

## ADME NTP Study S0818 Chromium picolinate monohydrate

The contract laboratory abbreviation for the test article is Cr3P for chromium picolinate (the parent) or Pcl-H for picolinic acid or PA in some tables. N-picolinoylglycine (metabolite) is abbreviated to NPG.

Species: adult male F344 rats and B6C3F1 mice.

Vehicles: intravenous, 0.9% saline (study Ha); oral, 1,2-propanediol (studies A, D, and Jb) and water slurry (studies Ba, F, Hb, J);

CASRN 27882-76-4 (chromium picolinate monohydrate) and 98-98-6 (picolinic acid)

Cr3P radiolabeled with carbon-14 with multiple sites in the aromatic rings; Chromium picolinate, [3, 4, 5, 6-pyridine-<sup>14</sup>C]

Pcl-H radiolabeled with carbon-14 (location not specified); [<sup>14</sup>C]Picolinic acid.

[<sup>14</sup>C]Cr3P, and [<sup>14</sup>C]Pcl-H were used for dosing. Analytes were chromium (Cr) and radiolabel (Cr3P or Pcl-H equivalents).

Studies Performed (dosing with [<sup>14</sup>C]Cr3P unless otherwise stated):

1. Single 15.3 mg/kg oral dose in male rats using 1,2-propanediol vehicle with sacrifice 52 hours postdose (Study A).
2. Single 17.4 mg/kg oral dose in male rats using water slurry vehicle with sacrifice at 1 and 48 hours postdose (Study Ba).
3. Single 0.22 mg/kg oral dose in male rats using 1,2-propanediol vehicle with sacrifice 52 hours postdose (Study D).
4. Single 17.4 mg/kg oral dose in male rats using water slurry vehicle with sacrifice 4 hours postdose (Study F).
5. Single 0.18 mg/kg intravenous dose in male rats using 0.9% sodium chloride vehicle with sacrifice 120 minutes postdose (Study Ha).
6. Single 17.8 mg/kg oral dose in male rats using water slurry vehicle with sacrifice 24 hours postdose (Study Hb).
7. Single 20.5 mg/kg oral dose in male mice using water slurry vehicle with sacrifice 48 hours postdose (Study J).
8. Single 19.0 mg/kg oral dose in male mice using 1,2-propanediol vehicle with sacrifice 48 hours postdose (Study Jb).
9. Single 17.2 mg/kg [<sup>14</sup>C]picolinic acid (Pcl-H) oral dose in male rats using water slurry vehicle with sacrifice at 6 and 24 hours postdose (Study PAa).

Toxicokinetic studies Ha (intravenous with jugular cannulated rats) and Hb (oral) studies included excreta (Hb) and tissue distribution (Ha) data. The bioavailability of Cr3P in the aqueous slurry, calculated from the blood AUC data (oral vs. intravenous) is 0.7%. There were no studies labeled C, E, G, or I in this report.

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Table 1

Recovery of Radioactivity and Cr from Male F-344 Rats Through 52 h  
Following Oral Administration of [<sup>14</sup>C]Cr3P at 15.3 mg/kg in 1,2-Propanediol  
(Study A)<sup>a</sup>

## I. Radiolabel

End of Collection Period (h)	Cumulative Percent Dose Excreted			
	Urine	Feces	CO <sub>2</sub> Breath	Total
8	22.8 ± 2.1	NC	0.1 ± 0.1	22.9 ± 2.1
24	53.4 ± 0.9	39.4 ± 4.9	1.5 ± 0.5	94.2 ± 6.1
48	56.3 ± 0.9	43.6 ± 3.4	2.2 ± 0.5	102 ± 3.8
52	56.4 ± 0.9	43.6 ± 3.4	2.2 ± 0.5	102 ± 3.8

## II. Total Cr

End of Collection Period (h)	Cumulative Percent Dose Excreted		
	Urine	Feces	Total
8	0.97 ± 0.26	NC	0.97 ± 0.26
24	1.18 ± 0.24	82.5 ± 12.2	83.7 ± 12.1
48	1.25 ± 0.24	97.5 ± 7.4	98.8 ± 7.3

<sup>a</sup> Values are mean ± SD for four rats.

NC No collection was scheduled for this time interval.

Table 2

Distribution of Radioactivity in Tissues of Male F-344 Rats at 52 h Following  
Oral Administration of [<sup>14</sup>C]Cr3P in 1,2-Propanediol as 15.3 mg/kg

(Study A)<sup>a</sup>

Tissue	ng-eq Cr3P per g Tissue	Tissue/Blood Ratio	% Dose in Total Tissue
Adipose	149 ± 52	2.70 ± 1.28	0.067 ± 0.022
Bladder	142 ± 44	2.54 ± 1.10	0.0005 ± 0.0003
Blood	62.5 ± 23.2	unity	0.021 ± 0.0079
Brain	35.0 ± 5.0	0.596 ± 0.140	0.002 ± 0.0002
Heart	71.8 ± 17	1.22 ± 0.353	0.001 ± 0.0003
Kidney	281 ± 29	4.82 ± 1.20	0.014 ± 0.0016
Liver	437 ± 163	7.01 ± 0.77	0.117 ± 0.047
Lung	71.8 ± 41.3	1.09 ± 0.23	0.002 ± 0.001
Muscle	33.1 ± 11.2	0.542 ± 0.129	0.103 ± 0.035
Skin	211 ± 45	3.75 ± 1.40	0.232 ± 0.052
Spleen	98.1 ± 21.5	1.71 ± 0.57	0.001 ± 0.0003
Testis	37.4 ± 7.0	0.631 ± 0.132	0.003 ± 0.0005
<b>Total in non-GI tract tissues</b>			<b>0.549 ± 0.099</b>
Stomach and contents			0.0094 ± 0.006
Small Intestine and contents			0.040 ± 0.011
Cecum and contents			0.072 ± 0.029
Large Intestine and contents			0.057 ± 0.015
<b>Total in GI tract tissues</b>			<b>0.177 ± 0.040</b>
<b>Total in all tissues</b>			<b>0.726 ± 0.100</b>

<sup>a</sup> Values are mean ± SD for four rats.

Table 3

Distribution of Cr in Selected Tissues of Male F-344 Rats at 52 h  
Following Oral Administration of [<sup>14</sup>C]Cr3P in 1,2-Propanediol at 15.3 mg/kg

(Study A)

Tissue	Animal Concentration (ng Cr/g Dry Tissue)			
	Blank	A1	A2	A3
Liver Homogenate <sup>a</sup>	BDL <sup>b</sup> BQL	BQL <sup>c</sup> BQL	BQL BQL	BQL BQL
Lung <sup>d</sup>	BQL	80 BQL	78 76	77
Spleen	84	71	93	96
Kidney <sup>a</sup>	95 BQL	108 110	112 115	121 103

<sup>a</sup> Duplicate samples were analyzed for each animal

<sup>b</sup> BDL = less than the limit of detection (6 ng/g)

<sup>c</sup> BQL = less than the limit of quantitation (60 ng/g)

<sup>d</sup> Duplicate analyses were performed on the same sample for animals A1 and A2

Table 4

Recovery of Radioactivity and Cr from Male F-344 Rats through 48 h  
Following Oral Administration of [<sup>14</sup>C]Cr3P in Water Slurry at 17.4 mg/kg  
(Study Ba)<sup>a</sup>

## I. Radiolabel

End of Collection Period (h)	Cumulative Percent Dose Excreted			
	Urine	Feces	CO <sub>2</sub> Breath	Total
4	3.6 ± 2.1	0.0 ± 0.0	NC	3.6 ± 2.1
8	15.5 ± 3.8	5.3 ± 10.6	0.1 ± 0.0	20.9 ± 11.1
12	26.6 ± 3.1	8.9 ± 8.3	0.1 ± 0.0	35.6 ± 7.8
24	40.9 ± 3.6	46.6 ± 6.8	1.4 ± 0.7	88.9 ± 4.7
48	43.4 ± 3.5	47.8 ± 6.9	1.7 ± 0.9	92.9 ± 4.4

## II. Total Cr

End of Collection Period (h)	Cumulative Percent Dose Excreted		
	Urine	Feces	Total
2	0.18 ± 0.14	NC	0.18 ± 0.14
4	0.34 ± 0.04	0.00 ± 0.0	0.34 ± 0.04
8	0.66 ± 0.05	7.64 ± 15.3	8.30 ± 15.3
12	0.84 ± 0.05	13.7 ± 11.5	14.6 ± 11.5
24	1.16 ± 0.34	92.9 ± 8.9	94.1 ± 8.8
48	1.53 ± 0.51	97.6 ± 7.4	99.2 ± 7.2

<sup>a</sup> Values are mean ± SD for four rats.

NC No collection was scheduled for this time interval.

Table 5

Recovery of Radioactivity from Male F-344 Rats through 2 h  
Following Oral Administration of [<sup>14</sup>C]Cr3P in Water Slurry at 17.4 mg/kg  
(Study Ba)<sup>a</sup>

End of Collection Period (h)	Cumulative Percent Dose Excreted			
	Urine	Feces	CO <sub>2</sub> Breath	Total
2	0.10 ± 0.12	NC	NC	0.10 ± 0.12
Bladder contents	4.9 ± 1.2			4.9 ± 1.2

<sup>a</sup> Values are mean ± SD for four rats.

Table 6

Distribution of Radioactivity in Tissues of Male F-344 Rats at 2 and 48 h  
Following Oral Administration of [<sup>14</sup>C]Cr3P in Water Slurry as 17.4 mg/kg  
(Study Ba)<sup>a</sup>

Tissue	ng-eq Cr3P per g Tissue		Tissue/Blood Ratio		% Dose in Total Tissue	
<b>2 h Following Dosing</b>						
Adipose	620	± 383	0.452	± 0.218	0.255	± 0.162
Bladder	6300	± 5780	5.18	± 4.54	0.015	± 0.016
Blood	1300	± 244	unity		0.401	± 0.078
Brain	251	± 42	0.194	± 0.016	0.012	± 0.002
Heart	830	± 63	0.652	± 0.104	0.017	± 0.002
Kidney	5410	± 511	4.28	± 0.90	0.243	± 0.028
Liver	819	± 338	0.623	± 0.212	0.198	± 0.074
Lung	712	± 194	0.551	± 0.127	0.017	± 0.005
Muscle	344	± 118	0.262	± 0.056	0.991	± 0.333
Skin, ear	631	± 102	0.490	± 0.063	0.644	± 0.087
Spleen	729	± 825	0.500	± 0.465	0.011	± 0.013
Testis	263	± 197	0.189	± 0.100	0.019	± 0.014
<b>Total in non-GI tract tissues</b>					2.94	± 0.97
Stomach and contents					14.4	± 3.9
Small Intestine and contents					64.2	± 11.5
Cecum and contents					13.0	± 9.3
Large Intestine and contents					0.16	± 0.13
<b>Total in GI tract tissues</b>					91.7	± 4.8
<b>Total in all tissues</b>					94.7	± 4.3
<b>48 h Following Dosing</b>						
Adipose	248	± 125	3.54	± 0.74	0.094	± 0.048
Bladder	114	± 50	1.65	± 0.17	0.0002	± 0.0001
Blood	66.9	± 24.7	unity		0.019	± 0.007
Brain	25.9	± 11.1	0.377	± 0.048	0.001	± 0.0006
Heart	66.9	± 28.0	0.977	± 0.192	0.001	± 0.0006
Kidney	235	± 76	3.57	± 0.26	0.010	± 0.004
Liver	263	± 89	4.00	± 0.61	0.049	± 0.018
Lung	125	± 55	1.81	± 0.317	0.003	± 0.001
Muscle	40.3	± 21.7	0.569	± 0.155	0.105	± 0.059
Skin	169	± 64	2.56	± 0.29	0.156	± 0.060
Spleen	133	± 62	1.89	± 0.46	0.002	± 0.0008
Testis	23.8	± 11.8	0.350	± 0.138	0.002	± 0.0008
<b>Total in non-GI tract tissues</b>					0.44	± 0.19
GI Tract and contents					0.15	± 0.07
<b>Total in GI tract tissues</b>					0.15	± 0.07
<b>Total in all tissues</b>					0.59	± 0.21

<sup>a</sup> Values are mean ± SD for four rats.



Table 7

Recovery of Radioactivity from Male F-344 Rats through 52 h  
Following Oral Administration of [<sup>14</sup>C]Cr3P at 0.22 mg/kg in 1,2-Propanediol  
(Study D)<sup>a</sup>

End of Collection Period (h)	Cumulative Percent Dose Excreted			
	Urine	Feces	CO <sub>2</sub> Breath	Total
8	22.8 ± 6.7	NC	2.1 ± 0.6	24.8 ± 6.1
24	40.0 ± 7.5	26.8 ± 5.9	10.5 ± 3.3	77.3 ± 9.5
48	41.7 ± 7.3	28.9 ± 5.8	11.4 ± 3.4	81.9 ± 8.5
52	41.8 ± 7.2	28.9 ± 5.8	11.4 ± 3.4	82.1 ± 8.3

<sup>a</sup> Values are mean ± SD for four rats.

NC No collection was scheduled for this time interval.

Table 8

Distribution of Radioactivity in Tissues of Male F-344 Rats at 52 h Following  
Oral Administration of [<sup>14</sup>C]Cr3P in 1,2-Propanediol at 0.22 mg/kg

(Study D)<sup>a</sup>

Tissue	ng-eq Cr3P per g Tissue	Tissue/Blood Ratio	% Dose in Total Tissue
Adipose	14.1 ± 4.60	3.17 ± 1.17	0.439 ± 0.137
Bladder	10.7 ± 5.42	2.20 ± 0.72	0.003 ± 0.002
Blood	4.62 ± 0.909	unity	0.109 ± 0.022
Brain	2.48 ± 0.461	0.538 ± 0.026	0.008 ± 0.002
Heart	5.20 ± 2.02	1.10 ± 0.26	0.007 ± 0.003
Kidney	7.83 ± 1.51	1.77 ± 0.60	0.028 ± 0.005
Liver	14.2 ± 5.8	3.29 ± 1.88	0.266 ± 0.126
Lung	9.10 ± 1.15	1.99 ± 0.182	0.016 ± 0.002
Muscle	2.59 ± 1.19	0.573 ± 0.245	0.551 ± 0.250
Skin	12.7 ± 4.4	2.69 ± 0.48	0.957 ± 0.332
Spleen	9.19 ± 3.09	1.99 ± 0.512	0.010 ± 0.004
Testis	2.68 ± 1.04	0.567 ± 0.146	0.015 ± 0.005
<b>Total in non-GI tract tissues</b>			<b>2.41 ± 0.44</b>
Stomach and contents			0.026 ± 0.008
Small Intestine and contents			0.191 ± 0.054
Cecum and contents			0.084 ± 0.031
Large Intestine and contents			0.068 ± 0.040
<b>Total in GI tract tissues</b>			<b>0.37 ± 0.11</b>
<b>Total in all tissues</b>			<b>2.78 ± 0.51</b>

<sup>a</sup> Values are mean ± SD for four rats.

Table 9

Recovery of Radioactivity in GI Tracts of Male F-344 Rats through 4 h  
Following Oral Administration of [<sup>14</sup>C]Cr3P in Water Slurry at 17.4 mg/kg  
(Study F)<sup>a</sup>

## I. Percent Dose

Time Post Dosing (h)	Percent Dose in			
	Stomach and Contents	Small Intestines and Contents	Cecum and Contents	Large Intestines and Contents
1	27.9 ± 6.9	62.4 ± 7.2	0.0 ± 0.0	0.1 ± 0.1
2	12.1 ± 8.3	52.7 ± 27.8	21.4 ± 34.3	0.6 ± 0.9
4	4.5 ± 3.3	6.3 ± 2.5	62.6 ± 4.0	4.7 ± 3.8

## II. Cumulative Percent Dose

Time Post Dosing (h)	Cumulative Percent Dose in			
	Stomach and Contents	Small Intestines and Contents	Cecum and Contents	Large Intestines and Contents
1	27.9 ± 6.9	90.3 ± 0.7	90.3 ± 0.7	90.4 ± 0.7
2	12.1 ± 8.3	64.9 ± 36.0	86.3 ± 1.8	86.8 ± 1.1
4	4.4 ± 3.3	10.8 ± 2.9	73.5 ± 3.3	78.2 ± 1.8

<sup>a</sup> Values are mean ± SD for four rats.

Table 10

**Distribution of Radioactivity and Cr3P in Tissues of Male F-344 Rats through 4 h  
Following Oral Administration of [<sup>14</sup>C]Cr3P in Water Slurry at 17.4 mg/kg  
(Study F)<sup>a</sup>**

Tissue	Collection Point (h)	Total % in Tissue	Cr3P (ng Cr3P per g)	Tissue/Blood Ratio for Cr3P
Blood	1	0.087 ± 0.012	31 ± 8.7	unity
	2	0.285 ± 0.047	17 ± 1.1	unity
	4	0.210 ± 0.050	6.0 ± 1.7	unity
Adipose	1	0.015 ± 0.003	5.1 ± 1.1	0.18 ± 0.09
	2	0.076 ± 0.032	5.5 ± 2.8	0.33 ± 0.18
	4	0.065 ± 0.049	2.3 ± 1.4	0.41 ± 0.24
Liver	1	0.086 ± 0.010	78 ± 10	2.8 ± 1.1
	2	0.218 ± 0.039	66 ± 12	3.9 ± 0.6
	4	0.143 ± 0.028	23 ± 7.1	4.0 ± 1.0
Muscle	1	0.258 ± 0.032	5.3 ± 2.2	0.20 ± 0.1
	2	0.854 ± 0.062	4.2 ± 1.4	0.25 ± 0.08
	4	0.663 ± 0.167	0.7 ± 0.4	0.11 ± 0.04

<sup>a</sup> Values are mean ± SD for four rats.

Table 11

Distribution of Cr3P and Metabolites in Tissues of Male F-344 Rats through 4 h  
Following Oral Administration of [<sup>14</sup>C]Cr3P in Water Slurry at 17.4 mg/kg

(Study F)<sup>a</sup>

Tissue	Collection Point (h)	Radioactivity (ng-eq Cr3P or ng per g of tissue) that Coelutes with:			Total (ng-eq Cr3P/g of tissue)	% <sup>14</sup> C Extracted by CH <sub>3</sub> CN
		PA	Cr3P	NPG		
Blood	1	55 ± 17	31 ± 8.7	4.9 ± 3.5	289 ± 30	40 ± 7
	2	199 ± 21	17 ± 1.1	41 ± 14	943 ± 131	30 ± 2
	4	128 ± 2.5	6.0 ± 1.7	32 ± 8.8	706 ± 150	31 ± 2
Adipose	1	16 ± 2.0	5.1 ± 1.1	1.9 ± 2.4	37 ± 8.6	76 ± 4
	2	95 ± 54	5.5 ± 2.8	12 ± 8.9	186 ± 76	76 ± 11
	4	104 ± 79	2.3 ± 1.4	15 ± 16	166 ± 130	69 ± 1
Liver	1	114 ± 21	78 ± 10	23 ± 4.9	320 ± 25	89 ± 3
	2	371 ± 13	66 ± 12	100 ± 21	840 ± 157	81 ± 7
	4	263 ± 55	23 ± 7.1	74 ± 18	598 ± 118	93 ± 3
Muscle	1	58 ± 15	5.3 ± 2.2	1.7 ± 2.1	93 ± 13	88 ± 3
	2	183 ± 15	4.2 ± 1.4	30 ± 22	308 ± 28	82 ± 4
	4	154 ± 33	0.7 ± 0.4	7.6 ± 1.0	214 ± 35	85 ± 1

<sup>a</sup> Values are mean ± SD for four rats. PA represents picolinic acid.

Table 12

**Distribution of Radioactivity in Tissue of Male F-344 Rats at 120 min  
Following Intravenous Administration of [<sup>14</sup>C]Cr3P in 0.9% Sodium Chloride at 0.18 mg/kg  
(Study Ha)<sup>a</sup>**

Tissue	ng-eq Cr3P per g Tissue	Tissue/Blood Ratio	% Dose in Total Tissue
Adipose	16.3 ± 18.3	0.599 ± 0.771	0.647 ± 0.728
Bladder	2410 ± 2130	73.1 ± 62.0	0.866 ± 0.865
Blood	30.4 ± 8.12	unity	0.918 ± 0.263
Brain	2.41 ± 0.65	0.079 ± 0.007	0.009 ± 0.002
Heart	10.6 ± 2.6	0.349 ± 0.026	0.020 ± 0.006
Kidney	113 ± 19	3.81 ± 0.50	0.471 ± 0.064
Liver	83.0 ± 15.9	2.82 ± 0.57	1.77 ± 0.284
Lung	20.8 ± 4.5	0.708 ± 0.163	0.0421 ± 0.009
Muscle	8.92 ± 1.60	0.303 ± 0.070	2.42 ± 0.432
Skin	14.5 ± 3.6	0.484 ± 0.073	1.41 ± 0.392
Spleen	15.5 ± 3.9	0.563 ± 0.268	0.019 ± 0.006
Testis	8.09 ± 1.65	0.282 ± 0.090	0.048 ± 0.006
<b>Total in non-GI tract tissues</b>			<b>8.74 ± 1.82</b>
<b>Total in GI tract tissues<sup>b</sup></b>			<b>8.16 ± 0.99</b>
<b>Total in all tissues</b>			<b>16.9 ± 1.0</b>

<sup>a</sup> Values are mean ± SD for five rats.

<sup>b</sup> Includes small intestines, cecum and large intestines plus contents of each.

Table 13

Recovery of Radioactivity from Male F-344 Rats through 24 h  
Following Oral Administration of [<sup>14</sup>C]Cr3P in Water Slurry at 17.8 mg/kg  
(Study Hb)<sup>a</sup>

End of Collection Period (h)	Cumulative Percent Dose Excreted		
	Urine	Feces	Total
4	4.1 ± 3.2	0.0 ± 0.0	4.1 ± 3.2
8	15.6 ± 1.2	2.1 ± 3.1	17.7 ± 4.0
12	27.6 ± 2.4	6.7 ± 5.8	34.3 ± 7.4
24	48.9 ± 3.2	30.5 ± 4.5	79.4 ± 2.4

<sup>a</sup> Values are mean ± SD for four rats.

Table 14

**Distribution of Radioactivity in Tissues of Male F-344 Rats at 24 h  
Following Oral Administration of [<sup>14</sup>C]Cr3P in Water Slurry at 17.8 mg/kg  
(Study Hb)<sup>a</sup>**

<b>Tissue</b>	<b>ng-eq Cr3P per g Tissue</b>	<b>Tissue/Blood Ratio</b>	<b>% Dose in Total Tissue</b>
<b>Blood</b>	229 ± 121	unity	0.061% ± 0.03%
<b>Liver</b>	1046 ± 582	4.71 ± 0.84	0.21% ± 0.11%
<b>Muscle</b>	59 ± 36	0.25 ± 0.04	0.15% ± 0.08%
<b>Adipose</b>	49 ± 32	0.19 ± 0.06	0.018% ± 0.01%

<sup>a</sup> Values are mean ± SD for four rats.



Table 15

Recovery of Radioactivity and Cr from Male B6C3F<sub>1</sub> Mice Through 48 h  
Following Oral Administration of [<sup>14</sup>C]Cr3P in 1,2-Propanediol at 19.0 mg/kg  
(Study Jb)<sup>a</sup>

## I. Radiolabel

End of Collection Period (h)	Cumulative Percent Dose Excreted					
	Urine		Feces		Total	
6	18.0	± 6.2	19.1	± 7.8	37.1	± 10.1
12	24.8	± 7.0	49.8	± 5.4	74.6	± 5.6
24	30.7	± 8.2	53.0	± 4.8	83.7	± 4.4
48	42.0	± 7.8	55.1	± 5.6	97.1	± 3.7

## II. Cr

End of Collection Period (h)	Cumulative Percent Dose Excreted					
	Urine		Feces		Total	
6	2.3	± 0.8	28.6	± 9.7	30.9	± 9.1
12	2.5	± 0.7	80.3	± 10.9	82.8	± 11.3
24	2.8	± 0.5	87.8	± 12.5	90.6	± 12.5
48	3.9	± 1.1	91.3	± 12.7	95.2	± 13.7

<sup>a</sup> Values are mean ± SD for four mice.

Table 16

Distribution of Radioactivity in Tissues of Male B6C3F<sub>1</sub> Mice at 48 h  
Following Oral Administration of [<sup>14</sup>C]Cr3P in 1,2-Propanediol at 19.0 mg/kg  
(Study Jb)<sup>a</sup>

Tissue	ng-eq Cr3P/g Tissue	Tissue/Blood Ratio	% Dose in Total Tissue
Blood	4.8 ± 0.8	unity	0.0019 ± 0.0003
Liver	63 ± 22	13.2 ± 4.3	0.014 ± 0.005
Muscle	7.6 ± 4.6	1.6 ± 0.9	0.018 ± 0.012
Adipose	7.9 ± 3.5	1.6 ± 0.5	0.0041 ± 0.0018
		GI tract and contents	0.047 ± 0.016
		Carcass	0.432 ± 0.203

<sup>a</sup> Values are mean ± SD for four mice.

Table 17

Recovery of Radioactivity from Male F-344 Rats Through 6 h  
Following Oral Administration of [<sup>14</sup>C]Pcl-H at 17.2 mg/kg  
(Study PAa)<sup>a</sup>

End of Collection Period (h)	Cumulative Percent Dose Excreted			
	Urine	Feces	CO <sub>2</sub> Breath	Total
4	29.6 ± 14	0.20 ± 0.22	NC	29.8 ± 14
6	82.6 ± 4.1	0.43 ± 0.53	NC	83.0 ± 4.5

<sup>a</sup> Values are mean ± SD for four rats.

Table 18

**Distribution of Radioactivity in Tissues of Male F-344 Rats at 6 h  
Following Oral Administration of [<sup>14</sup>C]Pcl-H in Water at 17.2 mg/kg  
(Study PAa)<sup>a</sup>**

<b>Tissue</b>	<b>ng-eq Pcl-H per g Tissue</b>	<b>Tissue/Blood Ratio</b>	<b>% Dose in Total Tissue</b>
Adipose	46.0 ± 41.7	0.120 ± 0.044	0.0176 ± 0.0154
Bladder	15700 ± 8860	46.4 ± 12.6	0.0261 ± 0.0122
Blood	344 ± 192	unity	0.0982 ± 0.0513
Brain	95.9 ± 60.2	0.279 ± 0.0863	0.00451 ± 0.00311
Heart	257 ± 134	0.761 ± 0.0742	1.09 ± 0.151
Kidney	1200 ± 592	3.59 ± 0.391	0.0504 ± 0.024
Liver	784 ± 216	2.52 ± 0.664	0.173 ± 0.0416
Lung	220 ± 127	0.643 ± 0.0687	0.00502 ± 0.00313
Muscle	90.5 ± 67.3	0.249 ± 0.0433	0.239 ± 0.169
Skin	360 ± 319	0.948 ± 0.290	0.334 ± 0.284
Spleen	186 ± 82.1	0.567 ± 0.0981	0.00257 ± 0.00113
Testis	138 ± 107	0.375 ± 0.0667	0.00914 ± 0.00691
<b>Total in non-GI tract tissues</b>			1.00
Stomach and contents			0.663 ± 0.705
Small Intestine and contents			0.202 ± 0.0633
Cecum and contents			1.09 ± 0.151
Large Intestine and contents			0.695 ± 0.215
<b>Total in GI tract tissues</b>			2.65
<b>Total in all tissues</b>			3.65

<sup>a</sup> Values are mean ± SD for four rats.

Table 19

Recovery of Radioactivity from Male F-344 Rats Through 20 h  
Following Oral Administration of [<sup>14</sup>C]Pcl-H at 17.2 mg/kg

(Study PAa)<sup>a,b</sup>

End of Collection Period (h)	Cumulative Percent Dose Excreted			
	Urine	Feces	CO <sub>2</sub> Breath	Total
4	45.7 ± 12	0.2 ± 0.1	NC	45.8 ± 12
8	68.4 ± 3.6	0.5 ± 0.3	0.1 ± 0.1	69.2 ± 3.7
12	82.0 ± 5.6	1.0 ± 0.4	0.1 ± 0.1	83.0 ± 5.8
20 <sup>a</sup>	93.4 ± 1.7	1.7 ± 0.0	0.3 ± 0.2	95.4 ± 1.5

<sup>a</sup> Animals died at ca. 20 h postdosing due to a malfunction of the breath (CO<sub>2</sub>) collection system.

<sup>b</sup> Values are mean ± SD for four rats.

Table 20

Concentrations of Radioactivity and Cr3P in Blood of Male F-344 Rats through 120 min Following Intravenous Administration of [<sup>14</sup>C]Cr3P in 0.9% Sodium Chloride at 0.18 mg/kg (Study Ha)<sup>a</sup>

## I. Mean values

Blood Collection Time Point (min)	Total Radiolabel in Blood (ng-eq Cr3P/g)	Percent Dose In Total Blood	Concentration of Cr3P in Blood (ng/g)
10	283 ± 47	8.3% ± 1.2%	160 ± 25 <sup>b</sup>
30	146 ± 24	4.3% ± 0.6%	71 ± 13
60	71 ± 6	2.1% ± 0.2%	25 ± 5
120	31 ± 8	0.9% ± 0.3%	6 ± 3 <sup>b</sup>

<sup>a</sup> Values are mean ± SD for five rats except where noted. The concentration of radiolabel in blood for one rat was such that it appeared that Cr3P had not been administered intravenously. The concentrations of radiolabel were 125, 155, 92, and 56 ng-eq Cr3P/g at 10, 30, 60, and 120 min, respectively.

<sup>b</sup> Values are mean ± SD for four rats.

## II. Individual values for total radiolabel.

Blood Collection Time Point (min)	Total Radiolabel in Blood (ng-eq Cr3P/g)				
	Rat 1	Rat 2	Rat 3	Rat 4	Rat 5
10	302	290	215	267	343
30	176	140	114	138	161
60	80	62	71	70	71
120	33	22	41	36	24

## III. Individual values for Cr3P.

Blood Collection Time Point (min)	Cr3P in Blood (ng/g)				
	Rat 1	Rat 2	Rat 3	Rat 4	Rat 5
10	166	191	133	151	SL
30	91	74	57	66	68
60	30	18	25	29	23
120	SL	4	9	8	4

SL = Sample lost.

Table 21

Concentrations of Radiolabel and Cr3P in Blood of Male F-344 Rats through 24 h  
Following Oral Administration of [<sup>14</sup>C]Cr3P in Water Slurry at 17.8 mg/kg  
(Study Hb)<sup>a</sup>

## I. Mean values

Blood Collection Time Point (h)	Total Radiolabel in Blood (ng-eq Cr3P/g)	Percent Dose In Total Blood	Concentration of Cr3P in Blood (ng/g)
0.5	273 ± 13	0.08% ± 0.007%	19 ± 8.4 <sup>b</sup>
1	361 ± 42	0.11% ± 0.009%	21 ± 8.4
2	1083 ± 150	0.32% ± 0.039%	15 ± 5.6
4	1039 ± 240	0.30% ± 0.051%	7.4 ± 1.6
6	785 ± 37	0.23% ± 0.027%	3.2 ± 2.7
9	602 ± 129	0.17% ± 0.026%	0.9 ± 0.7
12	523 ± 135	0.15% ± 0.028%	0.8 ± 0.7
15	385 ± 132	0.11% ± 0.030%	0.5 ± 0.4
24	229 ± 121	0.06% ± 0.032%	

<sup>a</sup> Values are mean ± SD for four rats except where noted.

<sup>b</sup> Values are mean ± SD for three rats.

## II. Individual values for total radiolabel.

Blood Collection Time Point (h)	Total Radiolabel in Blood (ng-eq Cr3P/g)			
	Rat 1	Rat 2	Rat 3	Rat 4
0.5	262	262	286	283
1	319	330	403	390
2	981	932	1182	1238
4	783	893	1195	1286
6	772	798	743	830
9	435	724	568	679
12	330	624	529	609
15	191	449	480	418
24	51	258	318	290

## III. Individual values for Cr3P.

Blood Collection Time Point (h)	Cr3P in Blood (ng /g)			
	Rat 1	Rat 2	Rat 3	Rat 4
0.5	10	25	22	SL
1	9.2	28	26	21
2	7.6	20	13	18
4	5.6	9.4	6.8	7.9
6	2.4	7.1	0.83	2.5
9	0.0	1.5	0.48	1.4
12	0.43	1.6	0.20	1.1
15	0.39	0.0	0.60	1.0

SL = Sample lost.

Table 22

**Blood Cr3P Pharmacokinetics in Male F-344 Rats  
Following Intravenous and Oral (Aqueous Slurry) Administration of [<sup>14</sup>C]Cr3P**

Rat #	Cr3P Dose mg/kg	Dose Route	Elimination Rate Constant <sup>a</sup> min <sup>-1</sup>	Terminal T <sub>1/2</sub> <sup>a</sup> min	AUC <sub>0</sub> <sup>∞</sup> a,b ng-min/g
1	0.18	IV	0.0344	20	7207
2	0.18	IV	0.0347	20	7295
3	0.18	IV	0.0200	35	6281
4	0.18	IV	0.0232	30	6947
5	0.18	IV	0.0311	22	6339
<b>Mean</b>	<b>0.18</b>		<b>0.0287</b>	<b>24<sup>c</sup></b>	<b>6814</b>
<b>S.D.</b>	<b>0</b>		<b>0.0067</b>		<b>478</b>
<b>CV%</b>	<b>0</b>		<b>23</b>		<b>7</b>
1	17.8	Oral	0.0041	168 <sup>d</sup>	2880
2	17.8	Oral	0.0046	150 <sup>d</sup>	6780
3	17.8	Oral	0.0054	126 <sup>d</sup>	4200
4	17.8	Oral	0.0039	180 <sup>d</sup>	5040
<b>Mean</b>	<b>17.8</b>		<b>0.0045</b>	<b>153<sup>c,d</sup></b>	<b>4725</b>
<b>S.D.</b>	<b>0</b>		<b>0.0007</b>		<b>1633</b>
<b>CV%</b>	<b>0</b>		<b>15</b>		<b>35</b>

**Oral Bioavailability<sup>e</sup> = 0.7%**

<sup>a</sup> All values were calculated by model-independent (noncompartmental) pharmacokinetic methods using WinNonlin software.

<sup>b</sup> AUC<sub>0</sub><sup>∞</sup>; area under the blood Cr3P concentration vs. time curve from time 0 to infinity.

<sup>c</sup> Calculated as harmonic mean.

<sup>d</sup> Likely influenced by slow absorption of Cr3P from gut. See Section 4.5

<sup>e</sup> Calculated from mean dose and AUC<sub>0</sub><sup>∞</sup> values.