ADME NTP Study K00862 Nickel (II) oxide

The contract laboratory used the chemical formula, ^{63}NiO, as an abbreviation for the test article.
Sex/Species: adult male F344/N rats.
Vehicles: oral, corn oil; inhalation, air with remaining aerosol of 3.4 mg/L (2300 ppm) ethanol.

CASRN 1313-99-1
Radiolabeled with nickel-63; ^{63}NiO. Only radiolabeled NiO was used for animal exposures.

Nickel (II) oxide Groups in Studies Performed:

- Group A – Nose-only inhalation of 9.9 mg/m^3 ^{63}NiO exposure for 70 minutes sacrificed immediately after exposure. (Tables 1 and 2; n= 4)

- Group B – Nose-only inhalation of 9.9 mg/m^3 ^{63}NiO exposure for 70 minutes. Excretion monitored for 14 days after exposure followed by removal from metabolism cages and transfer to polycarbonate shoe-box cages with sacrifice at 180 days after exposure. (Table 3; n= 3)

- Group C – Nose-only inhalation of 9.9 mg/m^3 ^{63}NiO exposure for 70 minutes with serial sacrifice at 2 hours (h), 6 h, 24 h, and 4, 8, 16, 30, 60, 90, 120, and 180 days after exposure. (Table 4; n = 3 per timepoint)

- Group D – Single oral gavage administration of 250 µg ^{63}NiO per rat with sacrifice 96 hours after exposure. (Table 5; n = 5)

^{63}NiO aerosol was generated from a suspension of particles in 40% ethanol (12 mg ^{63}NiO/mL) using a nebulizer. The mean ethanol concentration in the exposure atmosphere (± SD; n=2) was 3.4 ± 0.2 mg/L (2,300 ± 200 ppm).

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 ^{63}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.

^{63}N activity was detected only in fecal samples. No activity was detected in urine at any time or in the carcass or GI tract. Planned biweekly sampling of Group B animals from 14 days to 180 days was not done because no ^{63}Ni activity was detected in urine in any animals during the first 14 days post exposure.
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 $days^{-1}$.The calculated half-time for clearance of ^{63}NiO from the lung was 120 days (calculated using T½ = 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}NiO[a]
Toxicokinetics of ^{63}Ni After Inhalation of Nickel Oxide

Animal Number	Baseline Minute Volume mL/min	Exposure Minute Volume mL/min	Mean L Inhaled (± SEM)
A001	347 ± 7.62	271 ± 3.98	18.97
A002	289 ± 4.55	266 ± 2.68	18.62
A003	377 ± 3.63	364 ± 2.88	25.48
A004	280 ± 3.61	250 ± 3.20	17.50
MEAN (SEM)	323 (23.3)	288 (25.8)	20.14 (1.81)

[a]Values represent the mean ± SEM of 18 baseline values and 70 values taken during the expossure.

Table 2

Total and Regional Deposition of ^{63}Ni After Exposure of Rats to ^{63}NiO[a]
Toxicokinetics of ^{63}Ni After Inhalation of Nickel Oxide

Parameter	Value (mean ± SEM; n = 4)
μg ^{63}NiO Inhaled[b]	199 ± 18
Total ^{63}NiO Deposited[c]	21.9 ± 6.1
(% of Inhaled)	11.3 ± 3.4
^{63}NiO Deposited in Upper Respiratory Tract[d]	
μg ^{63}NiO Deposited	13.6 ± 6.7
% Inhaled	7.0 ± 3.6
% Total Deposited	53.4 ± 14
^{63}NiO Deposited in Lower Respiratory Tract[e]	
μg ^{63}NiO Deposited	8.3 ± 1.2
% Inhaled	4.3 ± 0.89
% Total Deposited	46.6 ± 14

[a]Data for individual animals are given in Appendix C, Table C-3.
[b]^{63}NiO inhaled is the product of aerosol concentration 9.9 μg NiO/m^3 x minute volume x exposure duration (70 min).
[c]Total ^{63}NiO deposited is the sum of ^{63}NiO detected in the nasal turbinates, skull, trachea/larynx, GI tract (plus contents), lung, and depelted carcass.
[d]Upper respiratory tract deposition includes ^{63}Ni detected in the nasal turbinates, skull, trachea/larynx and GI tract plus contents.
[e]Lower respiratory tract deposition includes ^{63}Ni detected in lungs and depelted carcass.

TABLE 3
CLEARANCE OF 63NIO FROM THE GI TRACTS OF RATS USED TO EVALUATE PATHWAYS OF 63Ni EXCRETION

Individual animal data

SAMPLE TYPE	TIME POINT	B005 (uCi)	B005 ug Ni	B006 (uCi)	B006 ug Ni	B007 (uCi)	B007 ug Ni	MEAN uCi/ TIME PT.
FECAL	4 HOURS	0.0000	0.0000	0.0048	0.1755	0.0059	0.2157	0.0036
FECAL	7 HOURS	0.0050	0.1828					0.0050
FECAL	16 HOURS	0.3657	13.3711	1.3679	50.0146	0.9934	36.3218	0.9090
FECAL	24 HOURS	1.4764	53.9817	0.4791	17.5174	0.9474	34.6399	0.9676
FECAL	48 HOURS	0.7906	28.9068	0.5429	19.8501	0.6860	25.0823	0.6732
FECAL	72 HOURS	0.0712	2.6033	0.0587	2.1463	0.1175	4.2962	0.0825
FECAL	96 HOURS	0.0632	2.3108	0.0155	0.5667	0.0195	0.7130	0.0327
FECAL	5 DAYS	0.0305	1.1152	0.0000	0.0000	0.0122	0.4461	0.0142
FECAL	6 DAYS	0.0091	0.3327	0.0729	2.6654	0.0000	0.0000	0.0273
FECAL	7 DAYS	0.0109	0.3985	0.0121	0.4424	0.0000	0.0000	0.0077
FECAL	8 DAYS	0.0115	0.4205	0.0077	0.2815	0.0000	0.0000	0.0064
FECAL	10 DAYS	0.0355	1.2980	0.0149	0.5448	0.0129	0.4717	0.0211
FECAL	12 DAYS	0.0000	0.0000	0.0000	0.0000	0.0132	0.4826	0.0044
FECAL	13 DAYS	0.0000	0.0000	0.0000	0.0000	0.0124	0.4534	0.0041
FECAL	14 DAYS	0.0100	0.3656	0.0000	0.0000	0.0000	0.0000	0.0033
LUNGS	FINAL	0.0762	2.7861	0.0688	2.5155	0.0582	2.1280	0.0677
TOTALS		2.9558	108	2.6453	96.7203	2.8786	105	2.8266

SAMPLE TYPE	SEM	MEAN ug/ TIME PT.	SEM
FECAL	0.0018	0.1304	0.0662
FECAL		0.1828	
FECAL	0.2924	33.2358	10.6900
FECAL	0.2881	35.3796	10.5328
FECAL	0.0718	24.6130	2.6249
FECAL	0.0179	3.0152	0.6539
FECAL	0.0153	1.1968	0.5586
FECAL	0.0089	0.5204	0.3241
FECAL	0.0229	0.9994	0.8385
FECAL	0.0038	0.2803	0.1407
FECAL	0.0034	0.2340	0.1237
FECAL	0.0072	0.7715	0.2641
FECAL	0.0044	0.1609	0.1609
FECAL	0.0041	0.1511	0.1511
FECAL	0.0033	0.1219	0.1219
LUNGS	0.0052	2.4765	0.1910
TOTALS	0.0933	103.3480	3.4125

No counts were detected in corresponding urine samples.
At final sacrifice, counts were found only in lung tissues.

Table 4

Percentage of Deposited ^{63}Ni Present in Tissues after Exposure of Rats to ^{63}NiO[a]
Toxicokinetics of ^{63}Ni After Inhalation of Nickel Oxide

Days Post Exposure	% Ni Deposited (mean ± SEM)						
	Lungs	Skull	Turbinates	Trachea/Larynx	GI Tract	Blood	Carcass
0	37.7 ± 5.73	0.0 ± 0.0	0.05 ± 0.05	0.94 ± 0.37	61.2 ± 30.8	0.04 ± 0.02	0.00 ± 0.00 (3)
0.08	46.1 ± 5.18	0.02 ± 0.01	0.47 ± 0.18	0.84 ± 0.53	225 ± 99.9[b]	0.00 ± 0.00	0.32 ± 0.32
0.25	38.3 ± 0.84	1.32 ± 1.32	0.0 ± 0.0	0.00 ± 0.00	324 ± 84[b]	0.00 ± 0.00	0.00 ± 0.00
1.0	35.8 ± 3.69	0.24 ± 0.24	0.21 ± 0.21	0.00 ± 0.00	26.9 ± 18.9	0.00 ± 0.00	ND
4.0	35.6 ± 2.80	0.0 ± 0.0	0.0 ± 0.0	0.05 ± 0.01	0.0 ± 0.0	0.00 ± 0.00	ND
8.0	31.2 ± 8.07	ND[c]	0.0 ± 0.0	0.06 ± 0.02	ND	0.00 ± 0.00	ND
16	43.3 ± 5.93	ND	0.0 ± 0.0	0.11 ± 0.04	ND	0.00 ± 0.00	ND
30	26.6 ± 4.17	ND	ND	0.03 ± 0.03 (n = 2)	ND	0.00 ± 0.00	ND
60	34.9 ± 2.79	ND	ND	0.01 ± 0.01	ND	ND	ND
90	23.8 ± 1.89	ND	ND	0.00 ± 0.00	ND	ND	ND
120	14.4 ± 3.14	ND	ND	ND	ND	ND	ND
180	14.2 ± 0.96	ND	ND	ND	ND	ND	ND

[a]Results represent the mean ± SEM of 3 values except in the cases of rats sacrificed immediately after exposure, where n = 4 and rats sacrificed after 180 days, where n = 9.
[b]Data are suspect.
[c]Samples not analyzed because no activity was detected in samples analyzed during the previous sacrifice or sacrifices.

TABLE 5
CLEARANCE OF GAVAGED 63NIO FROM THE
GI TRACTS OF RATS

TIME POINT	G001 uCi	G001 ug Ni	G002 uCi	G002 ug Ni	G003 uCi	G003 ug Ni	G004 uCi	G004 ug Ni	G005 uCi	G005 ug Ni	MEAN uCi/ TIME PT.	SEM	MEAN ug/ TIME PT.	SEM
4	0.0000	0.0000					0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
8	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000			0.0000	0.0000	0.0000	0.0000
12	0.0000	0.0000	0.0111	0.4059	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0022	0.0022	0.0812	0.0812
24	0.5155	18.8483	0.9114	33.3236	0.6473	23.6673	0.6794	24.8410	1.1987	43.8282	0.7905	0.1204	28.9016	4.4006
48	0.1023	3.7404	0.1789	6.5411	0.2459	8.9909	0.1473	5.3857	0.4670	17.0750	0.2283	0.0641	8.3466	2.3435
72	0.0090	0.3291	0.0000	0.0000	0.0094	0.3437	0.0000	0.0000	0.0000	0.0000	0.0037	0.0023	0.1346	0.0824
96	0.0175	0.6399	0.0112	0.4095	0.0000	0.0000	0.1173	4.2888	0.0000	0.0000	0.0292	0.0223	1.0676	0.8146
TOTAL	0.6443	23.5576	1.1126	40.6801	0.9026	33.0018	0.9440	34.5155	1.6657	60.9031	1.0538	0.1704	38.5316	6.2291

No activity was detected in corresponding urine samples.

Individual Animal Data