004609

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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Evaluation of IBT No. 8560-08924; 2-Year Chronic Feeding Study in Rats with N-Nitroso-Glyphosate.
CASWELL # 604AAB
Ref. CASWELL # 604I
and 661A

TO: Sherada Hobgood
RSERB
Registration Division (TS-767)

FROM: D. Stephen Saunders Jr., Ph.D. DSS 6/25/85
Section V, Toxicology Branch
Hazard Evaluation Division (TS-769)

THRU: Laurence D. Chitlik, DABT 6/25/85
Head, Section V
Toxicology Branch
Hazard Evaluation Division (TS-769)
and
Theodore M. Farber, Ph.D.
Chief, Toxicology Branch
Hazard Evaluation Division (TS-769)

Attached is the evaluation of IBT study no. 8560-08924, a two-year chronic feeding study in rats. The raw data validation report (prepared by Dynamac Corp. under contract no. 68-01-6561, accepted by EPA on 6/12/85) found the study to be Supplementary due to a lack of supporting records for clinical observations and organ weight measurements, and over- or underformulation of test dose solutions. After evaluation of this study for scientific content, the study was classified as Core-Invalid data due to excessive mortality in the control rats, apparently due to an error in the calculation of the control saline solutions.

16

004609

Data Evaluation Record

Chemical: N-nitroso-glyphosate (sodium salt), CP 76100; 19.8% a.i.

Study Identification: "Two-Year Oral Toxicity Study with CP 76100 in Albino Rats".

Accession No.:	247745-52
EPA Reg. No.:	524-308
Study No.:	8560-08924 (IBT)
Report date:	5/14/79
Submitted:	6/24/82
Sponsor:	Monsanto Agricultural Products Co. St. Louis, MO. 63166
Test facility:	Industrial Bio-Test Laboratories, Inc. Decatur, Illinois 62526
Study authors:	Leslie D. Morrow, et al.

Reviewed by: D. Stephen Saunders Jr., Ph.D.
Toxicologist, Section V
TOX/HED (TS-769)

Background

The study was conducted with the sodium salt of N-nitroso-glyphosate, which is a contaminant of the herbicide glyphosate. The Registrant apparently initiated this study because of concerns over the potential toxicity of the nitroso contaminant. Because this study was conducted at IBT, an audit of the raw data was performed. Based on the findings of that audit, the study was classified as Supplementary data due to deficiencies in supporting raw data for dose preparation, physical observations, and organ weight measurements.

Discussion/Conclusions

An appropriate control group was not used in this study. Because the test article was supplied as a sodium salt, the investigators attempted to treat control rats with an amount of sodium equivalent to that given high dose animals. An error in calculation resulted in control animals apparently receiving 30 mg/kg/day of NaCl, as reported on page 10 of the report narrative. This amount was reported by the investigators to be 4 times the amount of sodium that high dose rats received. The amount of salt given controls appears to have had a toxic effect. Survival was lowest in male and female control groups compared to treated animals, as tabulated below:

	MALES Month			FEMALES Month		
Dose	12	18	24	12	18	24
0	46/60[a] (77%)	38/60 (63%)	10/60 (17%)	48/60 (80%)	39/60 (65%)	16/60 (27%)
3	56/60 (93%)	50/60 (83%)	26/60 (43%)	59/60 (98%)	54/60 (90%)	28/60 (47%)
10	57/60 (95%)	48/60 (80%)	18/60 (30%)	57/60 (95%)	52/60 (87%)	33/60 (55%)
30	54/60 (90%)	41/60 (68%)	17/60 (28%)	57/60 (95%)	46/60 (77%)	32/60 (53%)

[a]number alive/number on test, does not include interim sacrifices.

17

The control group also had the lowest average body weight gain, compared to test groups, as evidenced by the 24-month average weight gain (grams ± std. dev.):

Dose	Male	Female
0	402 ± 92	249 ± 72
3	441 ± 91	302 ± 89
10	465 ±119	326 ± 70*
30	457 ± 76	325 ± 84*

*$p < 0.05$

Therefore, it is not possible to assess the effect of the test article on treated animals. No effect of treatment on the incidence of neoplasms was apparent, however it cannot be determined whether the doses tested were sufficiently high to detect an oncogenic effect. Approximately 10% decreases in erythrocyte count, hemoglobin content and hematocrit were noted in high dose females at 18 and 24 months, however it is not clear whether this apparent effect was the result of changes in the control group or in the treated animals.

The study is therefore compromised due to the lack of an adequate control group, and is considered to be invalid.

Classification: Core-Invalid Inappropriate control group.

18