ADME NTP Study S0003 Cobalt Naphthenate

The contract laboratory used the abbreviation of CoNap for the test article.
Sex/Species: adult male F344 rats.
Vehicles: oral, Emulphor:ethanol (2:1)

CASRN 61789-51-3

No radiolabel; Cobalt levels were determined following acid digestion by graphite furnace atomic absorption spectrophotometry.

Studies Performed:

Single 2.8 or 280 mg/kg oral gavage dose in rats with vehicle control and sacrifice 48 hours postdose. (disposition study)

Single 2.8, 28, or 280 mg/kg oral gavage dose in rats with sacrifice at 2, 4, 8, 12, 18, 24, and 36 hours or 48 hours (28 mg/kg group) postdose. (absorption study)

Cobalt naphthenate was ground to a fine powder and then solubilized in ethanol. The detection limit of cobalt was approximately 8 ng/L. The amount of cobalt appearing in excreta and tissues of control animals (dosed with vehicle) were subtracted from that present in excreta and tissues of the treated animals.

Toxicokinetics:

Percent dose of cobalt and the cobalt concentrations in blood results are given in Tables 14 and 15, respectively. No modeling information about the pharmacokinetic parameters in Table 16 was specified.

TABLE 1

PERCENT OF DOSE OF Co(II) IN EXCRETA VS. TIME FOLLOWING ORAL ADMINISTRATION OF COBALT NAPHTHENATE: DISPOSITION STUDY

TIME (HR)	URINE*	FECES*	TOTAL*
High Dose Group (280 mg/kg):			
6.0	4.95 ± 1.33	---	4.95 ± 1.33
12.0	6.59 ± 8.88	18.67 ± 11.18	25.26 ± 20.1
24.0	7.94 ± 1.37	30.00 ± 2.85	37.94 ± 4.22
36.0	3.51 ± 1.37	12.25 ± 4.87	15.76 ± 6.24
48.0	1.67 ± 0.93	3.75 ± 1.14	5.41 ± 2.07
Total %	24.7 ± 2.67	64.67 ± 5.22	89.32 ± 7.91
Low Dose Group (2.8 mg/kg):			
6.0	9.17 ± 5.66	---	9.17 ± 5.66
12.0	11.08 ± 8.30	18.52 ± 17.57	29.60 ± 25.9
24.0	3.25 ± 1.54	18.98 ± 5.43	22.23 ± 6.97
36.0	1.13 ± 1.17	5.65 ± 0.00	6.78 ± 1.17
48.0	0.80 ± 1.42	0.31 ± 0.00	1.11 ± 1.42
Total %	25.43 ± 2.67	43.46 ± 3.48	68.89 ± 4.57

*$\bar{X} \pm SD$ (n=5)

TABLE 2

μg Co(II) IN EXCRETA VS. TIME FOLLOWING ORAL ADMINISTRATION OF COBALT NAPHTHENATE: DISPOSITION STUDY

TIME (HR)	URINE*	FECES*	TOTAL*
High Dose Group (280 mg/kg):			
6.0	396.3 ± 106.3	---	396.3 ± 106.3
12.0	527.3 ± 70.67	1494.1 ± 894.7	2021.5 ± 965.3
24.0	635.7 ± 109.4	2401.1 ± 227.8	3036.8 ± 337.3
36.0	280.9 ± 109.5	980.4 ± 390.0	1261.2 ± 499.4
48.0	133.3 ± 74.26	299.8 ± 91.05	433.0 ± 165.3
Low Dose Group (2.8 mg/kg):			
6.0	7.02 ± 4.33	---	7.02 ± 4.33
12.0	8.47 ± 6.35	11.1 ± 13.4	19.58 ± 19.8
24.0	2.48 ± 1.18	11.5 ± 4.15	13.94 ± 5.33
36.0	0.87 ± 0.90	4.32 ± 0.00	5.18 ± 0.90
48.0	0.61 ± 1.09	0.24 ± 0.00	0.85 ± 1.09

*$\bar{x}$±SD (n=5)

TABLE 3

PERCENT OF DOSE OF Co(II) IN TISSUES 48 HR FOLLOWING ORAL ADMINISTRATION OF COBALT NAPHTHENATE: DISPOSITION STUDY

TISSUES	LOW DOSE: 2.8 mg/kg*	HIGH DOSE: 280 mg/kg*
Blood	1.990 ± 2.130	0.026 ± 0.021
Heart	0.165 ± 0.173	0.005 ± 0.002
Liver	2.250 ± 1.671	0.242 ± 0.096
Kidney	0.845 ± 0.731	0.033 ± 0.008
Testes	0.703 ± 0.769	0.007 ± 0.001
Lungs	0.208 ± 0.203	0.003 ± 0.001
Sm.Int.	0.624 ± 0.388	0.034 ± 0.014
Lg.Int.	0.443 ± 0.292	0.053 ± 0.022
Stomach	0.237 ± 0.201	0.008 ± 0.002
Sm.Int.C.	2.865 ± 0.485	0.057 ± 0.035
Lg.Int.C.	9.759 ± 3.680	0.848 ± 0.313
Stom. C.	1.208 ± 0.362	0.009 ± 0.004
Total %	21.29 ± 4.973	1.325 ± 0.231

*$\bar{x}$±SD (n=5)

TABLE 4

UPTAKE OF Co(II) BY TISSUES AT 48hr AFTER THE ORAL ADMINISTRATION OF COBALT NAPHTHENATE: DISPOSITION STUDY

TISSUES	Control*	2.8 mg/kg*	280 mg/kg*
Blood	0.040 ± 0.010[a]	0.071 ± 0.042[b]	0.173 ± 0.094[a,b]
Heart	0.033 ± 0.167[a]	0.126 ± 0.132[b]	0.368 ± 0.181[a.b]
Liver	0.553 ± 0.167[a]	1.719 ± 1.276[b]	19.37 ± 7.668[a,b]
Kidney	0.242 ± 0.052[a]	0.646 ± 0.559[b]	2.617 ± 0.666[a,b]
Testes	0.077 ± 0.052[a]	0.538 ± 0.588[b]	0.553 ± 0.112[a,b]
Lungs	0.191 ± 0.313	0.159 ± 0.155	0.229 ± 0.088
Sm.Int.	0.409 ± 0.317[a]	0.477 ± 0.297[b]	2.741 ± 1.143[a,b]
Lg.Int.	0.369 ± 0.210[a]	0.339 ± 0.224[b]	4.279 ± 1.777[a,b]
Stomach	0.083 ± 0.046[a]	0.181 ± 0.154[b]	0.609 ± 0.177[a,b]
Sm.Int.C.	1.351 ± 0.587[a]	2.191 ± 0.371[b]	4.566 ± 2.817[a,b]
Lg.Int.C.	5.783 ± 2.592[a]	7.464 ± 2.816[b]	67.85 ± 25.02[a,b]
Stom. C.	0.478 ± 0.284	0.924 ± 0.277	0.691 ± 0.299

*$\bar{x}$±SD (n=5)

*Data analyzed using an ANOVA and Duncan's multiple range test. Values sharing a common superscript are statistically significant from each other ($p \leq 0.05$).

TABLE 5

PERCENT OF DOSE OF Co(II) IN EXCRETA VS. TIME FOLLOWING ORAL ADMINISTRATION OF COBALT NAPHTHENATE: ABSORPTION STUDY

TIME (HR)	URINE*	FECES*	TOTAL*
High Dose Group (280 mg/kg):			
8.0	5.60 ± 0.81	9.89 ± 4.04	15.49 ± 4.85
12.0	14.20 ± 1.88	25.82 ± 5.16	40.02 ± 7.04
18.0	3.18 ± 0.75	20.76 ± 4.11	23.94 ± 4.86
24.0	2.63 ± 0.14	11.30 ± 0.93	13.93 ± 1.07
36.0	0.72 ± 0.37	5.37 ± 1.96	6.09 ± 2.33
Total %	26.33 ± 5.77	73.14 ± 3.46	99.47 ± 7.41
Low Dose Group (2.8 mg/kg):			
8.0	8.37 ± 1.61	5.19 ± 5.56	13.56 ± 7.17
12.0	16.76 ± 3.15	24.28 ± 6.69	41.04 ± 9.84
18.0	1.12 ± 0.11	9.94 ± 0.25	11.06 ± 0.36
24.0	3.87 ± 2.31	2.59 ± 0.50	6.46 ± 2.81
36.0	1.66 ± 0.00	nd**	1.66 ± 0.08
Total %	31.78 ± 1.99	42.00 ± 8.14	73.78 ± 5.70

*$\bar{x}$±SD (n=3)

**nd=not detected above background

TABLE 6

μg Co(II) IN EXCRETA VS. TIME FOLLOWING ORAL ADMINISTRATION OF COBALT NAPHTHENATE: ABSORPTION STUDY

TIME (HR)	URINE*	FECES*	TOTAL*
High Dose Group (280 mk/kg):			
8.0	380.8 ± 55.26	672.6 ± 274.4	1053.5 ± 329.7
12.0	829.7 ± 74.81	1506.5 ± 250.8	2336.2 ± 325.6
18.0	175.5 ± 41.16	1145.5 ± 226.9	1321.0 ± 268.1
24.0	156.1 ± 1.45	1264.6 ± 21.74	1420.7 ± 23.19
36.0	41.1 ± 21.3	305.3 ± 111.3	346.4 ± 132.6
Low Dose Group (2.8 mg/kg):			
8.0	8.39 ± 1.62	5.20 ± 5.57	13.60 ± 7.19
12.0	16.90 ± 3.56	24.24 ± 5.87	41.14 ± 9.43
18.0	1.08 ± 0.11	9.60 ± 0.24	10.68 ± 0.35
24.0	4.02 ± 2.36	2.71 ± 0.49	6.72 ± 2.85
36.0	1.74 ± 0.00	nd**	1.74 ± 0.00

*$\bar{X}$±SD (n=5)

**nd=not detected above background

TABLE 7

PERCENTAGE OF DOSE OF Co(II) IN TISSUES FOLLOWING ORAL ADMINISTRATION OF COBALT NAPHTHENATE: ABSORPTION STUDY: 280 mg/kg*

TISSUE	2 HOUR	4 HOUR	8 HOUR	12 HOUR	18 HOUR	24 HOUR	36 HOUR
Heart	0.01±0.00	0.01±0.00	0.01±0.01	0.01±0.00	0.01±0.00	0.01±0.00	0.01±0.00
Liver	0.27±0.03	0.30±0.06	0.57±0.19	0.31±0.18	0.26±0.14	0.23±0.13	0.18±0.08
Kidney	0.03±0.00	0.03±0.00	0.05±0.01	0.03±0.01	0.03±0.00	0.03±0.01	0.02±0.01
Spleen	0.01±0.00	0.01±0.00	0.01±0.00	0.01±0.00	0.01±0.00	0.01±0.01	0.01±0.00
Testes	0.01±0.00	0.01±0.00	0.01±0.00	0.01±0.00	0.01±0.00	0.01±0.00	0.01±0.00
Sm.Int.	0.59±0.27	0.77±0.16	0.79±0.75	0.60±0.84	0.15±0.05	0.03±0.03	0.03±0.01
Lg.Int.	0.04±0.01	0.15±0.02	0.45±0.23	0.50±0.26	0.17±0.03	0.07±0.03	0.03±0.00
Stomach	0.45±0.24	0.15±0.03	0.08±0.01	0.02±0.02	0.10±0.01	0.01±0.00	0.01±0.00
Sm.Int.C.	17.4±2.84	9.84±2.87	6.46±.936	6.25±9.22	0.81±0.37	0.32±0.10	0.11±0.06
Lg.Int.C.	3.51±2.06	29.5±2.18	43.0±6.87	24.5±8.75	16.7±4.75	11.2±3.85	0.84±0.16
Stom.C.	62.3±17.4	30.1±3.93	12.0±2.43	1.35±0.48	0.04±0.01	0.01±0.00	0.06±0.03

*$\bar{x}$±SD (n=3)

TABLE 8

PERCENTAGE OF DOSE OF Co(II) IN TISSUES FOLLOWING ORAL ADMINISTRATION OF COBALT NAPHTHENATE: ABSORPTION STUDY: 2.8 mg/kg*

TISSUE	2 HOUR	4 HOUR	8 HOUR	12 HOUR	18 HOUR	24 HOUR	36 HOUR
Heart	0.02±0.00	0.02±0.01	0.03±0.00	0.02±0.01	0.02±0.02	0.02±0.01	0.02±0.01
Liver	2.52±1.44	1.37±0.18	1.51±0.45	1.00±0.08	0.89±0.37	0.73±0.36	0.67±0.19
Kidney	0.10±0.13	0.37±0.11	0.43±0.08	0.32±0.03	0.25±0.06	0.38±0.06	0.20±0.04
Spleen	0.01±0.01	0.01±0.01	nd**	nd**	0.01±0.01	0.02±0.02	nd**
Testes	0.01±0.01	0.03±0.03	nd**	nd**	0.07±0.09	0.04±0.04	nd**

*$\bar{x}$±SD (n=3)

**nd=not detected above background

TABLE 9

TOTAL μg Co(II) IN TISSUES FOLLOWING ORAL ADMINISTRATION OF COBALT NAPHTHENATE: ABSORPTION STUDY: 280 mg/kg*

TISSUE	2 HOUR	4 HOUR	8 HOUR	12 HOUR	18 HOUR	24 HOUR	36 HOUR
Heart	0.14±0.05	0.14±0.04	0.28±0.08	0.14±0.05	0.13±0.03	0.15±0.07	0.14±0.04
Liver	15.9±1.70	19.3±3.68	38.3±12.7	18.8±10.6	10.7±4.63	14.1±7.91	10.2±4.80
Kidney	1.70±0.26	2.16±0.26	3.45±0.35	2.01±0.65	1.72±0.20	1.61±0.47	1.36±0.29
Spleen	0.07±0.01	0.09±0.04	0.17±0.05	0.09±0.03	0.08±0.00	0.39±0.61	0.09±0.00
Testes	0.30±0.05	0.32±0.09	0.65±0.21	0.40±0.26	0.42±0.14	0.24±0.24	0.40±0.16
Sm.Int.	34.9±16.3	48.9±10.3	53.5±26.8	36.5±50.8	8.20±2.81	1.90±1.78	1.94±.285
Lg.Int.	2.44±0.72	11.0±1.29	26.3±8.88	30.5±15.7	9.23±1.81	4.08±1.77	1.60±0.09
Stomach	27.0±14.3	9.55±1.80	5.57±0.85	1.40±1.44	0.64±0.32	0.37±0.10	0.35±0.10
Sm.Int.C.	1033±168.7	627.3±182.6	439.1±63.7	379.3±557.3	44.7±20.4	19.9±6.47	6.28±3.34
Lg.Int.C.	208.7±123	1878±138.7	2923±467.1	1489±531.2	920.9±261.8	691.7±238.7	47.8±9.02
Stom.C.	3707±1037	1971±250.6	812.8±165.1	81.7±29.4	2.10±.687	.535±.156	3.19±1.63

*$\bar{x}$±SD (n=3)

TABLE 10

TOTAL μg Co(II) IN TISSUES FOLLOWING ORAL ADMINISTRATION OF COBALT NAPHTHENATE: ABSORPTION STUDY: 2.8 mg/kg*

TISSUE	2 HOUR	4 HOUR	8 HOUR	12 HOUR	18 HOUR	24 HOUR	36 HOUR
Heart	0.02±0.01	0.02±0.01	0.03±0.00	0.02±0.01	0.02±0.02	0.02±0.01	0.02±0.01
Liver	2.53±1.44	1.39±0.18	1.52±0.45	0.97±0.08	0.86±0.36	1.79±0.37	0.70±0.20
Kidney	0.10±0.13	0.38±0.11	0.43±0.08	0.31±0.03	0.24±0.06	0.40±0.06	0.21±0.04
Spleen	0.01±0.01	0.01±0.02	nd**	nd**	0.01±0.01	0.02±0.02	nd**
Testes	.011±.012	.026±.035	0.01±0.10	0.01±0.01	0.07±0.09	0.04±0.04	nd**
Blood	2.11±0.34	1.53±0.19	1.44±.097	1.69±.180	2.04±.096	2.25±1.05	0.82±0.16

*$\bar{X}$±SD (n=3)

**nd=not detected above background

TABLE 11

TISSUE TO BLOOD RATIOS OF Co(II) FOLLOWING ORAL ADMINISTRATION OF COBALT NAPHTHENATE: ABSORPTION STUDY: 2.8 mk/kg*

TISSUE	2 HOUR	4 HOUR	8 HOUR	12 HOUR	18 HOUR	24 HOUR	36 HOUR
Heart	0.01±0.01	0.01±.006	0.02±0.00	0.01±0.01	0.01±0.01	0.01±0.00	0.03±0.02
Liver	1.20±0.69	0.91±0.12	1.06±0.31	0.57±0.05	0.42±0.18	0.73±0.17	0.86±0.24
Kidney	0.05±0.06	0.25±0.07	0.30±0.05	0.18±0.02	0.12±0.03	0.18±0.03	0.26±0.05
Spleen	nd**	0.01±0.01	nd**	nd**	nd**	0.01±0.01	nd**
Testes	0.01±0.01	0.02±0.02	nd**	nd**	0.03±0.05	0.02±0.02	nd**
Blood	1.0	1.0	1.0	1.0	1.0	1.0	1.0

*$\bar{x}$±SD (n=3)

**nd=not detected above background

TABLE 12

TISSUE TO BLOOD RATIOS OF Co(II) FOLLOWING ORAL ADMINISTRATION OF COBALT NAPHTHENATE: ABSORPTION STUDY: 280 mg/kg*

TISSUE	2 HOUR	4 HOUR	8 HOUR	12 HOUR	18 HOUR	24 HOUR	36 HOUR
Heart	0.03±0.01	0.02±0.01	0.05±0.01	0.04±0.02	0.06±0.01	0.07±0.03	0.12±0.03
Liver	3.40±.362	2.79±.532	7.19±2.38	6.01±3.40	5.11±2.20	5.99±3.36	8.37±3.95
Kidney	0.36±0.06	0.31±0.04	0.65±0.07	0.64±0.02	0.82±0.10	0.69±0.20	1.12±0.24
Spleen	0.06±.002	0.01±0.01	0.03±0.01	0.03±0.01	0.04±0.00	0.16±0.26	0.08±0.00
Testes	0.06±0.01	0.05±0.01	0.12±0.04	0.13±0.08	0.20±0.07	0.10±0.10	0.32±0.13
Sm.Int.	7.46±3.47	7.06±1.49	10.1±5.04	11.7±16.3	3.90±1.34	0.81±0.76	1.60±0.24
Lg.Int.	0.52±0.15	1.59±0.19	4.93±1.67	9.75±5.02	4.39±0.86	1.73±0.75	1.32±0.08
Stomach	5.77±3.04	1.38±0.26	1.05±0.16	0.45±0.46	0.30±0.15	0.16±0.04	0.29±0.08
Blood	1.0	1.0	1.0	1.0	1.0	1.0	1.0

*$\bar{x}$±SD (n=3)

TABLE 13

PERCENT OF DOSE OF Co(II) IN BLOOD FOLLOWING ORAL ADMINISTRATION OF COBALT NAPHTHENATE: ABSORPTION STUDY

TIME (HR)	LOW DOSE: 2.8 mg/kg*	INTERMEDIATE DOSE: 28.0 mg/kg*	HIGH DOSE: 280 mg/kg*
0.5	1.100 ± 0.000		0.049 ± 0.015
1.0		0.100 ± 0.018	
2.0	1.561 ± 0.000	0.103 ± 0.024	0.070 ± 0.001
4.0	0.976 ± 0.000		0.100 ± 0.012
6.5		0.119 ± 0.021	
8.0	0.894 ± 0.000	0.142 ± 0.064	0.070 ± 0.023
12.0	1.184 ± 0.000	0.129 ± 0.017	0.043 ± 0.011
18.0	1.551 ± 0.000		0.028 ± 0.000
24.0	1.657 ± 0.680	0.035 ± 0.016	0.029 ± 0.000
36.0	0.267 ± 0.000		0.012 ± 0.000
48.0		0.007 ± 0.011	

*$\bar{X}$±SD (n=3)

TABLE 14

PERCENT OF DOSE OF Co(II) IN BLOOD FOLLOWING ORAL ADMINISTRATION OF COBALT NAPHTHENATE: ABSORPTION STUDY

TIME (HR)	LOW DOSE: 2.8 mg/kg*	INTERMEDIATE DOSE: 28.0 mg/kg*	HIGH DOSE: 280 mg/kg*
0.5	1.100 ± 0.000		0.049 ± 0.015
1.0		0.100 ± 0.018	
2.0	1.561 ± 0.000	0.103 ± 0.024	0.070 ± 0.001
4.0	0.976 ± 0.000		0.100 ± 0.012
6.5		0.119 ± 0.021	
8.0	0.894 ± 0.000	0.142 ± 0.064	0.070 ± 0.023
12.0	1.184 ± 0.000	0.129 ± 0.017	0.043 ± 0.011
18.0	1.551 ± 0.000		0.028 ± 0.000
24.0	1.657 ± 0.680	0.035 ± 0.016	0.029 ± 0.000
36.0	0.267 ± 0.000		0.012 ± 0.000
48.0		0.007 ± 0.011	

*$\bar{X}$±SD (n=3)

TABLE 15

μg Co(II) IN BLOOD FOLLOWING ORAL ADMINISTRATION OF COBALT NAPHTHENATE: ABSORPTION STUDY

TIME (HR)	LOW DOSE: 2.8 mg/kg*	INTERMEDIATE DOSE: 28.0 mg/kg*	HIGH DOSE: 280 mg/kg*
0.5	1.484 ± 0.077		3.899 ± 1.376
1.0		2.790 ± 0.489	
2.0	2.105 ± 0.335	2.869 ± 0.671	4.687 ± 0.426
4.0	1.532 ± 0.192		6.923 ± 1.135
6.5		3.314 ± 0.570	
8.0	1.436 ± 0.097	3.930 ± 1.787	5.325 ± 1.874
12.0	1.691 ± 0.180	3.582 ± 0.462	3.125 ± 1.032
18.0	2.037 ± 0.096		2.103 ± 0.351
24.0	2.254 ± 1.048	0.966 ± 0.456	2.353 ± 1.021
36.0	0.819 ± 0.156		1.214 ± 0.294
48.0		0.182 ± 0.315	

*$\bar{x}$±SD (n=3)

TABLE 16

PHARMACOKINETIC PARAMETERS CALCULATED FOR THE ABSORPTION STUDY BLOOD RESULTS

Dose	Time To Peak (hr)	Peak Conc. Co(II) (μg)	$t_{½\alpha}$	$t_{½\beta}$	AUC
2.8 mg/kg	---	---	---	---	---
28 mg/kg	5.78	3.75	4.23	12.5	75.61
280 mg/kg	6.36	6.63	4.06	12.2	107.0