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

MEMORANDUM JUL 21 1982

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

TO: Robert Taylor (25)
Registration Division (TS-767)

THRU: Orville E. Paynter, Chief
Toxicology Branch
Hazard Evaluation Division (TS-769)

SUBJECT: "Addendum to Pathology Report For A Three-Generation Reproduction Study in Rats With Glyphosate. R.D. #374; Special Report MSL-1724; July 6, 1982". EPA Registration No. 524-308, Action Code 401, Accession No. 247793 CASWELL#661A

Recommendations:

1) The NOEL for the glyphosate reproduction study is established at 10 mg/kg/day on the basis of histopathological findings of renal focal tubular dilation in high dose level F_{3b} male weanlings.

2) Classification of the reproduction study is upgraded from Supplementary Data to Core-Minimum.

Background:

During the review of "A Three-Generation Reproduction Study in Rats with Glyphosate (Final Report; Bio/dynamics Project No. 77-2063; March 31, 1981) it was found (memo of October 7, 1981 from W. Dykstra to R. Taylor) that a NOEL could not be established because the high incidence of focal tubular dilation in the kidneys of the male F_{3b} high-dose offspring was considered to be treatment-related, and the registrant was asked to histologically examine the kidneys of the low- and mid-dose male F_{3b} offspring. This addendum report is in response to that request.

A. Review:

Dose groups for the glyphosate reproduction study were 0, 3, 10 and 30 mg/kg/day.

Newly prepared sections of kidneys from control, low-, mid- and high-dose group male F_{3b} pups were examined microscopically.

Additionally, kidney sections from control male F_{3b} pups of the same rat strain from three other studies at Bio/dynamics, Inc., conducted concurrently with this glyphosate study were examined. The same pathologist that had examined the animals in the glyphosate study evaluated the kidneys sections from the four studies submitted in this addendum using a "blind" procedure and similar criteria for interpretation of the findings.

The incidence* of renal focal tubular dilation found in the additional slides examined from the glyphosate study was as follows:

		Control	3	10	30 mg/kg/day
Renal focal tubular dilation:	Unilateral	2/10	3/10	2/9	7/10
	Bilateral	0/10	1/10	1/9	1/10

The incidence of unilateral dilation ranged from 22.2% (2/9 in mid-dose) to 70% (7/10 in high-dose) for the treated groups; when data for unilateral and bilateral dilation were combined, the incidence ranged from 33.3% (3/9 in mid-dose) to 80% (8/10 in high-dose). (When the kidneys of F_{3b} weanlings were first examined there was no incidence of renal dilation in control pups [see data in Part B]).

*Mistakes were noted in Part 1 of the addendum report for tabular incidencies for both treated and control rats and in the text-stated maximum percentage incidence for unilateral dilation in control rats.

The incidence* of this renal finding in the three groups of control pups taken from concurrently-run studies was as follows:

		STUDY		
		A	B	C
Renal focal tubular dilation:	Unilateral	1/10	3/10	5/15
	Bilateral	0/10	1/10	1/15

These data show that the incidence of renal focal tubular dilation in historical control weanling male rats varies widely, ranging from 10 (1/10 for Study A) to 33.3% (5/15 for Study C) for unilateral dilation, and from 10 (1/10 for Study A) to 40% (6/15 for Study C) for combined unilateral and bilateral dilation. When data from these three studies are pooled, the overall historical incidence is 31.4% (11/35) for a combination of unilateral and bilateral dilation.

*Mistakes were noted in Part 1 of the addendum report for tabular incidencies for both treated and control rats and in the text-stated maximum percentage incidence for unilateral dilation in control rats.

B. Discussion and comparison with data from the reproduction final report (March 31, 1981, Accession No. 245909; Bio/dynamics Project No. 77-2063).

Histopathological findings for the kidneys of F_{3b} weanlings in the final report of this study were as follows:

Kidney:

	Group I (Control)		Group IV (30 mg/kg/day)	
	M	F	M	F
No. examined	10	10	10	10
No. not remarkable	10	10	3	5
Focal tubular dilation, unilateral			6	1
Interstitial mononuclear cell infiltrate, unilateral			1	
Focal tubular nephrosis, unilateral			2	2
Focal tubular dilation, bilateral			1	2
Total, focal tubular dilation (unilateral & bilateral)			7	3

These data show that there was no incidence of renal focal tubular dilation in the concurrent control pups upon first examination. When additional sections of the same kidneys were made, the incidence (addendum report) was only 20% (2/10), yet data from control F_{3b} weanlings from other studies run at Bio/dynamics concurrently with this reproduction study show that the incidence (unilateral + bilateral) in a single study can reach 40% (Study C), while the incidence in pooled data (Studies A, B & C) was 31.4%. Adding the incidence for males in the glyphosate study control group (second examination, 2/10) to that of male historical controls (11/35) gives an overall incidence in untreated male weanlings of 28.8% (13/45).

Consideration of all these data show that although the incidence of this finding in the low- and mid-level glyphosate-treated weanlings is comparable to that in untreated weanlings, the incidence is increased in the high-level treated pups.

C. Conclusion:

The NOEL for the glyphosate reproduction study is established at 10 mg/kg/day on the basis of renal focal tubular dilation in F_{3b} male weanlings in the high level (30 mg/kg/day), since there were no other significant differences considered to be biologically meaningful between control and treated groups in the reproduction study (memo of October 7, 1981 from W. Dykstra to R. Taylor).

D. Classification:

The reproduction study is upgraded from Supplementary Data to Core-Minimum.

7/20/82

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