ADME NTP Study S0116 9-Aminoacridine hydrochloride

The contract laboratory used the abbreviation 9AA for the test article.
Sex/Species: adult male Fischer 344 rats and 2-3 year old cynomolgus monkeys.
Vehicles: intravenous, 20% ethanol or water; oral, water; dermal 100% ethanol.

CASRN 134-50-9

Radiolabeled with carbon-14 in the ring; 9-Aminoacridine-[Ring-UL-^{14}C] hydrochloride

Studies Performed:

Experiment A:

- Group I – Single 0.113 mg dermal administration to rats which were kept in a lighted room after dosing with covered dose site and sacrifice 72 hours (hr) postdose.

- Group II – Single 0.113 mg dermal administration to rats which were maintained in darkness up to 24 hours after dosing with covered dose site and sacrifice 72 hours postdose.

- Group III – Single 0.0226 mg dermal administration to rats which were kept in a lighted room after dosing with covered dose site and sacrifice 72 hours.

- Group IV – Single 0.0226 mg dermal administration to rats which were maintained in darkness up to 24 hours after dosing with covered dose site and sacrifice 72 hours.

- Group V – Single 0.802 mg/kg intravenous administration to rats with sacrifice 24 hours postdose (vehicle, 20% ethanol).

Experiment B:

- Group I – Single 1.48 mg/kg oral gavage administration to rats with sacrifice 24 hours postdose (low dose).

- Group II – Single 20.4 mg/kg oral gavage administration to rats with sacrifice 24 hours (medium dose).

- Group III – Single oral gavage administration to rats with intended sacrifice 24 hours postdose (high dose). However, the rats in this group died and the precise dose (radioactivity) was not determined. The protocol called for a high dose of 200 mg/kg.

Experiment C:

- Group I-VII – Single 0.746 mg/kg intravenous administration to rats with sacrifice at 5, 15, 30, 60, 120, or 240 minutes, as well as at 24 hours (3 rats per time point; vehicle, water).

Experiment D:

- Single 1.97 mg dermal administration to monkey with covered dose site, serial blood collection, and sacrifice 24 hours postdose (low dose; N=1).

- Single 26.5 mg dermal administration to monkey with covered dose site, serial blood collection, and sacrifice 24 hours postdose (high dose; N=1).

For the dermal administration groups in experiment A, more than 5% of the dose was found on one or more of the appliance caps in groups II, III, and IV at 72 hours allowing possible urine contamination.

The serial plasma and tissue data for experiment C were given in figures and are not shown here except for the 24-hour data (Table 3).

None of the blood or plasma samples collected from monkeys at 2, 4, 8, 12, and 24 hours postdose contained radioactivity in concentrations greater than 0.02 nCi/mL. Most of the radioactivity remained on the skin at the site of application: 95.6% of the low dose and 87.1% of the high dose.

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Table 1 (Experiment A)

Recovery of a Topically Administered Dose at the Site of Application[a]

Time after Dosing (hr)	Group I	Group II	Group III	Group IV
		(% of Dose)		
0	98.1 ± 2.5	-[b]	97.2 ± 2.7	-[b]
4	89.5 ± 0.4	93.9 ± 0.5	95.2 ± 3.0	97.3 ± 1.7
24	89.2 ± 4.0	80.7 ± 12.4[c,d]	86.2 ± 12.5[d]	99.8 ± 1.9[c]
72	87.0 ± 3.4	83.0 ± 3.8[c]	77.4 ± 17.6[c,d]	86.4 ± 6.4[c]

[a]Values represent % of dose on excised skin plus that rinsed from the covering caps.

[b]Rats in Group I sacrificed at 0 time serve as controls for Group II. Similarly, those in Group III sacrificed at 0 time serve as controls for Group IV.

[c]More than 5% of the dose was found on one or more caps in these groups.

[d]One value in each of these groups was low (below 75%).

Table 2 (Experiment A)

Urinary Excretion of Radioactivity Derived from [^{14}C] 9AA Administered Topically to Rats

Time after Dosing (hr)	Dose (mCi)	Rats maintained in Light (% of Dose)	Rats maintained in Dark (% of Dose)
4	0.00749	0.003 ± 0.001	0.005 ± 0.004
24	0.00749	0.022 ± 0.004	0.051 ± 0.040
72	0.00749	0.331 ± 0.296	0.278 ± 0.310
4	0.00150	0.004 ± 0.002	0.002 ± 0.002
24	0.00150	0.031 ± 0.005	0.056 ± 0.066
72	0.00150	1.26 ± 1.67	0.152 ± 0.132

Table 3 (Experiment A)

Distribution of Radioactivity at 2, 4 and 24 hr[a] in Rats Dosed Intravenously with [^{14}C] 9AA

Sample	2 Hr			4 Hr			24 Hr	
	Rat #1	Rat #2	Rat #3	Rat #4	Rat #5	Rat #6	Rats #7-9	(Experiment C)[a]
	(% of Dose)							
Urine	0.192	2.24	1.52	3.37	7.55	5.55	23.3 ± 4.9	(26.1 ± 0.8)
Feces	-[b]	0.012	0.059	0.025	0.017	0.074	44.4 ± 4.2	(60.5 ± 4.9)
Gut contents	11.9	33.8	12.4	18.1	21.8	50.1	11.8 ± 2.0	(7.46 ± 3.21)
Gut tissue	4.34	6.53	3.77	3.95	3.51	4.58	0.675 ± 0.195	(0.990 ± 0.332)
Liver	4.01	5.65	3.18	2.95	3.12	3.85	1.37 ± 0.05	(1.62 ± 0.05)
Kidneys	2.35	2.11	1.80	1.27	0.998	0.683	0.077 ± 0.015	(0.063 ± 0.008)
Lungs	0.326	0.285	0.253	0.219	0.197	0.130	0.027 ± 0.003	(0.025 ± 0.001)
Spleen	0.170	0.149	0.123	0.073	0.076	0.055	0.005 ± 0.001	(-[b])
Brain	0.120	0.183	0.117	0.084	0.081	0.084	0.002 ± 0.001	(-[b])
Muscle (1.1 g)	0.251	0.359	0.186	0.138	0.104	0.124	0.011 ± 0.003	(0.003 ± 0.001)
Fat (0.6 g)	0.019	0.020	0.010	0.009	0.008	0.008	0.001 ± 0.001	(0.001 ± 0.001)
Skin (ears)	0.024	0.046	0.018	0.018	0.022	0.029	0.004 ± 0.002	(0.004 ± 0.006)
Whole blood (5 ml)	0.189	0.195	0.127	0.169	0.128	0.162	0.075 ± 0.004	(0.068 ± 0.004)
Tail[c]	49.1	9.46	50.1	38.2	37.8	0.737	0.713 ± 0.033	(0.122 ± 0.111)
Total	73.0	61.0	73.7	68.5	75.4	66.2	82.4±2.3	(96.9 ± 3.9)

[a]Values in parentheses, from Experiment C, are placed here for comparison with values in the adjacent column.

[b]No sample collected.

[c]Due to the large and variable amounts in this organ, standard deviations were not calculated for any of the tissues taken at 2 or 4 hr after dosing.

Table 4 (Experiment B)

Distribution of Radioactivity in Rats 24 hr After Oral Dosing with [^{14}C] 9AA

	1.48 mg/kg (% of Dose)			20.4 mg/kg (% of Dose)		
Urine	20.0	±	1.9	21.0	±	4.3
Feces + gut contents	67.8	±	5.9	57.4	±	2.1
Stomach	0.043	±	0.021	0.030	±	0.034
Large intestine	0.417	±	0.155	1.30	±	0.53
Small intestine	0.114	±	0.028	0.442	±	0.365
Liver	1.36	±	0.03	1.19	±	0.22
Kidneys	0.053	±	0.002	0.088	±	0.038
Lungs	0.013	±	0.002	0.016	±	0.002
Spleen	0.004	±	0.000	0.006	±	0.002
Brain	<0.001			0.002	±	0.002
Muscle (2.5 g)	0.004	±	0.000	0.009	±	0.004
Fat (0.9 g)	0.001	±	0.001	0.003	±	0.001
Skin (ears)	0.002	±	0.000	0.002	±	0.000
Whole blood (5 ml)	0.073	±	0.006	0.079	±	0.021
Carcass	0.660	±	0.566	0.669	±	0.191
Total recovery	90.6	±	3.9	82.2	±	5.3

Table 5 (Experiment D)

Distribution of Radioactivity in Monkeys
24 Hr After Topical Dosing with [^{14}C] 9AA

	Low dose	High Dose
	(% of Dose)	
Urine	0.077	0.663
Feces	<0.001	<0.001
Liver	<0.001	0.017
Kidneys	<0.001	0.007
Lungs	0.001	0.007
Muscle (5.7 g)	0.003	<0.001
Fat (2 g)	<0.001	<0.001
Skin area	95.6	87.1
	(nCi/ml)	
Blood	<0.01	0.02
Plasma	<0.01	0.02
Bile	1.20	2.00