6-25-85

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

004609

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Evaluation of IBT No. 8580-08922; 2-Year Chronic Feeding Study in Dogs 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.
Section V, Toxicology Branch
Hazard Evaluation Division (TS-769)
DSS 6/25/85

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

Attached is the evaluation of IBT study no. 8580-08922, a two-year chronic feeding study in dogs. The raw data validation report (prepared by Dynamac Corp. under contract no. 68-01-6561, accepted by EPA on 6/5/85) found the study to be Supplementary due to a lack of supporting records for gross examinations at necropsy, ocular examinations, clinical observations, and dose preparation. After evaluation of this study for scientific content, the study was classified as Core-Supplementary data on the basis of the findings contained in the raw data validation report.

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Data Evaluation Record

Chemical: N-nitroso-glyphosate (sodium salt), CP 76100.

Study Identification: "Two-Year Chronic Oral Toxicity Study with CP 76100 in Dogs".

Accession No.:	247753
EPA Reg. No.:	524-308
Report No.:	8580-08922 (IBT)
Report date:	5/8/79
Submitted:	6/24/82
Sponsor:	Monsanto Agricultural Products Co. St. Louis, Missouri 63166
Test facility:	Industrial Bio-Test Laboratories, Inc. Decatur, Illinois 62526
Study Authors:	Donald H. Jenkins, et al.

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

Conclusions

LEL = 30 mg/kg/day Increased absolute and relative kidney weights.

NOEL = 10 mg/kg/day by gavage

Classification: Core-Supplementary Per validation report.

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 supporting raw data was performed as part of the Agency's validation process for IBT studies (Dynamac contract no. 68-01-6561, accepted by EPA 6/5/85). Based on the findings of that audit, the study was classified as Supplementary data due to deficiencies in the supporting raw data (see "Methods").

Materials and Methods

A. Materials: 1) Test material- N-nitroso-glyphosate, sodium salt; CP 76100; Lot # T-107; the % a.i. was not stated.

2) Doses tested- 0, 3, 10, and 30 mg/kg/day via gelatin capsule.

3) Test animal- Purebred beagle dogs, obtained from IBT breeding colony.

(con't)

B. Methods: The methods used and all supporting raw data were reviewed as part of the EPA validation process for IBT studies. The validation report found that raw data were lacking for gross observations at necropsy, ocular examinations, clinical observations, and for preparation of test doses. The validation report concluded that the study could only be considered as Supplementary data.

Other than the lack of supporting raw data, no deficiencies in the methods used were noted.

Results

A. Clinical Signs and Mortality- The only clinical observations reported were for a single male of the low dose group (3 mg/kg) who had a "minor respiratory infection" at week 16, and was treated successfully with an antibiotic. It was noted in the audit validation, however, that raw data supporting physical examinations were lacking.

No deaths were reported.

B. Body Weights and Food Consumption- No treatment-related effects on body weight gain or food consumption were noted.

C. Clinical Pathology: (1) Hematology- Apparently treatment-related decreases of about 10% in erythrocyte count, hemoglobin concentration, and hematocrit were noted in high dose male and female dogs at 24 months. Other parameters were unaffected.

(2) Serum Chemistries- No effect of treatment on BUN, SGOT, SGPT, or SAP was apparent. An apparent increase in serum glucose of about 10% was noted in high dose females that appeared to be treatment-related.

(3) Urinalysis- No effect of treatment on these parameters was apparent.

D. Ophthalmological Examinations- No effect of treatment on the incidence of eye lesions was apparent. However, it was noted in validation report for this study that raw data for these examinations was lacking.

E. Necropsy Data: (1) Organ Weights- Although occassional alterations in absolute organ weights were noted, these generally could be attributed to fluctuations in body weight. The only organ for which relative weights were altered was kidney. Absolute kidney weight, kidney/body and kidney/brain weight ratios were increased in high dose females by about 25%.

(2) Gross Observations- The report narrative stated that the only apparent treatment-related change was enlarged spleen, observed in high dose males. This lesion was noted in 1/4 control, 0/4 low and mid dose, and 2/4 high dose males. However, the absolute spleen weights of the affected animals were not different from control. Therefore the significance of this apparent finding is unclear.

The validation report of the raw data audit questioned the adequacy of gross examinations because no gross observations were recorded for 3/8 control and 8/24 treated dogs.

(3) Histopathology- No effects of treatment on organ histology were noted. Common findings without apparent relation to dose included "few degenerate glomeruli" and focal or diffuse congestion of the spleen. No effects in the kidney were reported that correlated with the apparent increase in absolute and relative weights that was noted in high dose females.

Discussion

The only apparent treatment-related effect was an increase in absolute and relative kidney weights in high dose females. This finding, however, was not supported by a corresponding effect on gross or microscopic observations, or on BUN, an index of kidney function. An increase in blood glucose in high dose females could indicate altered kidney function, however. Therefore, the apparent increase in kidney weight is of uncertain toxicological significance.

LEL = 30 mg/kg/day Increased absolute and relative kidney weights, increased blood glucose in females.

NOEL = 10 mg/kg/day

Classification: Core-Supplementary Per raw data audit validation report: raw data missing for preparation of test doses, clinical observations, gross observations at necropsy, and ocular examinations.

RIN 1712-95

GLYPHOSATE TOXICOLOGY REVIEW

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____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Evaluation of IBT No. 8580-09117, BTL 76-82; Delayed Neurotoxicity Study in Hens with Glyphosate.
CASWELL # 661A

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

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

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

The attached IBT study no. 8580-09117, a delayed neurotoxicity study in hens with glyphosate, was evaluated for scientific content, and was CORE classified as Invalid data. This classification is based on the results of the raw data audit which found a lack of supporting records for dose preparation, clinical observations, and histopathological examinations in control animals, which were apparently common to two other studies.

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Data Evaluation Record

Chemical: Glyphosate Technical, CP 67573.

Study Identification: "Neurotoxicity Study with Roundup in Chickens"

Accession No.:	229184
MRID No.:	00054404
EPA Reg. No.:	524-EX-29
Study No.:	8580-09117, BTL-76-82 (IBT)
Report date:	12/17/76
Submitted:	Unknown
Sponsor:	Monsanto Agricultural Products Co. St. Louis, MO. 63166
Test facility:	Industrial Bio-Test Laboratories, Inc. Decatur, Illinois 62526
Study authors:	Fletcher, D. and Arceo, R.J.

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

Conclusions

No evidence of neurotoxicity. Invalid study due to missing raw data (per validation report), use of animals with disease (see "Discussion").

Classification: Core-Invalid Deficiencies as noted.

Background

This DER is a scientific evaluation of an IBT study that was declared valid after an audit of the raw data supporting this study. The validation report (dated 8/3/78) noted an absence of raw data for dose preparation, body weight measurements, and histopathology in controls, which were common to two other studies. In spite of these deficiencies, the validation report considered the study to be valid.

Materials and Methods

A. Materials: (1) Test Material- Technical glyphosate (CP 67573), lot QH-68, 94% a.i.

(2) Doses Tested- 1.25 g/kg two times/day days 1-3 and days 21-23, total cumulative dose of 15.0 g/kg over the course of the study. Positive control birds received 500 mg/kg of triorthocresylphosphate (TOCP), however the protocol did not state on what days positive control was administered, or whether it was done concurrently with this study.

(3) Test Animal- Strain and source of hens not stated, 10/group.

(con't)

B. Methods: A photocopy of the submitted methods is appended. Since the study was conducted at IBT, an audit of the raw data supporting this study was performed, and the following deficiencies were noted in the validation report (dated 8/3/78):

(1) No records of dose preparation or administration were available.

(2) No records of body weight measurements were available.

(3) No records of pathological observations were available for untreated or positive control birds. The control groups were evidently shared with other studies, however it was not stated whether these birds were treated concurrently with birds administered the test article.

Results

A. Body Weights- Data for this parameter were submitted in the study report as individual animal values on days 0, 21, and 42 for untreated control and test birds. The validation report narrative noted an absence of raw data for body weight determinations.

The study report indicated that over days 0-21, 9/10 treated birds lost body weight, and average weight gain in these birds was -104.0 ± 113 grams. Weight gain in controls was 77.5 ± 89.5 grams, and 9/10 birds gained weight over this period. Over days 21-42, average weight gain in treated birds was 95.0 ± 85.2 grams, and 8/10 birds gained. Weight gain in controls over days 21-42 averaged 11.5 ± 37.3 grams, and 6/10 birds gained weight over this period.

B. Clinical Signs and Mortality- The validation report noted that "No new toxicity grading data [for daily observations] were presented although data for the untreated control were available". No data for clinical signs were submitted with the study report, however the report narrative stated that "test and control birds appeared normal throughout the 42-day test period....No mortalities occurred in the test or control groups".

C. Necropsy- The validation report did not discuss the raw data for gross observations at necropsy. Data for gross observations were not submitted with the study report, however the report narrative stated that "gross pathologic examination of all animals at the time of sacrifice revealed no abnormal tissue alterations".

Histological examinations were confined to "representative specimens of brain, spinal cord, and sciatic nerve of the untreated control, positive control, and test groups". Data were submitted in the study report as individual animal findings for 10 untreated control, 4 positive control, and 10 treated birds. The raw data validation report noted an absence of raw data for histopathological examinations in untreated and positive control animals, and stated that they were common to two other studies (J9116 and J9120). It was not clear from the submitted methods or the validation report whether the control animals were treated concurrently with the test animals.

The submitted data demonstrated axonal degeneration and demyelination of the spinal cord and sciatic nerve in positive control (TOCP) birds only. Perivascular lymphoid infiltration was noted in the brain, spinal cord, and sciatic

nerve, and interstitial lymphoid infiltration of the sciatic nerve were noted in all test animals without relationship to treatment with the test article. The report narrative stated that the lymphoid infiltrates were due to "lymphomatosis (Marek's Disease), a naturally occurring viral disease of chickens". The 1982 Pesticide Assessment Guidelines state that "Healthy animals shall be used...". The presence (in control and treated birds) of a disease affecting the nervous system, the target organ in the present study, complicates the interpretation of the study and is considered to be a major deficiency.

Discussion

The test article did not appear to induce a delayed neurotoxicity syndrome in hens. The raw data validation noted an absence of supporting documentation for dose preparation and administration, body weight measurements, and histopathological examinations.

Classification: Core-Invalid Deficiencies as noted above and in "Methods".

RIN 1712-95

GLYPHOSATE TOXICOLOGY REVIEW

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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.

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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.

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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.

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