

ADME NTP Study S0176 Methylene bis(thiocyanate)

Sex/Species: male F344 rats.

Vehicles: oral, water:ethanol (7:3)

CASRN 6317-18-6

Radiolabeled with carbon-14 in the methylene carbon (NCS¹⁴CH₂SCN); [¹⁴C]Methylene bis(thiocyanate)

Studies Groups:

- Single 0.2, 1, or 10 mg/kg oral dose of methylene bis(thiocyanate) to rats with sacrifice 48 hours postdose (n=3 per dose group).
- Single 10 mg/kg oral dose of methylene bis(thiocyanate) to rats with sacrifice 0.5, 1.0, 2.0, 4.0, 6.0, 12.0, and 24.0 hours postdose (n=3 per time point).

Virtually no radioactivity was found in the traps designed to collect volatile organics so the radioactivity of the expired air is that of ¹⁴CO₂. The stomach (Stom.), small intestine (Sm Int), and large intestine (Lg Int) contents (Cont) were included in the excreta. "S. Cut." fat was not specified.

Toxicokinetics:

The blood methylene bis(thiocyanate) [¹⁴C]-equivalents concentration versus time data exhibited apparent first order elimination of total radioactivity from the blood. Total radioactivity includes parent and any metabolites bearing the methylene carbon. Values for total radioactivity were fit to an exponential function of the form $Ae^{-\alpha t} + Be^{-\beta t}$ using the nonlin curve fitting program.

The background level of plasma thiocyanate was found to be 2.05 ug/ml \pm 0.33 (n=7) in control animals. Whole blood cyanide in control animals can be estimated at 98 ng/mL by back extrapolation of the calibration curve (14.4% relative error). Table 2 shows blood levels of cyanide and thiocyanate over 24 hours. Blood cyanide and thiocyanate values are expressed as the mean difference between observed and control values.

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TABLE 1

48 hr. Cumulative Totals as Percent of Dose
CH₂(SCN)₂ Summary Sheet

TISSUE	10 mg/kg	1 mg/kg	0.2 mg/kg
Blood	0.64 ± 0.28	0.29 ± 0.006	0.24 ± 0.03
Brain	0.02 ± 0.006	0.02 ± 0.006	0.013 ± 0.006
Kidney	0.24 ± 0.10	0.15 ± 0.03	0.11 ± 0.012
Lg Int	0.14 ± 0.05	0.08 ± 0.006	0.08 ± 0.03
Liver	1.09 ± 0.29	0.69 ± 0.08	0.50 ± 0.14
Lung	0.05 ± 0.02	0.03 ± 0.01	0.03 ± 0.006
Muscle	1.30 ± 0.19	1.15 ± 0.14	0.73 ± 0.10
Skin	0.56 ± 0.04	0.46 ± 0.13	0.53 ± 0.30
Sm Int	0.30 ± 0.11	0.17 ± 0.04	0.17 ± 0.06
Stomach	1.96 ± 1.18	0.16 ± 0.06	0.13 ± 0.04
Testes	0.06 ± 0.03	0.04 ± 0.01	0.03 ± 0.006
Fat (\bar{x})	0.12 ± 0.05	0.08 ± 0.03	0.03 ± 0.02
-Testicular	0.09 ± 0.02	0.06 ± 0.03	0.013 ± 0.02
-S. Cut.	0.15 ± 0.11	0.12 ± 0.06	0.06 ± 0.02
Tissue Total	6.48 ± 0.91	3.31 ± 0.31	2.57 ± 0.56
Excreta			
Feces	14.14 ± 2.44	26.50 ± 1.78	28.08 ± 2.77
Stom. Cont	0.05 ± 0.02	0.05 ± 0.0	0.02 ± 0.015
Sm Int Cont	0.19 ± 0.10	0.10 ± 0.03	0.07 ± 0.04
Lg Int Cont	1.27 ± 1.26	0.24 ± 0.09	0.39 ± 0.11
Feces & Cont	15.63 ± 1.62	26.86 ± 1.87	28.55 ± 2.82
Urine	62.72 ± 8.60	52.18 ± 5.28	58.85 ± 1.51
Expired	10.52 ± 1.39	9.94 ± 0.49	8.99 ± 0.58
Excreta total	88.91 ± 9.30	88.98 ± 3.97	96.39 ± 2.12
Total Recovery	95.39 ± 8.87	92.29 ± 4.05	98.96 ± 2.40

Table 2. Summary of Results

Time (hours)	14C equivalents (% of dose)	Mean increase in blood CN ⁻ (ng/ml)*	Mean increase in plasma SCN ⁻ (ug/ml)*
0.5	15.50 ± 5.67	198.2 ± 26.9	1.71 ± 0.68
1.0	11.46 ± 1.27	64.9 ± 5.5	0.51 ± 0.27
2.0	10.72 ± 2.22	-8.8 ± 11.8	9.66 ± 3.14
4.0	8.94 ± 2.37	27.1 ± 38.8	3.03 ± 0.77
6.0	5.99 ± 0.51		3.72 ± 0.53
12.0	4.20 ± 0.78		1.05 ± 0.14
24.0	1.17 ± 0.26		0.78 ± 0.01

*-Values for control blood or plasma have been subtracted.

Table 3. Derived Constants

A = 48.757 α = 5.182 α half life = 0.13 ± .28 hr
 B = 12.409 β = 0.098 β half life = 7.06 ± .45 hr
 correlation r = 0.995