ADME NTP Study S0819 o-Chloropyridine Toxicokinetics

The contractor used the abbreviation of 2-CP for the test article (synonym 2-chloropyridine).
Sex/Species: male F344 rats and B6C3F1 mice.
Vehicle: Alkamuls EL-620 (no more than 15 % of dose):water

CASRN 109-09-1

Radiolabeled with carbon-14 in the 2 and 6 position of the ring; 2-Chloropyridine, [Ring-2,6-^{14}C]

Studies Performed:

- Single 10.0 mg/kg gavage dose to rats with sampling at 0.083, 0.25, 0.5, 1,1.5, 2, 3, 4, 5, 6, 12, 24, 48, and 72 hours postdose and sacrifice 72 hour postdose. (n = 6, jugular vein cannulated, Study E)

- Single 1.0 mg/kg intravenous dose to rats with sampling at 0.083, 0.17, 0.25, 0.5, 1, 1.5, 2, 3, and 4 hours postdose. (n = 6, jugular vein cannulated, Study D)

- Single 1.0 mg/kg intravenous dose to mice with sacrifice at 0, 0.083, 0.17, 0.25, 0.5, 1, 1.5, 2, 3, and 4 hours postdose and sacrifice at 4 hours postdose. (n = 4 per time point with average actual dose of 1.14 ± 0.06 mg/kg, Study G)

Toxicokinetics:

Total radioactivity and 2-CP concentration-time data for toxicokinetic studies were analyzed by model-dependent methods using WinNonlin (Version 1.0). The theoretical curve that best-fit the data using one of the weighting schemes (uniform, 1/y, and $1/y^2$) was used to generate pharmacokinetic parameter estimates. A statistical F test was used for the selection of the appropriate number of compartments for the best-fit model.

For the oral dose in rats, the total radioactivity concentration-time data were best fit using a two-compartmental model. For the 10 mg/kg oral dose, the absorption period (T_{max}) was circa 30 minutes.

For the intravenous dose in rats, the parent 2-CP concentration-time data were best fit using a two-compartmental model with uniform weighting. The C_{max} of the parent in blood was circa 0.57 ug 2-CP/g blood and measured at the earliest collection point (5 minutes postdose).

For the intravenous dose in mice, the parent 2-CP concentration-time data were best fit using a one-compartmental model with $1/y^2$ weighting. The C_{max} of the parent in blood was circa 0.628 ug 2-CP/g blood and was measured at 10 minutes postdose. For total radioactivity, a two-compartment model with $1/y^2$ weighting resulted in the best fit to the

data. Radioactive components remained in blood through 4 hours but by 1.5 hours postdosing, the concentration of 2-CP associated radioactivity had decined to negligible values.

Individual animal blood concentration and percent dose data is shown in a separate Excel file.

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Table 1

Concentration of Total Radioactivity in Blood of Male F-344 Rats 72 h Following Oral Administration of [^{14}C]2-Chloropyridine at 10.0 mg/kg (Study E)[a]

Blood Collection Timepoint	ng-eq per g Blood	Percent Dose in Total Blood
5 min	2062 ± 316	1.07 ± 0.16
15 min	3376 ± 738	1.75 ± 0.38
30 min	3807 ± 462	1.97 ± 0.24
1 h	3278 ± 570	1.70 ± 0.29
1.5 h	2687 ± 243	1.39 ± 0.12
2 h	2192 ± 305	1.14 ± 0.16
3 h	1573 ± 166	0.814 ± 0.086
4 h	1224 ± 111	0.634 ± 0.057
5 h	1153 ± 78	0.597 ± 0.040
6 h	1092 ± 73	0.565 ± 0.038
12 h	917 ± 102	0.475 ± 0.053
24 h	724 ± 87	0.375 ± 0.045
48 h[b]	475 ± 58	0.246 ± 0.030
72 h[c]	353 ± 23	0.183 ± 0.012

a Values are mean ± SD for six rats.

b Values are mean ± SD for five rats.

c Values are mean ± SD for four rats.

Table 2

PK Data of Total Radioactivity Concentration in Blood vs. Time Following Oral Administration of [^{14}C]2-Chloropyridine at 10 mg/kg (Study E)

Dose = 10 mg/kg = 10,000 μg/kg

Conc = ng-eq/g = ng-eq/mL = μg-eq/L Time = hr

Final Parameters

Parameter	Estimate	Std Error	CV%	UnivarCI Lower	UnivarCI Upper
A	2129	110.1	5.17	1880	2378
B	546.5	51.16	9.36	430.7	662.2
K01	6.71	0.540	8.05	5.48	7.93
Alpha	0.607	0.0613	10.1	0.468	0.746
Beta	0.0151	0.00354	23.5	0.00706	0.0231

Elimination half-life of Total Radioactivity: $t_{1/2}$=0.693/beta

$t_{1/2}$=46.0 h for total radioactivity

Table 3

Concentration of [^{14}C]2-Chloropyridine and Total Radioactivity in Blood of Male F-344 Rats 4 h Following iv Administration of 1.0 mg 2-CP/kg (Study D)[a]

Time (h)	2-Chloropyridine ng/g Blood	Total Radioactivity ng-eq/g Blood	Total Radioactivity Percent Dose in Total Blood
0.083	567 ± 23	632 ± 146	4.09 ± 0.99
0.17	437 ± 31	422 ± 39	2.76 ± 0.27
0.25	360 ± 31	356 ± 5	2.30 ± 0.06
0.5	220 ± 20	286 ± 35	1.85 ± 0.26
1	123 ± 10	209 ± 37	1.35 ± 0.24
1.5	100 ± 43	138 ± 11	0.893 ± 0.075
2	73.2 ± 53.4	100 ± 9	0.646 ± 0.069
3	ND	74.9 ± 6.1	0.484 ± 0.041
4	ND	74.9 ± 4.8	0.483 ± 0.025

[a] Values are mean ± SD for four rats.
ND Not determined

Table 4

PK Parameters for Concentration of 2-CP Blood Following iv Administration of [^{14}C]2-CP to Male Rats at 1 mg/kg (Study D)[a]

Values from 2-Compartmental Simulation of Parent 2CP in Blood [b]:			
Parameter	**Mean**	**Std Dev**	**CV%**
Volume of Distribution (mL/kg)	982	221	22.5
Alpha (hr $^{-1}$)	6.71	3.42	50.9
Beta (hr $^{-1}$)	0.669	0.028	4.22
Distribution half-life (hr)	0.103	NA	NA
Elimination half-life (hr)	1.04	NA	NA
Clearance (mL/min/kg)	29.8	2.5	8.39

[a] Values are mean ± SD for four rats.

[b] Values are mean ± SD for three rats; rat 5 dropped from the simulation due to variability in the concentration of 2CP present at the latest two time points for this animal; simulation was skewed with rat 5 included.

[NA] Not Applicable.

Samples beyond 2 h contained insufficient radioactivity for analysis.

Table 5

Concentration of [^{14}C]2-Chloropyridine and Total Radioactivity in Blood of Male B6C3F$_1$ Mice Following iv Administration of 1.0 mg 2-CP/kg (Study G)[a]

Time (h)	2-Chloropyridine ng/g Blood	Total Radioactivity ng-eq/g Blood	Total Radioactivity Percent Dose in Total Blood
0.083	616 ±240	669 ± 205	4.31 ± 1.30
0.17	628 ±100	681 ± 35	4.45 ± 0.18
0.25	404 ±121	566 ± 95	3.78 ± 0.58
0.50[b]	113 ± 42	264 ± 27	1.75 ± 0.13
1	7.97 ± 5.47	232 ± 178	1.58 ± 1.23
1.5	ND	81.8 ± 8.7	0.547 ± 0.057
2	ND	71.2 ± 9.3	0.453 ± 0.043
3	ND	88.5 ± 25.3	0.603 ± 0.175
4	ND	72.7 ± 29.0	0.522 ± 0.185

[a] Values are mean ± SD for four mice.
ND Not Determined.

Table 6

Pharmacokinetic Parameters for Total Radioactivity and 2-CP Concentration in Blood After 1.14 mg/kg iv Dose in Male B6C3F$_1$ Mice (Study G)

	Best-Fit Number of Pharmacokinetic Compartments	Best-Fit Weighting Function	AUC_0^∞ (dpm-h/mL)	α (h^{-1})	$T_{1/2\alpha}$ (h)	β (h^{-1})	$T_{1/2\beta}$ (hr)	V_{ss} (mL)	CL_s (mL/min)
Total Radioactivity*	2	$1/Y^2$	-	2.32	0.298	$1x10^{-4}$	6931	417	$6.95x10^{-4}$
2CP	1	$1/Y^2$	188225	4.90	0.142	NA	NA	23.5	1.92

AUC_0^∞ Area under the curve

α Initial disposition rate constant

$T_{1/2\alpha}$ Half-life of initial disposition (two-compartmental) or half-life of terminal elimination (one-compartmental)

β Terminal elimination rate constant

$T_{1/2\beta}$ Half-life of terminal elimination

V_{ss} Volume of distribution at steady state

CL_s Systemic clearance

NA Not applicable

* Data should be interpreted with caution due to the small sampling interval.