

Glyphosate / Tox

CASWELL FILE

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



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MEMORANDUM:

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: EPA Reg. #: 524-308; Glyphosate; miscellaneous data;
one-year dog study
Record No. 162078
Caswell No. 661A
Accession No. 260021
Project No. 954

TO: Robert Taylor
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2/28/86
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3/11/86

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3/12/86

Requested Action:

Review of submitted one-year dog study with glyphosate.

Background:

A two-year oral dog study (No. 651-00565) done at IBT was evaluated and declared invalid by the Canadian Government.

The present one-year dog study is a replacement of the previous invalid two-year dog study.

Recommendation:

The absolute and relative pituitary weights of the mid- and high-dose male dogs are suggestive of a possible compound-related effect. The registrant is requested to further address the pituitary findings and the relationship to treatment.

Review:

1. Twelve month study of glyphosate administered by gelatin capsule to Beagle dogs. (Monsanto Company Environmental Health Laboratory; Project No. ML-83-137; Study No. 830116; 8/22/85.)

Test Material:

Glyphosate technical; Lot No. NBP 2472136; purity 96.13%; white granular solid.

Randomized groups of six male and six female beagle dogs were fed, by gelatin capsule, dosages of 0, 20, 100, and 500 mg/kg/day of test material daily for one year.

Criteria evaluated included toxic signs, mortality, body weight, food consumption, ophthalmologic evaluation, hematology, (RBC, WBC, Hct, Hgb, MCV, MCH, MCHC) clinical chemistry (albumin, SAP, BUN, CaTT, Cl⁻, Chol, creatinine, direct bilirubin, gamma-GT, glucose, phosphorus, potassium, SGPT/ALT, SGOT/AST, total bilirubin and total protein), urinalysis, (pH, protein, glucose, ketone, blood, bilirubin, urobilinogen) organ weights (adrenals, brain, heart, kidneys, liver, ovaries, testes, pituitary, thyroid/parathyroid), and histopathology of selected tissues and all gross lesions.

Statistical analyses of the data were performed.

Results:

All animals survived the duration of the study.

Toxic signs were observed more frequently in glyphosate treated dogs than controls. They consisted of redness of ears and skin in dog 1M003 of the low-dose males, dog 2F004 of the mid-dose females, and dog 3F004 of the high-dose females. Increased incidences of abnormal stool were observed more frequently in dog 1F005 of the low-dose females and dog 3F006 of the high-dose females. These findings were not considered biologically significant since they occurred in a few dogs and were not dose-related.

Ophthalmologic findings were unaffected by treatment.

Body weight and food consumption were comparable between control and exposed dogs.

Hematological values showed occasional increased or decreased values in treated animals as compared to controls. These values occurred as increased RBC and hemoglobin values at six months in low-dose females and increased values in MCHC in low- and mid-dose female dogs at three and twelve months.

However, the findings were within the range of control values and were not considered compound-related.

At three months, decreased sodium and potassium levels were noted in high-dose females and mid- and high-dose males. Decreased phosphorus levels occurred in low-dose females at three months and high-dose females at three and twelve-months.

These differences were within the range of control values. Other clinical chemistry results during the study were not dose-related and were within the range of control values.

Terminal body weights were comparable among control and exposed dogs.

Absolute brain weights of mid-dose males were significantly decreased. This was considered incidental to treatment. Decreased pituitary weights (absolute and relative) were observed in mid- and high-dose male dogs. Although there were no underlying histopathological changes in that organ, the individual values of the mid- and high-dose dogs were generally not within the range of control values.

Individual pituitary weights are presented below:

| <u>Dogs</u> | <u>Pituitary in males</u> | | | |
|-------------|---------------------------|--------------|--------------|--------------|
| | <u>Control</u> | <u>Low</u> | <u>Mid</u> | <u>High</u> |
| 1) | 0.088 | 0.079 | 0.066 | 0.064 |
| 2) | 0.096 | 0.069 | 0.050 | 0.070 |
| 3) | 0.076 | 0.090 | 0.061 | 0.055 |
| 4) | 0.080 | 0.073 | 0.054 | 0.062 |
| 5) | 0.083 | 0.089 | 0.071 | 0.074 |
| 6) | <u>0.079</u> | <u>0.077</u> | <u>0.067</u> | <u>0.080</u> |
| Mean | 0.084 | 0.080 | 0.062 | 0.068 |
| S.E. | 0.003 | 0.003 | 0.003 | 0.004 |

Relative pituitary weight are shown below:

Percent Relative to Terminal Body Weight

Pituitary in Males

| <u>Dogs</u> | <u>Control</u> | <u>Low</u> | <u>Mid</u> | <u>High</u> |
|-------------|----------------|----------------|----------------|----------------|
| 1) | 0.00073 | 0.00057 | 0.00061 | 0.00059 |
| 2) | 0.00106 | 0.00056 | 0.00047 | 0.00064 |
| 3) | 0.00069 | 0.00066 | 0.00053 | 0.00061 |
| 4) | 0.00065 | 0.00063 | 0.00054 | 0.00061 |
| 5) | 0.00090 | 0.00099 | 0.00068 | 0.00069 |
| 6) | <u>0.00068</u> | <u>0.00066</u> | <u>0.00059</u> | <u>0.00060</u> |
| Mean | 0.00079 | 0.00066 | 0.00057 | 0.00062 |

Therefore the decreased pituitary weights of the mid- and high-dose males are suggestive of a possible compound-related effect.

There were no histopathological findings considered treatment-related.

The incidence and grade of microscopic lesions were comparable between control and exposed dogs.

Conclusion:

The absolute and relative pituitary weights of the mid- and high-dose male dogs are suggestive of a possible compound-related effect. Other studies with glyphosate do not show compound-related effects in the pituitary. The tentative NOEL is 20 mg/kg/day (low-dose) for this study. The registrant is requested to further address the pituitary findings and the relationship to treatment.

Classification: Guideline (tentative).