UNITED STATES ENVIRONMENTAL

Tox Rev 266 ✓ OK

DATE: August 7, 1978

SUBJECT: Review of Monsanto Chemical Co. validation of Industrial Bio-Test Lavoratories Report No. E-567; BTL 71-35 Mutagenic Study submitted in support of Reg. No. 524-308. EPA Acc. No. 234-134 (Roundup).

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TO: Mr. Robert Taylor, PM #25

An examination of the avialiable Roundup Petition file 5F-1536 and the package submitted to EPA for review of the Roundup data validation indicate that no previous review for a "Mutagenic Study in Mice" has been made by Toxicology Branch for the Roundup product. Therefore a review of available data is included in the present report.

Registration No.

524-308

Monsanto
802 N-Lindburgh Blvd.
St. Louis, Missouri 63166

Formulation (active ingredients tested)

N-phosphonomethyl-glycine (Roundup)
, or metabolite;

aminomethylphosphonic acid

Conclusions

1. The Monsanto validation's conclusion that IBT test No. E-567 "reflects the supporting data reviewed", excepting some minor corrections is accurate, with one major reservation; no raw data to substantiate IBT's claim for inclusion of positive controls in the test was provided to the validator

2. This study (IBT no. E-567, dominant lethal mutagenic study in mice) is designated SUPPLEMENTARY DATA

NOTE:
a. No positive control data was provided to the Monsanto validator for review. (IBT presented + control summaries in their final report that employed 300 mg/kg of a + mutagen- but no raw data).

b. This study should have included a much higher maximally tolerated high dose, and intermediate dose levels, to make the test meaningful. (The test actually employed dose levels of 5 or 10 mg/kg, only).

Review of Data

The study was designed to evaluate Roundup's potential to induce a dominant lethal mutation in male mice. Positive results may include:

1). inability of an affected germ cell to fertilize an egg.

2). having fertilized, failure to develop beyond the blastocyst stage (implantation).

Treated males (single I.P. dose) mice are mated with untreated females. Each group of 12 male mice, were singly placed in a cage with 3 untreated virgin females immediately after dosing. After 1 week, females removed and replaced by another group of 3 females. This procedure repeated for 6 weeks.(maturation of male germ cells). Females sacrificed 1 week after removal from breeding cage. Nos. of implantation sites, resorption sites and embryos were recorded. (Female pregnant if compona lutea present in ovaries).

| Group | Dose levels (mg/kg) | No. Treated Male Mice |
|---|---|---|
| untreated controls | | 12 |
| + Controls (ethylmethane sulfonate | 300 | 12 |

NOTE: validator was not provided raw data for + controls

| | | |
|---|---|---|
| Treatment I (Roundup) | 5 | 12 |
| Treatment II (Roundup) | 10 | 12 |

Mutagenic induces

1). mating index - $\frac{\text{no pregnant females}}{\text{no. females mated}} \times 100$

2). pre implantation losses - $\frac{\text{no. compona lutea} - \text{no. implatation sites}}{\text{no. corpota lutea}} \times 100$

3). early resorptions/ total implantiations - $\frac{\text{no. early resorption sites}}{\text{no. implantation sites}} \times 100$

4). pre implantation losses - $\frac{\text{embryo test group/female}}{\text{embyro control group/female}} \times 100$

Study data and data summaries are useful on a limited basis, and are not commented on in the present report because the validator was not provided the following raw data for his review:

1). No positive control data provided to validator.

2). No raw data provided to validator to establish a maximum tolerated dose.

3). IBT referred to "previous experience and historical data", but did not document or reference any of this material.

4). No evidence was provided to validator to confirm that treated animals received intended doses.

5). Statistical analyses of experimental results were not conducted by IBT, nor were they attempted by the validator; precumeably because the positive control experiment was not conducted concurrently with the test treatment experiment.

NOTE:

1). at least 3 (instead of 2) treatment on dose levels, should have been tested.

2). Draft Guidelines for Registering Pesticides in the U.S. (3/31/78) State for mertagenicity testing: "All assays must be seen with concurrent positive and negative controls".

Classification - SUPPLEMENTAL DATA

B 8/28/78