

## ADME NTP Study K61654 Nickel subsulfide

The contract laboratory used the chemical formula,  $^{63}\text{Ni}_3\text{S}_2$ , as an abbreviation for the test article.

Sex/Species: adult male F344/N rats.

Vehicles: oral, RPMI culture media; inhalation, air

CASRN 12035-72-2

Radiolabeled with nickel-63;  $^{63}\text{Ni}_3\text{S}_2$ . Only radiolabeled  $\text{Ni}_3\text{S}_2$  was used for animal exposures.

### Nickel subsulfide Groups in Studies Performed:

- Group A – Nose-only inhalation of  $5.7 \text{ mg/m}^3$   $^{63}\text{Ni}_3\text{S}_2$  exposure for 120 minutes in rats with sacrifice immediately after exposure. (Tables 1 and 2; n= 4)
- Group B – Nose-only inhalation of  $5.7 \text{ mg/m}^3$   $^{63}\text{Ni}_3\text{S}_2$  exposure for 120 minutes. Excretion monitored for 14 days after exposure followed by removal from metabolism cages and sacrifice on day 32 after exposure. (Table 3; n= 3)
- Group C – Nose-only inhalation of  $5.7 \text{ mg/m}^3$   $^{63}\text{Ni}_3\text{S}_2$  exposure for 120 minutes with serial sacrifice at 4, 8, and 24 hours and at 2, 5, 8, 16, and 32 days after exposure. (Table 4; n = 3 per timepoint)
- Group D – Single oral gavage administration of  $250 \text{ ug}$   $^{63}\text{Ni}_3\text{S}_2$  per rat with sacrifice at 96 hours postdose. (Table 5; n = 5)

The theoretical amount of aerosol inhaled by each rat was calculated based on the minute volume (calculated from respiratory frequency and tidal volumes from each animal using individual plethysmographic units), aerosol concentration, and the exposure duration. The actual amount inhaled was determined by summing the amount of Ni present in the respiratory tract and nonrespiratory tract tissues of each of the four rats upon their sacrifice immediately after the end of exposure.

Group B rats were returned to metabolism cages on day 29 to determine if Ni was still being excreted but no activity was found in these later samples. Tissues from these rats sacrificed at 32 days also contained no  $^{63}\text{Ni}$  activity.

Respiratory tract lung clearance data were fit with single- and two-component, negative-exponential functions. The single-component negative exponential best fit equation was  $F(t) = Ae^{(-Bt)}$  where t is days after the end of exposure, A is the percentage of the initial body burden, and B is the first order rate constant in  $\text{days}^{-1}$ . The calculated half-time for clearance of Ni from the lung was 4.6 days (calculated using  $T_{1/2} = \ln 2/B$  where B is the first order rate constant).

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Table 1

Minute Volumes of Rats Before and During Exposure to  $^{63}\text{Ni}_3\text{S}_2$   
 Toxicokinetics of  $^{63}\text{Ni}$  After Inhalation of  $^{63}\text{Ni}_3\text{S}_2$

Animal Number	Baseline Minute Volume mL/min (n) <sup>a</sup>	Exposure Minute Volume mL/min (n) <sup>a</sup>	Mean L Inhaled
A001	288 ± 14.4 (10)	270 ± 11.6 (14)	32.4
A002	310 ± 23.7 (8)	311 ± 14.5 (14)	37.3
A003	315 ± 26.3 (4)	318 ± 15.9 (5)	38.2
A004	316 ± 18.6 (5)	236 ± 6.75 (11)	28.3
Mean ± SEM	307 ± 6.5	284 ± 19	34.0 ± 2.3

<sup>a</sup>Results represent the mean ± SEM of the number of values given in parentheses

Table 2

Total and Regional Deposition of Ni in Rats Inhaling  $^{63}\text{Ni}_3\text{S}_2$   
 Toxicokinetics of  $^{63}\text{Ni}$  After Inhalation of  $^{63}\text{Ni}_3\text{S}_2$

Parameter	Value Mean $\pm$ SEM (n = 4)
$\mu\text{g Ni Inhaled}^{\text{a}}$	142 $\pm$ 9.52
$\mu\text{g Ni Deposited}^{\text{b}}$	17.97 $\pm$ 0.98
Fraction of Inhaled Ni that was deposited	0.13 $\pm$ 0.01
<b>Deposition in the Upper Respiratory Tract<sup>b</sup></b>	
$\mu\text{g Ni Deposited}^{\text{c}}$	11.9 $\pm$ 1.02
Fraction of that inhaled	0.08 $\pm$ 0.01
Fraction of that deposited	0.66 $\pm$ 0.03
<b>Deposition in the Lower Respiratory Tract<sup>b</sup></b>	
$\mu\text{g Ni Deposited}^{\text{d}}$	6.09 $\pm$ 0.55
Fraction of that inhaled	0.04 $\pm$ 0.002
Fraction of that deposited	0.34 $\pm$ 0.03

<sup>a</sup>Individual animal data are presented in Appendix C, Table C-1 and C-2.

<sup>b</sup>Individual animal data are given in Appendix C, Table C-3.

<sup>c</sup>Sum of the  $\mu\text{g Ni}$  present in the skull, nasal turbinates, larynx/trachea, and Gi tract (plus contents) of Group A rats.

<sup>d</sup>Sum of  $\mu\text{g Ni}$  present in the blood, soft tissue, lungs, urine, and depelleted carcass of Group A rats.

Table 3

Excretion of Ni in Urine and Feces of Group B Rats Exposed by Inhalation to Nickel Subsulfide<sup>a</sup>  
 Toxicokinetics of <sup>63</sup>Ni After Inhalation of Nickel Subsulfide

Days Post Exposure	µg Ni in Feces	µg Ni in Urine	Total µg Ni	Fraction in Feces	Fraction in Urine
0.17	0.07 ± 0.07	0.14 ± 0.03	0.22	0.34	0.66
0.33	0.19 ± 0.19	0.21 ± 0.03	0.40	0.48	0.52
1.0	4.94 ± 0.79	0.70 ± 0.08	5.64	0.87	0.12
2.0	29.4 ± 10.2	1.09 ± 0.20	30.5	0.96	0.04
3.0	2.96 ± 0.44	0.92 ± 0.06	3.89	0.76	0.24
4.0	1.00 ± 0.30	0.82 ± 0.05	1.82	0.55	0.45
5.0	0.46 ± 0.24	0.79 ± 0.04	1.25	0.37	0.63
6.0	0.19 ± 0.19	0.72 ± 0.09	0.92	0.21	0.79
7.0	0.07 ± 0.07	0.74 ± 0.02	0.81	0.08	0.92
8.0	0.10 ± 0.05	0.56 ± 0.04	0.66	0.15	0.85
9.0	ND <sup>b</sup>	0.44 ± 0.02	0.44	0	1.0
10	ND	0.44 ± 0.02	0.44	0	1.0
11	0.04 ± 0.04	0.28 ± 0.02	0.32	0.12	0.88
12	0.06 ± 0.03	0.20 ± 0.03	0.26	0.24	0.75
13	ND	0.15 ± 0.01	0.15	0	1.0
14	0.03 ± 0.03	0.14 ± 0.01	0.17	0.18	0.82

<sup>a</sup>Results represent the mean ± SEM of three values. Individual animal data are presented in Appendix E, Tables E-1 and E-2.

<sup>b</sup>ND - no <sup>63</sup>Ni detected in the samples.

Table 4

Percentages of Deposited  $^{63}\text{Ni}$  Present in Tissues After Exposure of Rats to  $^{63}\text{Ni}_3\text{S}_2$   
 Toxicokinetics of  $^{63}\text{Ni}$  After Inhalation of  $^{63}\text{Ni}_3\text{S}_2$

Days Post Exposure	% Ni Deposited (mean $\pm$ SEM) <sup>a</sup>										
	Lungs	Skull	Turbinates	Trachea/Larynx	LALN	Kidneys	Carcass	Blood <sup>b</sup>	Bladder	Liver	GI Tract
0.17	23.5 $\pm$ 0.89	0.23 $\pm$ 0.06	0.50 $\pm$ 0.06	0.14 $\pm$ 0.11	ND <sup>c</sup>	0.03 $\pm$ 0.00	1.35 $\pm$ 0.68	0.008 $\pm$ 0.0003	ND	ND	74.2 $\pm$ 8.87
0.33	21.5 $\pm$ 1.28	0.14 $\pm$ 0.05	0.36 $\pm$ 0.02	0.11 $\pm$ 0.02	ND	0.06 $\pm$ 0.02	2.20 $\pm$ 2.20	0.004 $\pm$ 0.002	ND	ND	67.9 $\pm$ 9.61
1.0	20.4 $\pm$ 1.94	0.12 $\pm$ 0.01	0.19 $\pm$ 0.03	0.04 $\pm$ 0.00	ND	0.03 $\pm$ 0.01	3.39 $\pm$ 2.19	0.004 $\pm$ 0.004	ND	ND	13.3 $\pm$ 4.29
2.0	16.3 $\pm$ 1.19	0.07 $\pm$ 0.04	0.12 $\pm$ 0.01	0.01 $\pm$ 0.01	0.03 $\pm$ 0.01	0.03 $\pm$ 0.00	ND	0.004 $\pm$ 0.004	ND	ND	1.37 $\pm$ 0.28
5.0	12.0 $\pm$ 1.14	0.11 $\pm$ 0.11	0.03 $\pm$ 0.02	0.00 $\pm$ 0.00	0.06 $\pm$ 0.06	0.12 $\pm$ 0.01	ND	0.002 $\pm$ 0.002	ND	ND	1.34 $\pm$ 0.84
8.0	6.65 $\pm$ 0.89	0.04 $\pm$ 0.04	0.00 $\pm$ 0.00	0.01 $\pm$ 0.01	0.02 $\pm$ 0.02	0.13 $\pm$ 0.01	ND	ND	ND	ND	0.20 $\pm$ 0.20
16	2.08 $\pm$ 0.20	0.10 $\pm$ 0.03	0.33 $\pm$ 0.33	ND	ND	0.05 $\pm$ 0.01	ND	ND	0.003 $\pm$ 0.003	ND	0.17 $\pm$ 0.17
32	ND	ND	ND	— <sup>d</sup>	—	ND	—	—	—	ND	ND

<sup>a</sup>Results represent the mean  $\pm$  SEM of three values. Initial total body burden was based on the mean total amount of Ni found in all tissues from rats sacrificed 4 hours following the  $^{63}\text{Ni}_3\text{S}_2$  exposure.

<sup>b</sup>These data are represented as  $(\mu\text{g Ni/mL blood})/(\text{initial lung burden}) \times 100$ .

<sup>c</sup>ND - no  $^{63}\text{Ni}$  detected in sample.

<sup>d</sup>Tissue not analyzed because no activity was detected at the previous sacrifice period.

Table 5

Gastrointestinal Uptake of Nickel Subulfide Administered to Rats by Oral Gavage<sup>a</sup>  
Toxicokinetics of <sup>63</sup>Ni After Inhalation of Nickel Subulfide

Days Post Gavage	µg Ni in Feces	µg Ni in Urine	Total µg Ni	Fraction in Feces	Fraction in Urine
0.17	ND	0.04 ± 0.003	0.04	0	1.0
0.33	5.77 ± 3.95	0.03 ± 0.009	5.80	0.995	0.005
0.50	3.99 ± 1.62	0.01 ± 0.002	4.00	0.996	0.004
1.0	26.1 ± 6.01	0.01 ± 0.03	26.1	1.0	0
2.0	4.16 ± 0.82	0.01 ± 0.004	4.17	0.997	0.003
3.0	0.15 ± 0.08	ND <sup>b</sup>	0.14	1.0	0
4.0	0.02 ± 0.02	ND	0.02	1.0	0
Total µg Ni	40.2	0.11	40.3		

No Ni was detected in lung, GI tract, or carcass of rats sacrificed 4 days after gavage with Ni<sub>3</sub>S<sub>2</sub>.

<sup>a</sup>Results represent the mean ± SEM of five values. See Appendix F, Tables F-1 and F-2 for individual animal data.

<sup>b</sup>ND - no <sup>63</sup>Ni detected in the samples.