ADME NTP Study S0095 Glyphosate

Species: male F344 rats.
Vehicles: intravenous, not indicated; oral gavage and dosed water, deionized distilled water; intraperitoneal, not indicated.

CASRN 1071-83-6
Radiolabeled with carbon-14; [^{14}C]glyphosate

Studies performed:

Study 1: Single 56 or 5.6 mg glyphosate/kg body weight oral gavage dose in male rats sacrificed at 96 hours postdose.

Study 2: Single 5.6 mg glyphosate/kg oral gavage dose in male rats with sacrifice 24 hours postdose. For comparison, a single 5.6 mg glyphosate/kg intraperitoneal dose was also given to two male rats with sacrifice 24 hours postdose.

Study 3: Single 5.6 mg glyphosate/kg oral gavage dose and repeat Roundup® exposure in dosed water given to male rats with excretion followed for 24 hours.

> Roundup®, at 0.5 or 10 ppm in drinking water, was given to the rats for 16 days. Rats were also treated with a single oral gavage dose of radiolabelled glyphosate either on day one prior to or on day 16 of Roundup® treatment.

Study 4: Single oral gavage (5.6 or 56 mg glyphosate/kg) or intravenous (5.6 mg glyphosate/kg dose in male rats with sacrifice at 72 hours (oral) or 48 hours (intravenous) postdose (toxicokinetic study). The number of rats per time point was three for the oral study and two for the intravenous study.

Glyphosate is the major component and active ingredient of Roundup®.

The toxicokinetic data was displayed in figures and is not shown here. Radioactivity in the blood after an oral dose of glyphosate reached peak concentrations within one to two hours with the higher dose peaking slightly later. The concentration of the radiolabel was approximately 3.5 times greater than that of the lower dose. A second oral absorption study at earlier and later time points showed peak blood level at 30 minutes. After an intravenous dose, the blood level of glyphosate was approximately 10% of the given dose at 10 minutes. The radioactive level rapidly decreased to less than 1% of the dose by 3 hours.

Table I ^{14}C Recovery in Tissues[a]

Time (hours)

Tissue	3[n = 2][c]	6[n = 2]	12[n = 2]	24[n = 3]	96[n = 3]
Small Intestine	7.72(8.95,6.49)[b]	10.20(6.31, 14.08)	4.12(5.71,2.53)	0.48 ± 0.51	0.03 ± 0.01
Large Intestine	1.21 (1.97, 0.45)	0.50(0.50,0.51)	0.45(0.65,0.26)	0.17 ± 0.17	0.01 ± 0
Liver	0.10(0.10,0.10)	0.07(0.04,0.09)	0.10(0.10,0.11)	0.14 ± 0.08	0.05 ± 0.05
Kidney	0.35(0.49,0.22)	0.48(0.18,0.78)	0.31(0.35,0.27)	0.10 ± 0.07	ND
Skin	0.70(0.38,1.02)	0.18(0,0.36)	0.21(0.12,0.29)	ND[d]	ND
Blood	0.27(0.27,0.28)	0.18(0.14,0.22)	0.31(0.24,0.38)	0.03 ± 0.06	ND
Tissue Total	12.00(12.23,11.76)	11.67(7.22,16.12)	5.54(7.20,3.87)	0.89 ± 0.84	0.10 ± 0.06

a These data are represented as percent of dose administered, either as the average or as the mean ± standard deviation. Dose is 5.6 mg/kg [^{14}C]Glyphosate.
b The numbers in parentheses are the results from individual rats.
c The numbers in brackets are the number of rats per time point.
d ND means that the values were not determined as the amount of radioactivity in the samples was below the level of accurate analytical measurement (<100 dpm).
e Male Fischer F344 rats were administered orally ^{14}C-glyphosate. They were killed at the indicated time points and the % of dose present in the tissues determined by combustion to $^{14}CO_2$.

Table 2. Recovery of Radioactivity in Male Fischer 344 Rats 24 Hours Following Oral Gavage, Intravenous, and Intraperitoneal Administration of 5.6 mg/kg [^{14}C]Glyphosate

Percent Dose Recovered in Excreta (24 hours)[a]
(Comparison of Administration Routes)

Route	Number of Animals	Urine	Feces
Oral gavage	2-7[b]	32.2 ± 16.4	58.7 ± 15.1
Intravenous	3	110.8 ± 11.4	3.0 ± 1.9
Intraperitoneal	2	107.9 (109.4, 106.5)	6.8 (4.7, 8.8)

[a] The results are shown as mean ± standard deviation except for when n = 2 where individual animal values are shown in parentheses.
[b] The data shown for the oral treatment are the pooled results from several experiments; therefore, the number of rats vary per data point (2-7).

Table 3. Recovery of Radioactivity in Male Fischer 344 Rats 24 Hours Following Intravenous Administration of 5.6 mg/kg [^{14}C]Glyphosate

Percent Dose Recovered in Excreta (24 hours)[a]

End of Collection Period (h)	Urine	Feces
3	83.8 ± 2.1	NG
6	NG[b]	0.3 ± 0.5
24	NG	2.2 ± 1.1

[a] The results are shown as mean ± standard deviation. N = 3. Values taken from text of report.
[b] NG = not given in numbers. Values were shown in a figure.

Table 4. Recovery of Radioactivity 96 Hours Following Single Oral Gavage Administration of 5.6 and 56 mg/kg [^{14}C]Glyphosate to Male Fischer 344 Rats

Distribution Summary (Percent Dose Recovered)

Dose (mg/kg)	Total Recovery	Urine	Feces	Tissues
5.6 mg/kg	94.0 ± 6.0	18.9 ± 1.9	74.7 ± 5.6	0.41 ± 0.22
56 mg/kg	92.8 ± 3.5	34.3 ± 11.8	58.1 ± 15.0	0.32 ± 0.12

[a] The results are shown as mean ± standard deviation. N = 3. Values taken from text of report. Rats received a single 5.6 or 56 mg/kg oral gavage dose

Table 5. Recovery of Radioactivity in Male Fischer 344 Rats Following Oral Administration of 5.6 mg/kg [^{14}C]Glyphosate as a Single Dose Alone or on Day 16 of 16 Days of 0.5 or 10 ppm Roundup® Drinking Water Exposure[a]

Percent Dose Recovered in Excreta

Treatment	Total Recovery	Urine	Feces
5.6 mg/kg single dose	103.3 ± 3.4	36.6 ± 27.5	66.0 ± 29.8
5.6 mg/kg single dose after 0.5 ppm for 16 days	102.1 ± 3.2	44.3 ± 8.7	57.4 ± 5.8
5.6 mg/kg single dose after 10 ppm for 16 days	92.5 ± 3.0	30.7 ± 15.2	61.7 ± 16.4

[a] The results are shown as mean ± standard deviation. N = 3. Values taken from text of report. Rats received a single 5.6 mg/kg [^{14}C]Glyphosate oral gavage dose or a single 5.6 mg/kg [^{14}C]Glyphosate oral gavage dose following 16 days of drinking water exposure (*ad libitum*) to 0.5 or 10 ppm Roundup®. Roundup® contained 30% glyphosate or 41% isopropylamine salts of glyphosate.

Table 6. Recovery of Radioactivity in Male Fischer 344 Rats Following 5.6 mg/kg [^{14}C]Glyphosate Single Oral Gavage Administration Prior to or After 16 Days of 0.5 ppm Roundup® Drinking Water Exposure

Distribution Summary (Percent Dose Recovered)[a]

Dose (mg/kg)	Total Recovery	Urine	Feces	Tissues
5.6 mg/kg dose prior to 0.5 ppm Roundup for 16 days	102.5 ± 3.4	44.3 ± 8.8	57.6 ± 5.7	Non-measurable
5.6 mg/kg dose after 0.5 ppm for 16 days	103.8 ± 3.4	36.3 ± 27.5	66.1 ± 29.8	0.48 ± 0.21

[a] The results are shown as mean ± standard deviation. N = 3. Values taken from text of report. Rats received a single 5.6 mg/kg [^{14}C]Glyphosate oral gavage dose prior to or Day 16 of 16 days of drinking water exposure (*ad libitum*) to 0.5 or 10 ppm Roundup®. Roundup® contained 30% glyphosate or 41% isopropylamine salts of glyphosate.