ADME NTP Study S0085 D&C Yellow No. 11

The contract laboratory abbreviation is DCY. The test article name is D&C Yellow No. 11 and the chemical is 2-(2-Quinolyl)-1,3-indandione.
Species: male F344 rats.
Vehicles: intravenous, ethanol:Emulphor:water (3:3:4, v/v); dosed feed, pulverized NIH-07 mouse and rat rations.

CASRN 8003-22-3
Radiolabeled with carbon-14 in the indane phenyl; 2-(2-Quinolyl)-1,3-indandione, [indane phenyl-UL-^{14}C]-

Studies performed:

Single 1 mg/kg intravenous administration to rats with sacrifice at 5, 15, 30 minutes and 1, 2, 4, 24, 48, and 72 hours postdose (Study A).

- Pharmacokinetic half-lives were estimated with modified form of the NONLIN (Metzler CM, Elfring GL, and McEwen AJ. A package of computer programs for pharmacokinetic modeling. Biometrics 30:562-563, 1974) and CSTRIP (Sedman AJ and Wagner TG. CSTRIP, a Fortran IV computer program for obtaining initial poly-exponential parameter estimates. J. Pharm. Sci. 65:1006-1010, 1976) programs. The data were fitted to three-compartment open models. Statistical weight were determined from the measured concentrations.

Repeat 11-day dosed feed exposure of 4.49, 37.2, 379, 4110, or 42200 mg/kg doses (as calculated from food consumption) to rats with sacrifice on day 12 (Study B).

- Animals were dosed with unlabled DCY in feed on study days 1-7, with [^{14}C]DCY and unlabeled DCY on study day 8, and again with unlabeled DCY on study days 9-11 and then sacrificed on study day 12.

Single 1 mg/kg intravenous dose biliary excretion study with sacrifice at 4 hours postdose (Study C).

Table I (Experiment A)

Disposition of Radioactivity in Rats Dosed Intravenously with [d^{4}Cl] DCY (0.932 mg/kg)

Sample	Time After Dosing: 5 Min		½ Min		30 Min		1 Hr		2 Hr		4 Hr		24 Hr		48 Hr		72 Hr	
	% of Dose	nCl/g or ml	% of Dose	nCl/g or ml	% of Dose	nCl/g or ml	% of Dose	nCl/g or ml	% of Dose	nCl/g or ml	% of Dose	nCl/g or ml	% of Dose[b]	nCl/g or ml[b]	% of Dose[b]	nCl/g or ml	% of Dose[b]	nCl/g or ml[b]
Urine	-[a]	-	-	-	-	-	-	-	-	-	-	-	16.0 ± 0.9[i]	-	16.7	-	16.9	-
Feces	-	-	-	-	-	-	-	-	-	-	-	-	81.1 ± 5.2[i]	-	97.5	-	98.1	-
Gut contents	5.58 ± 0.76[b]	-	13.5 ± 1.3	-	23.4 ± 2.5	-	40.7 ± 5.5	-	54.1 ± 5.6	-	62.8 ± 8.8	-	5.12	-	-	-	0.613	-
Gut tissue	3.71 ± 0.41	180 ± 13	6.61 ± 0.86	341 ± 34	10.8 ± 0.8	540 ± 13	13.4 ± 3.1	717 ± 147	16.8 ± 3.8	813 ± 172	5.93 ± 0.62	309 ± 44	0.348	17.4	-	-	0.112	5.26
Liver	18.1 ± 1.7	552 ± 75	17.9 ± 0.5	575 ± 28	14.8 ± 2.0	486 ± 62	9.16 ± 1.29	275 ± 45	8.26 ± 0.10	195 ± 9	4.57 ± 0.52	154 ± 08	2.49	88.2	-	-	1.48	48.8
Lungs	1.12 ± 0.08	275 ± 2100	0.837 ± 0.045	205 ± 4	0.563 ± 0.008	138 ± 18	0.312 ± 0.037	84.5 ± 4.9	0.291 ± 0.026	73.7 ± 2.9	0.241 ± 0.017	65.9 ± 9.1	0.187	43.8	-	-	0.0935	21.7
Kidneys	2.03 ± 0.13	331 ± 13	3.18 ± 0.14	337 ± 35	2.21 ± 0.13	360 ± 32	1.85 ± 0.32	312 ± 48	1.43 ± 0.08	225 ± 1	0.994 ± 0.156	174 ± 22	0.621	97.3	-	-	0.343	50.2
Fat[c]	0.869 ± 0.237	14.8 ± 4.3	1.99 ± 0.81	48.8 ± 10.5	5.56 ± 2.63	85.1 ± 45.8	5.48 ± 3.31	92.8 ± 43.5	4.08 ± 1.06	87.8 ± 18.1	1.55 ± 0.58	44.3 ± 09.8	0.239	3.75	-	-	0.120	2.01
Skin[d]	4.83 ± 0.18	35.4 ± 1.4	7.97 ± 1.83	59.3 ± 11.5	8.87 ± 2.02	64.4 ± 16.2	5.75 ± 00.98	42.0 ± 8.3	3.42 ± 0.10	25.4 ± 0.5	1.56 ± 0.16	11.3 ± 1.2	0.761	5.47	-	-	0.563	3.82
Muscle[e]	41.9 ± 2.5	98.0$_0$ ± 7.9	28.3 ± 1.5	83.4 ± 4.8	17.9 ± 2.3	42.8 ± 8.6	8.31 ± 00.79	18.4 ± 1.6	3.03 ± 0.40	7.16 ± 0.84	2.07 ± 0.88	3.03 ± 2.08	0.753	1.73	-	-	0.484	1.01
Plasma[f]	3.62 ± 0.14	84.5 ± 8.7	3.30 ± 0.96	73.9 ± 3.8	2.71 ± 0.93	64$_0$3 ± 9.9	2.32 ± 0.44	58.1 ± 11.4	1.60 ± 0.03	39.4 ± 000.3	1.38 ± 0.15	33.5 ± 00.4	0.599	13.6	-	-	0.236	5.15
Whole blood[g]	8.54 ± 0.35	65.2 ± 6.2	5.00 ± 0.20	65.8 ± 4.5	4.04 ± 8.34	53$_0$3 ± 5.8	3.15 ± 00088	41.5 ± 6.7	2.60 ± 0.09	34.2 ± 001.2	1.20 ± 0.13	26.2 ± 6.3	1.64	20.8	-	-	0.957	11.6
Tail	2.17 ± 0.43	33.7 ± 9.5	2.22 ± 1.82	33.7 ± 24.0	1.92 ± 1.60	26.9 ± 26.2	1.56 ± 01.53	20.6 ± 19.4	0.351 ± 0.220	5.39 ± 3.03	0.622 ± 0.580	7.54 ± 5.88	0.287	2.42	-	-	0.241	3.39
Total	86.9 ± 0$_0$3	-	65.4 ± 2.0	-	89.5 ± 0.3	-	82.7 ± 11.8	-	92.4 ± 2.5	-	83.5 ± 9.8	-	110	-	-	-	111	-

[a] Not applicable or not determined.

[b] The numbers are the means ± std. dev. for 3 rats, except as indicated.

[c] Considered to be 7% of body weight.

[d] Considered to be 16% of body weight.

[e] Considered to be 30% of body weight.

[f] Considered to be 5% of body weight (not included in calculation of total recovery).

[g] Considered to be 9% of body weight.

[h] Average of 2 rats, except as indicated.

[i] Average of 4 rats.

Table 2 (Experiment A)

Half-Life Values Derived for Elimination of Radioactivity from Plasma and Various Tissues of Rats Dosed Intravenously with [^{14}C] DCY (0.932 mg/kg)

	Elimination Phase		
Sample	Absorption	Alpha	Beta
		(min)	
Gut tissue	32	79	1368
Liver	9[a]	17	1205
Lungs	-[b]	14	2533
Kidneys	16[a]	41	2374
Fat	14	141	3260
Skin	6	52	3811
Muscle	-[b]	23	1910
Plasma	-[b]	49	1604
Whole blood	-[b]	19	2900

[a]Since there is no significant difference between the tissue concentrations of radioactivity at 5, 15, and 30 min after dosing, the existence of this phase is questionable.

[b]No absorption phase noted.

Table 3 (Experiment B)

Disposition of Radioactivity from [^{14}C] DCY in Rats Fed Unlabeled DCY in the Diet on Days 1-7 and 9-11 and [^{14}C] DCY in the Diet on Day 8

Sample	Dose: 42,200 mg/kg body weight		4,110 mg/kg body weight		379 mg/kg body weight		37.2 mg/kg body weight		4.49 mg/kg body weight	
	% of Dose	nCi/g or ml	% of Dose	nCi/g or ml	% of Dose	nCi/g or ml	% of Dose	nCi/g or ml	% of Dose	nCi/g or ml[h]
Urine + rinse	1.41 ± 0.33[a]	-[b]	4.98 ± 0.42	-	6.25 ± 1.21	-	6.04 ± 1.66	-	6.19 ± 0.98	-
Feces	65.1 ± 6.1	-	92.6 ± 3.7	-	91.3 ± 3.5	-	89.1 ± 3.5	-	93.9 ± 3.4	-
Gut contents	0.165 ± 0.110	-	0.248 ± 0.023	-	0.235 ± 0.103	-	0.239 ± 0.073	-	0.162 ± 0.007	-
Gut tissue	0.035 ± 0.005	2.00 ± 0.21	0.042 ± 0.017	2.56 ± 0.99	0.030 ± 0.003	1.93 ± 0.17	0.042 ± 0.007	2.79 ± 0.45	0.045 ± 0.008	0.963 ± 0.071
Liver	0.264 ± 0.025	6.55 ± 0.64	0.879 ± 0.078	25.3 ± 0.7	0.588 ± 0.074	20.1 ± 2.0	0.583 ± 0.043	20.2 ± 1.3	0.477 ± 0.029	5.23 ± 0.52
Lungs	0.002 ± 0.001	0.614 ± 0.143	0.006 ± 0.000	1.88 ± 0.05	0.009 ± 0.001	3.01 ± 0.10	0.011 ± 0.000	3.37 ± 0.16	0.007 ± 0.001	0.762 ± 0.042
Kidneys	0.029 ± 0.003	5.16 ± 0.52	0.097 ± 0.001	18.3 ± 1.1	0.094 ± 0.012	18.6 ± 0.2	0.109 ± 0.013	20.9 ± 1.8	0.089 ± 0.006	5.57 ± 0.42
Fat[c]	0.096 ± 0.026	1.88 ± 0.22	0.102 ± 0.006	2.07 ± 0.03	0.101 ± 0.010	2.10 ± 0.08	0.065 ± 0.067	1.29 ± 1.29	0.025 ± 0.005	0.163 ± 0.033
Skin[d]	0.056 ± 0.005	0.498 ± 0.111	0.115 ± 0.007	1.03 ± 0.05	0.113 ± 0.008	1.02 ± 0.03	0.151 ± 0.009	1.35 ± 0.06	0.143 ± 0.010	0.403 ± 0.032
Muscle[e]	0.641 ± 0.344	1.70 ± 0.62	0.469 ± 0.038	1.34 ± 0.08	0.544 ± 0.059	1.58 ± 0.11	0.438 ± 0.334	1.25 ± 0.91	0.064 ± 0.011	0.058 ± 0.012
Plasma[f]	0.014 ± 0.001	0.382 ± 0.054	0.051 ± 0.002	1.47 ± 0.10	0.058 ± 0.006	1.69 ± 0.06	0.091 ± 0.010	2.58 ± 0.19	0.086 ± 0.008	0.777 ± 0.075
Whole blood[g]	0.085 ± 0.013	1.31 ± 0.03	0.130 ± 0.029	2.06 ± 0.39	0.154 ± 0.020	2.48 ± 0.19	0.228 ± 0.007	3.63 ± 0.16	0.228 ± 0.019	1.14 ± 0.09
Total	68.1 ± 6.0	-	99.6 ± 3.8		99.5 ± 4.4	-	97.0 ± 4.8	-	101 ± 4	-

[a] The numbers are the means ± std. dev. for 3 rats.

[b] Not applicable or not determined.

[c] Considered to be 7% of body weight.

[d] Considered to be 16% of body weight.

[e] Considered to be 50% of body weight.

[f] Considered to be 5% of body weight (not included in calculation of total recovery)

[g] Considered to be 9% of body weight.

[h] These rats were dosed with less radioactivity than the others. To normalize the concentration values, they should be multiplied by a factor of 3.0.

Table 4 (Experiment C)

Biliary Excretion of Radioactivity by Rats Dosed Intravenously with [^{14}C] DCY (0.931 mg/kg)

Time After Dosing (hr)	Dosage Recovery[a]	
	% of Dose	nCi/ml
0.25	1.05 ± 0.28[a]	1600 ± 340
0.50	6.18 ± 0.13	8890 ± 940
0.75	6.08 ± 0.54	9920 ± 360
1.0 hr	6.32 ± 0.12	10100 ± 300
1.5 hr	11.9 ± 1.1	8750 ± 700
2.0 hr	8.57 ± 0.35	6310 ± 290
2.5 hr	5.54 ± 0.37	4090 ± 380
3.0 hr	3.96 ± 0.34	2840 ± 290
3.5 hr	2.71 ± 0.21	2010 ± 260
4.0 hr	2.08 ± 0.22	1500 ± 200
Total	54.4 ± 1.1	

[a]The numbers are the means ± std. dev. for 3 rats.