ADME NTP Study K10022 Hydroquinone Toxicokinetics

The contractor used the abbreviation HQ for the test article.
Sex/Species: male Harlan Sprague Dawley rats and B6C3F1/N mice.
Vehicle: intravenous, saline; oral, distilled water; dermal 95% ethanol.

CASRN 123-31-9

Radiolabeled with carbon-14 uniformly in the ring; Hydroquinone, [ring-^{14}C(U)]-

Studies Performed:

- Single 5 or 50 mg/kg oral gavage dose to male rats with blood sampling at 0.08, 0.17, 0.25, 0.33, 0.50, 1.0, 2.0, 4.0, and 8.0 hours postdose. (n=4 per group, Groups 30 and 29)

- Single 5 mg/kg intravenous dose to male rats with blood sampling at 0.08, 0.17, 0.25, 0.33, 0.50, 1, 2, 4, and 8 hours postdose. (n=4, Group 31)

- Single 5 mg/kg oral gavage dose to male mice with blood sampling at 0.08, 0.17, 0.25, 0.33, 0.50, 1.0, 2.0, 4.0, and 8.0 hours postdose. (n=4, Group 33)

- Single 5 mg/kg intravenous dose to male mice with blood sampling at 0.08, 0.17, 0.25, 0.33, 0.50, 1, 2, and 4 hours postdose. (n=4, Group 34)

- Single 2% (20 mg/kg) or 10% (100 mg/kg) dermal dose to male mice with covered dose site and blood sampling at 0.50, 1.00, 2.00, 4.00, 8.00, 24.0, 32.0 and 48.0 hours postdose. (n=3 per group, Groups 37 and 38)

Toxicokinetics:

Individual animal data is shown here in tables. Total radioactivity concentration and HQ (parent) concentration in plasma was converted from ng-eq/g or ng/g to ng-eq/mL or ng/mL using an assumed plasma density of 1.0 g/mL prior to toxicokinetic modeling in order to produce parameters with the more familiar volume basis.

Toxicokinetic parameters were calculated using Phoenix WinNonlin software (WinNonlin, Version 6.3, Pharsight Corporation, Cary, NC). Plasma concentration (ng HQ/g plasma and/or ng-eq/g plasma) versus time data were analyzed for each dose group first using noncompartmental analysis. However, this modeling did not adequately describe the data, so one-compartment and then two-compartment models were investigated.

Two-compartment models best fit the mean concentration versus time data for the groups. For intravenous data, Model 7 (intravenous bolus dosing) was used and whenever possible Model 11 (extravascular dosing) was used for gavage data. Some

gavage data sets did not contain an intitial rise in concentrations indicating an absorption phase and, in those cases, the data were analyzed using Model 7.

For the 5 mg/kg gavage group in rats, the parent (HQ) plasma values were below the limit of quantitation and were not modeled.

For the mouse total radioactivity concentrations versus time data, modeling the dermal studies was unsuccessful due to the persistence of radioactivity in plasma throughout the measured time course for both 2% and 10% doses. Two-compartment Model 7 was used for both gavage and intravenous groups.

For the 10% dermal dose in mice, the parent HQ plasma values were below the limit of quantitation. The parent (HQ) plasma concentration data versus time best fit for the gavage and intravenous dose groups was Model 7 (two-compartment) and for the 2% dermal dose, a one-compartment first order model (Model 3).

Note on Accessibility: Persons with disabilities or using assistive technology may find some documents are not fully accessible. For assistance, contact Central Data Management or use our contact form and identify the documents/pages for which access is required. We will assist you in accessing the content of the files. NIEHS has helpful information on accessibility.

Table 1
Glossary of Toxicokinetic Parameters

TK Parameter	WinNonlin Output	Units[a]	Definition
V1, V2	V1, V2	mL/kg	Volume of distribution in central (1) or peripheral (2) compartment
V1_F, V2_F	V1_F, V2_F	-	Apparent volume of distribution in central (1) or peripheral (2) compartment for extravascular models, where the fraction of the dose absorbed cannot be estimated, so volume is actually volume/F where F is the fraction of dose absorbed
Vss	Vss	mL/kg	Volume of distribution at steady state
K01	K01	1/h	Absorption rate constant, ka
K10	K10	1/h	Elimination rate constant from the central compartment
K12, K21	K12, K21	1/h	Distribution rate constant from first to second compartment (12) or second to first compartment (21), etc.
AUC	AUC	h*ng/mL	Area under the plasma concentration-time curve.
K01_Half-Life	K01_HL	h	Half-life of the absorption process to the central compartment
K10_Half-Life	K10_HL	h	Half-life for the elimination process from the central compartment
Alpha	Alpha	1/h	Hybrid rate constant of the alpha phase
Beta	Beta	1/h	Hybrid rate constant of the beta phase
Alpha_Half-life	Alpha_HL	h	Half-life for the alpha phase
Beta_Half-Life	Beta_HL	h	Half-life for the beta phase
A	A	ng/mL	Alpha phase zero time intercept
B	B	ng/mL	Beta phase zero time intercept
Cl1	CL	mL/h/kg	Clearance of central compartment
Cl1_F	CL_F	mL/h/kg	Apparent oral clearance of the central compartment, also Cl_F for gavage groups in non-compartmental model
Cl2	CLD2	mL/h/kg	Clearance of the secondary compartment
Cl2_F	CLD2_F	mL/h/kg	Apparent clearance of the secondary compartment
AUMC	AUMC	h*h*ng/mL	Area under the moment curve
MRT	MRT	h	Mean residence time
Tmax	Tmax	h	Time at which C_{max} occurs
Cmax	Cmax	ng/mL	Maximum observed plasma concentration
F	F	%	Fraction of dose absorbed (extravascular dosing) – expressed as %

Table 2

Concentration of HQ Equivalents (ng-eq/g) in Plasma Following Gavage Administration of [^{14}C]HQ (50 and 5 mg/kg) to Male HSD Rats – Groups 29 and 30

Group 29, 50 mg/kg

Time Point (h)	29_01	29_02	29_03	29_04	Average	SD
0.08	13938	8014	8441	7648	9510	2969
0.17	23967	13462	14281	15008	16680	4899
0.25	26613	17823	17506	16268	19553	4755
0.33	28791	19653	21279	18344	22017	4673
0.50	31100	21934	23891	21830	24689	4378
1.0	23238	20456	19424	19374	20623	1813
2.0	8199	11019	8737	5548	8376	2247
4.0	7044	5304	6930	5514	6198	916
8.0	1890	2093	1050	3013	2012	806

Group 30, 5 mg/kg

Time Point (h)	30_01	30_02	30_03	30_04	Average	SD
0.08	1963	1664	1934	1841	1851	135
0.17	2962	2937	3751	2383	3008	562
0.25	3572	3672	3842	2517	3401	600
0.33	3882	3970	4067	2917	3709	534
0.50	3903	4080	3833	3302	3780	335
1	2396	2472	2313	2339	2380	71
2	948	840	1010	830	907	87
4	584	336	361	322	401	123
8	253	300	271	151	244	65

Table 3

Concentration of HQ Equivalents (ng-eq/g) in Plasma Following Intravenous Administration of [^{14}C]HQ (5 mg/kg) to Male HSD Rats – Group 31

Time Point (h)	31_01	31_02	31_03	31_04	Average	SD
0.08	8300	9099	8474	8563	8609	344
0.17	7890	8834	8600	8884	8552	458
0.25	7254	8365	8636	8210	8116	602
0.33	6420	7500	7686	7591	7299	591
0.50	4832	5444	5678	5723	5419	410
1	1765	1923	2086	2097	1968	157
2	491	599	666	661	604	81
4	155	221	199	202	194	28
8	108	137	127	131	126	12

Table 4

Estimated Toxicokinetic Parameters for Total Radioactivity from [^{14}C]HQ Administered by Gavage to Male Rats – Groups 29 and 30

2 Compartment Model 11, HQ ng-eq/mL data

Parameter	Units	Group 29 Estimate	Group 29 StdError	Group 29 CV%	Group 30 Estimate	Group 30 StdError	Group 30 CV%
A	ng-eq/mL	762598	263941125	34611	8965	959	11
Alpha	1/h	2.45	24.46	1000	1.51	0.09	5.84
Alpha_Half-life	h	0.283	2.835	1000	0.459	0.027	5.85
AUC	h*ng-eq/mL	69521	4010	6	9081	251	3
B	ng-eq/mL	13228	4756	36	590	44	7
Beta	1/h	0.230	0.052	22.7	0.111	0.011	9.79
Beta_Half-life	h	3.01	0.68	22.5	6.27	0.61	9.80
Cl1_F	mL/h/kg	719	42	6	551	15	3
Cl2_F	mL/h/kg	1085	4951	456	526	17	3
Cmax	ng-eq/mL	23632	1854	8	3799	46	1
K01	1/h	2.59	25.09	969	4.37	0.28	6.31
K01_Half-life	h	0.268	2.593	968	0.159	0.010	6.30
K10	1/h	0.778	7.478	961	0.709	0.043	6.00
K10_Half-life	h	0.891	8.571	962	0.978	0.059	6.00
K12	1/h	1.17	16.63	1420	0.677	0.043	6.36
K21	1/h	0.724	0.471	65.1	0.236	0.021	9.07
Tmax	h	0.485	0.052	10.8	0.391	0.008	2.01
V1_F	mL/kg	924	8889	962	777	35	5
V2_F	mL/kg	1499	6027	402	2230	203	9

Table 5

Estimated Toxicokinetic Parameters for Total Radioactivity from [^{14}C]HQ Administered Intravenously to Male Rats – Group 31

2 Compartment Model 7, HQ ng-eq/mL data

Parameter	Units	Estimate	StdError	CV%
A	ng-eq/mL	10851	693	6
Alpha	1/h	1.603	0.213	13.3
Alpha_Half-life	h	0.432	0.058	13.3
AUC	h*ng-eq/mL	11211	22269	199
AUMC	h*h*ng-eq/mL	113934	1242506	1090
B	ng-eq/mL	180	300	167
Beta	1/h	0.040	0.261	644
Beta_Half-life	h	17.1	110.5	645
Cl1	mL/h/kg	446	887	199
Cl2	mL/h/kg	269	861	320
Cmax	ng-eq/mL	11030	730	7
K10	1/h	0.984	1.975	201
K10_Half-life	h	0.704	1.413	201
K12	1/h	0.594	1.891	319
K21	1/h	0.066	0.299	453
MRT	h	10.2	90.7	892
V1	mL/kg	453	30	7
V2	mL/kg	4080	31464	771
Vss	mL/kg	4533	31473	694

Table 6

Concentration of HQ (ng/g) in Plasma Following Gavage (50 mg/kg) or Intravenous (5 mg/kg) Administration of [^{14}C]HQ to Male HSD Rats – Groups 29 and 31

Group 29, 50 mg/kg, Gavage

Time Point (h)	29_01	29_02	29_03	29_04	Average	SD	HQ as Percent of Total Radioactivity
0.083	447	96	22	98	166	191	1.74
0.16	188	47	25	43	76	75	0.45
0.25	103	36	17	26	46	39	0.23
0.33	45	22	21	26	28	11	0.13
0.5	24	17	17	21	20	4	0.08
1	6	10	5	10	8	3	0.04

Group 31, 5 mg/kg, IV

Time Point (h)	31_01	31_02	31_03	31_04	Average	SD	HQ as Percent of Total Radioactivity
0.083	1135	1377	1782	1428	1430	267	16.6
0.16	316	462	536	743	514	178	6
0.25	148	138	195	171	163	26	2
0.33	52	62	71	116	75	28	1
0.5	18	9	19	28	19	8	0.3
1	2	1	2	3	2	1	0.1

Table 7

Estimated Toxicokinetic Parameters for HQ Administered by Gavage (50 mg/kg) to Male Rats – Group 29

2 Compartment Model 7, HQ ng/mL data

Parameter	Units	Estimate	StdError	CV%
A	ng/mL	368	28	8
Alpha	1/h	12.6	1.1	8.7
Alpha_Half-life	h	0.055	0.005	8.71
AUC	h*ng/mL	54.7	1.6	3.0
AUMC	h*h*ng/mL	17.9	2.5	14.2
B	ng/mL	41.9	7.1	16.9
Beta	1/h	1.643	0.246	15.0
Beta_Half-life	h	0.422	0.063	15.0
Cl1	mL/h/kg	913863	27496	3
Cl2	mL/h/kg	486499	32208	7
Cmax	ng/mL	410	33	8
K10	1/h	7.485	0.545	7.28
K10_Half-life	h	0.093	0.007	7.28
K12	1/h	3.984	0.460	11.6
K21	1/h	2.763	0.440	15.9
MRT	h	0.326	0.041	12.4
V1	mL/kg	122098	9726	8
V2	mL/kg	176075	27771	16
Vss	mL/kg	298173	33551	11

Table 8

Estimated Toxicokinetic Parameters for HQ Administered Intravenously (5 mg/kg) to Male Rats – Group 31

2 Compartment Model 7, HQ ng/mL data

Parameter	Units	Estimate	StdError	CV%
A	ng/mL	4333	530	12
Alpha	1/h	13.77	0.83	6.04
Alpha_Half-life	h	0.050	0.003	6.06
AUC	h*ng/mL	340	26	8
AUMC	h*h*ng/mL	29.468	1.235	4.19
B	ng/mL	96	34	35
Beta	1/h	3.799	0.380	10.0
Beta_Half-life	h	0.182	0.018	9.99
Cl1	mL/h/kg	14714	1123	8
Cl2	mL/h/kg	590	115	19
Cmax	ng/mL	4429	549	12
K10	1/h	13.034	0.692	5.31
K10_Half-life	h	0.053	0.003	5.32
K12	1/h	0.523	0.122	23.3
K21	1/h	4.014	0.446	11.1
MRT	h	0.087	0.004	4.34
V1	mL/kg	1129	140	12
V2	mL/kg	147	19	13
Vss	mL/kg	1276	149	12

Table 9

Concentration of Radiolabeled HQ Equivalents (ng-eq/g) in Plasma Following Gavage Administration of [^{14}C]HQ (5 mg/kg) to Male B6C3F1/N Mice – Group 33

Time Point (h)	Mouse 1*	Mouse 2*	Mouse 3*	Average	SD
0.08	6362	4086	5345	5264	1140
0.17	3612	5409	5505	4842	1066
0.25	5788	3303	6133	5074	1544
0.33	3794	4519	4125	4146	363
0.50	3038	3122	3066	3075	43
1.0	1302	749	1647	1232	453
2.0	192	183	281	219	54
4.0	75	45	75	65	17
8.0	45	31	30	35	9

*Concentration determined from LSS of weighed aliquots of plasma.

Table 10

Concentration of HQ Equivalents (ng-eq/g) in Plasma Following Intravenous Administration of [^{14}C]HQ (5 mg/kg) to Male B6C3F1/N Mice – Group 34

Time Point (h)	Mouse 1*	Mouse 2*	Mouse 3*	Average	SD
0.08	7627	7448	9861	8312	1345
0.17	7265	7731	5904	6967	950
0.25	5222	5703	5880	5602	341
0.33	5707	6787	5189	5894	815
0.50	3797	2112	4159	3356	1093
1.0	626	1067	803	832	222
2.0	590	232	330	384	185
4.0	181	201	148	177	27

Concentration determined from LSS of weighed aliquots of plasma.

Table 11

Concentration of HQ Equivalents (ng-eq/g) in Plasma Following Dermal Administration of [^{14}C]HQ (2% and 10%) to Male B6C3F1/N Mice – Groups 37 and 38

Group 37 – 2% HQ*

Time Point (h)	Mouse 1	Mouse 2	Mouse 3	Average	SD
0.50	31	152	63	82	62
1.00	53	51	141	82	51
2.00	65	107	137	103	36
4.00	85	134	128	116	27
8.00	140	167	111	139	28
24.0	111	105	119	112	7
32.0	141	153	117	137	18
48.0	89	0	89	59	51

Group 38 -10% HQ*

Time Point (h)	Mouse 1	Mouse 2	Mouse 3	Average	SD
0.50	231	717	179	376	297
1.00	286	62	130	159	115
2.00	109	205	118	144	53
4.00	126	177	593	298	256
8.00	188	131	264	194	67
24.0	251	184	84	173	84
32.0	265	116	124	168	84
48.0	155	0	155	103	89

*Concentration determined from LSS of weighed aliquots of plasma.

Table 12

Estimated Toxicokinetic Parameters for Total Radioactivity from [^{14}C]HQ Administered by Gavage (5 mg/kg) to Male Mice - Group 33

2 Compartment Model 7 HQ ng-eq/mL data

Parameter	Units	Estimate	StdError	CV%
A	ng-eq/mL	6975	455	7
Alpha	1/h	1.88	0.10	5.56
Alpha_Half-life	h	0.368	0.020	5.57
AUC	h*ng-eq/mL	4477	220	5
AUMC	h*h*ng-eq/mL	8031	2735	34
B	ng-eq/mL	98.9	30.0	30.4
Beta	1/h	0.128	0.046	35.9
Beta_Half-life	h	5.43	1.95	35.9
Cl1	mL/h/kg	1117	55	5
Cl2	mL/h/kg	197	29	15
Cmax	ng-eq/mL	7074	461	7
K10	1/h	1.58	0.10	6.08
K10_Half-life	h	0.439	0.027	6.08
K12	1/h	0.279	0.038	13.5
K21	1/h	0.152	0.053	34.7
MRT	h	1.79	0.56	31.3
V1	mL/kg	707	46	7
V2	mL/kg	1296	569	44
Vss	mL/kg	2003	584	29

Table 13

Estimated Toxicokinetic Parameters for Total Radioactivity from [^{14}C]HQ Administered Intravenously (5 mg/kg) to Male Mice - Group 34

2 Compartment Model 7, HQ ng-eq/mL data

Parameter	Units	Estimate	StdError	CV%
A	ng-eq/mL	10356	926	9
Alpha	1/h	2.50	0.48	19.2
Alpha_Half-life	h	0.28	0.05	19.2
AUC	h*ng-eq/mL	7397	19210	260
AUMC	h*h*ng-eq/mL	43340	561483	1296
B	ng-eq/mL	254	535	211
Beta	1/h	0.078	0.604	7742
Beta_Half-life	h	8.89	68.91	7752
Cl1	mL/h/kg	676	1757	260
Cl2	mL/h/kg	474	1694	357
Cmax	ng-eq/mL	10609	1031	10
K10	1/h	1.43	3.78	264
K10_Half-life	h	0.483	1.274	264
K12	1/h	1.01	3.56	354
K21	1/h	0.136	0.714	526
MRT	h	5.86	60.72	1036
V1	mL/kg	471	46	10
V2	mL/kg	3489	30762	882
Vss	mL/kg	3960	30780	777

Table 14

Concentration of HQ (ng/g) in Plasma Following Gavage (5 mg/kg), Intravenous (5 mg/kg), or Dermal (2%) Administration of [^{14}C]HQ to Male B6C3F1/N Mice – Groups 33, 34, and 37

Group 33 (5 mg/kg Gavage)

Time Point (h)	Mouse 1	Mouse 2	Mouse 3	Average	SD
0.08	13	10	19	14	5
0.17	5	755[a]	15	258	430
0.25	3	3	12	6	5
0.33	5	6	4	5	1
0.50	3	4	1	3	2
1.0	1	1	3	1	1

Group 34 (5 mg/kg IV)

Time Point (h)	Mouse 1	Mouse 2	Mouse 3	Average	SD
0.08	1665	1057	2273	1665	608
0.17	345	224	631	400	209
0.25	116	204	98	140	57
0.33	97	136	42	92	47
0.50	49	10	93	51	42
1.0	7	3	2	4	3

Group 37 (2% Dermal)

Time Point (h)	Mouse 1	Mouse 2	Mouse 3	Average	SD
0.5	1.47	4.57	2.33	2.79	1.60
1	1.80	1.84	3.00	2.22	0.68
2	2.66	3.47	3.50	3.21	0.48
4	3.50	3.43	4.95	3.96	0.86
8	5.20	9.98	3.94	6.37	3.19
24	1.57	1.84	2.45	1.95	0.45
32	1.66	2.43	1.53	1.87	0.48
48	1.00	0.61	0.47	0.69	0.27

[a] This value is an outlier and was excluded from the WinNonlin modeling.

Table 15

Estimated Toxicokinetic Parameters for HQ Administered by Gavage (5 mg/kg, Group 33), Intravenously (5 mg/kg,Group 34), or Dermal (2%, Group 37) to Male Mice

Group 33, Gavage, 5 mg/kg, 2 Compartment Model 7, HQ ng/mL data

Parameter	Units	Estimate	StdError	CV%
A	ng/mL	19.9	2.6	13.1
Alpha	1/h	5.21	1.73	33.2
Alpha_Half-life	h	0.13	0.04	33.5
AUC	h*ng/mL	18.5	490.7	2653
AUMC	h*h*ng/mL	176	12212	6939
B	ng/mL	1.23	3.73	304
Beta	1/h	0.08	3.04	3638
Beta_Half-life	h	8.28	301.2	3635
Cl1	mL/h/kg	270390	7181708	2656
Cl2	mL/h/kg	890004	7064581	794
Cmax	ng/mL	21.2	2.0	9.3
K10	1/h	1.15	30.5	2663
K10_Half-life	h	0.61	16.1	2660
K12	1/h	3.77	29.7	787
K21	1/h	0.38	3.84	1008
MRT	h	9.52	408	4288
V1	mL/kg	236146	21962	9
V2	mL/kg	2337239	42065156	1800
Vss	mL/kg	2573386	42080767	1635

Group 34, Intravenous, 5 mg/kg, 2 Compartment Model 7, HQ ng/mL data

Parameter	Units	Estimate	StdError	CV%
A	ng/mL	8114	463	6
Alpha	1/h	20.3	1.0	4.8
Alpha_Half-life	h	0.03	0.00	4.84
AUC	h*ng/mL	469	11	2
AUMC	h*h*ng/mL	43.45	7.64	17.6
B	ng/mL	198	71	36
Beta	1/h	2.89	0.91	31.3
Beta_Half-life	h	0.24	0.07	31.3
Cl1	mL/h/kg	12794	301	2
Cl2	mL/h/kg	1533	162	11
Cmax	ng/mL	8312	519	6
K10	1/h	17.7	0.8	4.6
K10_Half-life	h	0.04	0.00	4.62
K12	1/h	2.12	0.24	11.1
K21	1/h	3.31	1.03	31.1
MRT	h	0.09	0.02	17.6
V1	mL/kg	722	45	6
V2	mL/kg	464	181	39
Vss	mL/kg	1186	212	18

Table 15 (continued)

Group 37, Dermal, 2%, 1 Compartment Model 3, HQ ng/mL data

Parameter	Units	Estimate	StdError	CV%
V_F	mL/kg	291923	88683	30
K01	1/h	0.39	0.23	59.32
K10	1/h	0.04	0.02	51.25
AUC	h*ng/mL	177	58	33
K01_Half-life	h	2	1	59
K10_Half-life	h	18	9	51
Cl1_F	mL/h/kg	11323	3706	33
Tmax	h	7	2	32
Cmax	ng/mL	5	1	16