incidence of proximal tubule epithelial basophilia and hypertrophy in female mice. Additionally, there were decreased body weights in male and female mice at 30,000 ppm which are considered compound-related.

Classification:

Core minimum data.