Glyphosate/Tox

(29)

DRAFT

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DATA EVALUATION RECORD

GLYPHOSATE

Absorption and Elimination Studies in Monkeys

STUDY IDENTIFICATION: Maibach, H.I. (a) Elimination of ^{14}C-glyphosate in Rhesus monkeys following a single parenteral dose. (b) Percutaneous absorption of ^{14}C-glyphosate in ROUNDUP formulation in Rhesus monkeys following a single topical dose. (Unpublished study No. 81-349 prepared by H.I. Maibach, University of California, San Francisco, CA. for Monsanto Company, St. Louis, MO.; dated April 1, 1983. Accession No. 252142.)

APPROVED BY:

I. Cecil Felkner, Ph.D.
Program Manager
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1. CHEMICAL: N-(phosphono-^{14}C-methyl)glycine, ^{14}C-glyphosate, ROUNDUP.

2. TEST MATERIAL: ^{14}C-glyphosate was mixed with isopropylamine and unlabeled isopropylamine salt of glyphosate and diluted in water to produce a parenteral dosing solution containing 4 mg/ml glyphosate or 2 µCi/ml (specific activity 84.6 microcurie/mmole). For dermal application, 0.74 mg of ^{14}C-glyphosate was diluted with ROUNDUP formulation containing 357 mg unlabeled glyphosate at a final concentration of 8.9 mg/25 µl or 1 µCi/25 µl (specific activity 19.4 µCi/mmole).

3. STUDY/ACTION TYPE: Absorption and elimination studies in monkeys.

4. STUDY IDENTIFICATION: Maibach, H.I. (a) Elimination of ^{14}C-glyphosate in Rhesus monkeys following a single parenteral dose. (b) Percutaneous absorption of ^{14}C-glyphosate in ROUNDUP formulation in Rhesus monkeys following a single topical dose. (Unpublished study No. 81-349 prepared by H.I. Maibach, University of California, San Francisco, CA. for Monsanto Company, St. Louis MO.; dated April 1, 1983. Accession No. 252142.)

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7. CONCLUSIONS:

A. Following intramuscular injection of ^{14}C-glyphosate into Rhesus monkeys, elimination of radiolabel was mainly via the urine. Elimination of radiolabel was rapid and biphasic, with half-lives of 6.9 and 35.1 hours.

B. The data on dermal absorption and elimination of ^{14}C-glyphosate in ROUNDUP formulation were inadequate for evaluation.

8. RECOMMENDATIONS:

Not applicable.

9. BACKGROUND:

Not applicable.

10. DISCUSSION OF INDIVIDUAL TESTS OR STUDIES:

Not applicable.

11. MATERIALS AND METHODS (PROTOCOLS):

The materials and methods used in each study are presented in Appendix A.

12. REPORTED RESULTS:

A. Following a single intramuscular injection of ^{14}C-glyphosate in monkeys, the average excretion of radiolabel in urine was 85.59, 88.78, and 89.86% of the administered dose after 1, 4, and 7 days. Elimination occurred biphasically, and the half-lives in these two phases were 6.9 and 35.1 hours, respectively (Figure 1). The distribution of the label remaining (approximately 10 percent) was not determined.

B. Following dermal application of the ROUNDUP formulation containing ^{14}C-glyphosate, the average excretion of radiolabel in urine was 0.4, 1.15, and 1.65% of the applied dose after 1, 4, and 7 days. The peak excretion was 8-36 hours after application, and the average elimination half-life was estimated to be 59 hours.

Washings obtained from the application site 24 hours after application contained an average of 14.2% of the applied radiolabel.

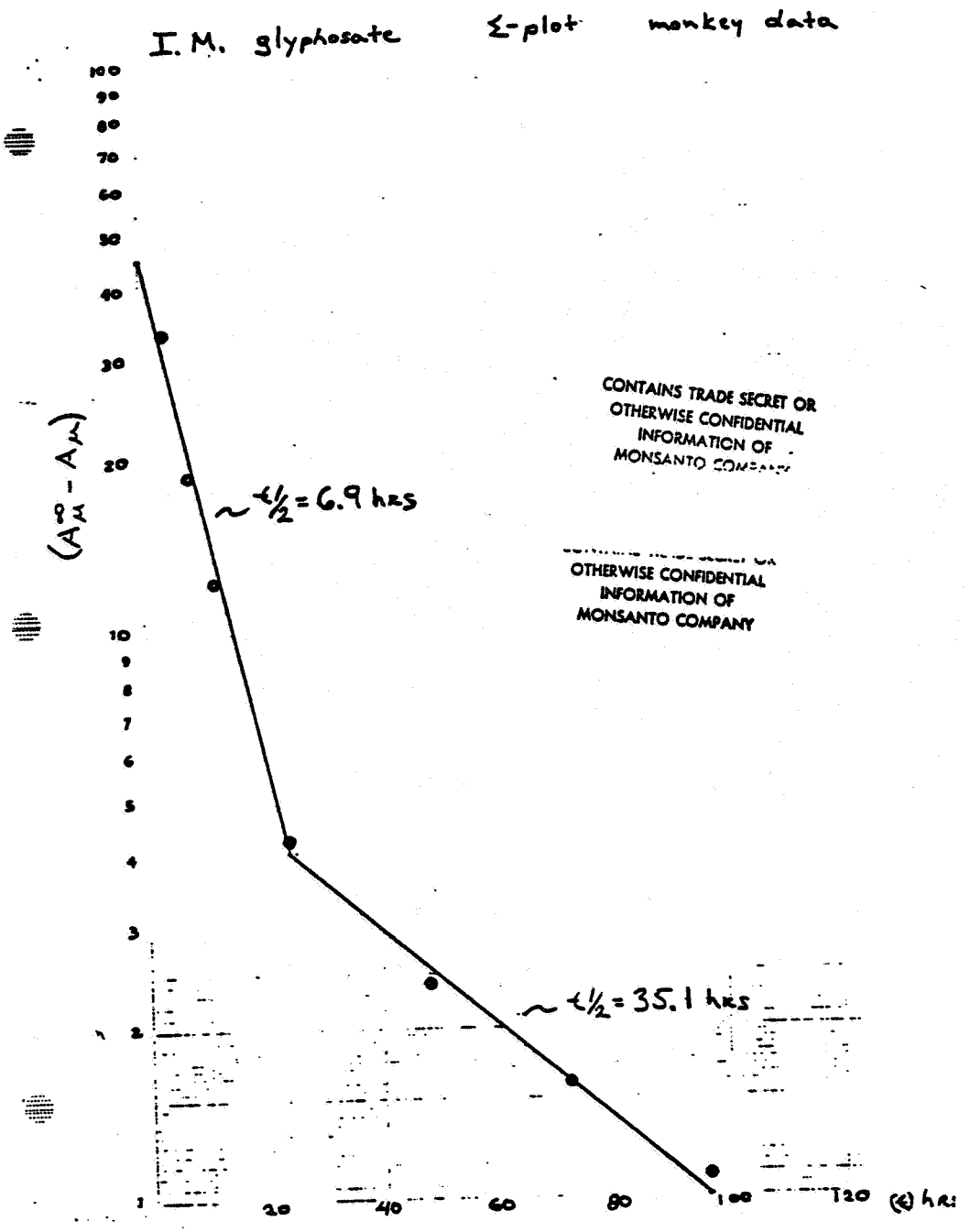

Figure 1. Role of ^{14}C elimination in urine of Rhesus Monkeys following intra muscular injection of ^{14}C glyphosate

13. STUDY AUTHOR'S CONCLUSIONS/QUALITY ASSURANCE MEASURES:

A. Following intramuscular injection of ^{14}C glyphosate into Rhesus monkeys, radiolabel elimination (89.9%) was biphasic via the urine. However, following dermal application of a ROUNDUP formulation containing ^{14}C-glyphosate only $\leq$ 2% of the dose was eliminated in the urine during a 7-day period and about 14% was recovered from the application site. The author suggested that binding of test material to or in the skin resulted in the low recovery, however, he was unable to provide a definitive explanation.

B. A quality assurance statement was not present for this report.

14. REVIEWER'S DISCUSSION AND INTERPRETATION OF STUDY RESULTS:

A. Data from the first study support the author's conclusion that the major route of glyphosate elimination, following an intramuscular injection, is biphasic via the urine.

B. The data from the second study (dermal absorption) are inadequate to evaluate the rate of dermal absorption and elimination of ^{14}C-glyphosate in ROUNDUP formulations, primarily because of low recovery. Although the author suggested that low recovery may have been due to binding of the test material to or in the skin, this statement is not supported by data. Moreover, it is not clear from the report whether the application site was covered so that loss of radioactivity was not due to mechanical factors such as physical rubbing. Other deficiencies include the absence of individual animal data (e.g., metabolism, age, weight, and animal husbandry) and data on the radiochemical purity.

15. COMPLETION OF ONE-LINER FORM FOR STUDY:

Not applicable.

16. CBI APPENDIX:

Appendix A - Materials and Methods.

Appendix A

Elimination of C-14 Labeled Glyphosate in Rhesus Monkeys Following a Single Parenteral Dose

Introduction:

This study was performed to determine the excretion parameters of the C-14 label on glyphosate into the urine from a single parenteral dose utilizing the rhesus monkey experimental animal model.

Procedures:

Four adult male rhesus monkeys each received a single one ml dose of C-14 labeled glyphosate (specific activity of 84.6 uCi/mM, molecular weight of 169.1) by intramuscular injection into the thigh. Scintillation counting determinations showed that a 1.0 ml dose contained 1.49 microcuries of C-14 labeled glyphosate. Urine samples were collected at 4, 8 and 12 hours the first day, then every 24 hours for seven days. A five ml aliquot of each urine sample was assayed in 14 ml PCS (Amersham Corp.) with a liquid scintillation spectrophotometer. A C-14 internal standard was added to triplicate vial of each sample to determine the extent of quenching.

A sigma-minus analysis was performed to determine the C-14 elimination half-life. The differences between the total % dose excreted over all the collection intervals and the total % dose excreted up to the end of each collection interval are equivalent to the amount of the compound not yet excreted. A semilog plot of these differences versus time yields a straight line with a slope proportional to the elimintation half-life. The rate constant, ke, is equivalent to the slope times 2.303 and the elimination half-life equal to 0.693 divided by ke (Fundamentals of Clinical Pharmacokinetics, first edition; Wagner, J., pg 77).

Results:

The enclosed table lists the dpm values, the total volume of urine collected and the calculated % of the applied dose excreted during each collection time interval for each subject. For example, under 0-4 hours for subject 1, 13522.4 and 13489.2 are the calculated dpm values, 245 is the volume of urine collected in milliliters, and 22.071 is the calculated % of the applied dose excreted. On the bottom of each column the average % dose excreted, the number of hours in the collection interval, and the rate of excretion in % dose per hour are reported. The urine contained an average total value of 89.9% (standard deviation of 12.5%) of the C-14 label on the glyphosate. Peak excretion occured between 0-4 hours.

Three graphs are enclosed. The first is a linear plot of the % dose excreted per hour versus time. The second is a semilog plot of the % dose excreted per hour versus time. The last is a sigma-minus plot. The C-14 label on the glyphosate had an average elimination half-life of 19.7 hours; however, two phases of excretion were noted. The first phase from 0-24 hours had an elimination half-life of 6.9 hours, whereas the second phase of excretion had an elimination half-life of 35.1 hours.

Percutaneous Absorption of Glyphosate in the Roundup Formulation

Introduction:

Carbon-14 labeled glyphosate in the Roundup formulation was applied to the abdomen of rhesus monkeys. Percutaneous absorption of the glypnosate was determined by measurement of the total amount of the C-14 label excreted into the urine.

Procedures:

Six male rhesus monkeys each recieved a single dose of 0.80 microcuries (as determined by scintillation counting) C-14 labeled glyphosate (specific activity of 19.4 uCi/mM, molecular weight of 169.1). Twenty-five microliters of the glyphosate preparation was applied over 7.9 square centimeters of abdomen lightly clipped of hair using an Oster clipper. After 24 hours, the site of application was washed two times with distilled water, two times with acetone, then two times with distilled water. The wash solvent was applied to a cotton ball attached to a pair of curved blunt forceps. The site of application was wiped with the solvent laden cotton ball. The amount of C-14 label from the wash was then determined by scintillation spectroscopy of the cotton ball. A C-14 internal standard was subsequently added to each sample to determine the extent of quenching.

Urine samples were collected at 4, 8 and 12 hours the first day, every 12 hours the second day, then every 24 hours for 7 days. A five ml aliquot of each urine sample was assayed in 14 ml PCS (Amersham Corp.) with a liquid scintillation spectrophotometer. A C-14 internal standard was added to a triplicate vial of each sample to determine the extent of quenching.

A sigma-minus analysis was performed to determine the C-14 elimination half-life. The differences between the total % dose excreted over all the collection intervals and the total % dose excreted up to the end of each collection interval are equivalent to the amount of the compound not yet excreted. A semilog plot of these values versus time yields a straight line with a slope proportional to the elimination half-life. The rate constant, ke, is equivalent to the slope times 2.303 and the elimination half-life equal to 0.693 divided by ke (Fundamentals of Clinical Pharmacokinetics, first edition; Wagner, J., pg 77).

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