Table 2. Nickel Absorption in Humans via the Ingestion Route

Dose	Carrier	Fasting status	Ni in serum	Effect on Nickel in Urine	Absorption	Reference
0.84-3.5 mg Ni (nickel sulfate hexhydrate)/person (12-50 Fg Ni/kg)	Water or food	Fasted	Peak at 3 hr	Peak excretion with 3-9 hr, depending on dose	27% in water; 0.7% in food	Sunderman et al., 1989
5.6 mg Ni (nickel sulfate hexhydrate)/person (0.08 mg Ni/kg)	Capsule	Not fasted	Peak at 2.5 hr	Maximum in 8 hr	5.7% *	Christensen and Lagesson, 1981
5.6 mg Ni (nickel sulfate)/person[1] (0.08 mg Ni/kg)	Tablet	Not fasted	N/A	Increase after 1-2 days	1.7%-2.2% *	Menne et al., 1978
1 mg Ni (nickel sulfate hexhydrate)/person (0.01 mg Ni/kg)	Capsule	Fasted	No change at 3 hr	Increase during 24 hr	N/A	Hindsen et al., 1994
2.5 mg Ni (nickel sulfate) /person (0.036 mg Ni/kg)	Capsule	Fasted	N/A	N/A	12-32%	Cronin et al., 1980
12 Fg Ni/kg (form not specified)	Water	Fasted	Peak at 1 hr	Peak excretion within ~5 hr	23.2%	Nielsen et al. 1999
12 Fg Ni/kg (form not specified)	Water	Not Fasted	Peak at 3 hr	Peak excretion within ~5 hr	2-3%	Nielsen et al. 19
5 mg Ni (nickel sulfate hexhydrate)/person (0.07 mg Ni/kg)	Water Beverages Food	Fasted	Peak at 3 hr Increase but less than in water No increase	N/A	N/A	Solomons et al., 1982

*As reanalyzed by Diamond et al., 1998

[1] Hydration state not reported

N/A = not available

Table 3. Nickel Tissue Distribution in Rats After Inhalation Exposure or Intratracheal Instillation

Dose or Concentration	Time after exposure	Relative Tissue concentration of nickel	Reference
Inhalation of 0, 0.8, 1.6, 3.3, 6.7 mg Ni/m^3 ($NiSO_4$) for 12 days	0	kidney > liver Not found in lymph nodes, ovaries, testes	Benson, 1988
Intratracheal instillation of 1.27 Fg Ni ($NiCl_2$)	35 min 21 day	lung > kidney > heart, spleen, testes, liver, skin, bone, blood lung > kidney	Carvalho and Ziemer, 1982
Intratracheal injection of 5.9 Fg Ni ($NiCl_2$) 5.9 Fg Ni (NiO)	0.5 hr 0.5 hr	lung = mediastinal lymph nodes > kidney > ovaries > blood > femur > heart > adrenals > skin >pancreas > duodenum > pituitary >liver > spleen lung = lymph nodes > heart > femur > duodenum > kidney > pancreas > ovaries > spleen > blood > adrenals > skin > pituitary > liver	English et al., 1981
Intratracheal injection of 1 Fg, 11 Fg Ni ($NiSO_4$) Intratracheal injection of 106 Fg (1800 nmoles) Ni	4, 24, 96 hr 4, 24, 96 hr	High tissue concentrations: lung > trachea = larynx > urinary bladder > kidney Low tissue concentrations: muscle, fat, bone, liver, brain High tissue concentrations: lung > kidney > trachea = larynx	Medinsky et al., 1987
Intratracheal injection of 1000 Fg Ni ($NiCl_2$)	6 hr & 24 hr 72 hr	kidney > lung > adrenal > liver > pancreas > spleen > heart > testis lung > kidney > adrenal > spleen > testis > pancreas > liver > heart	Clary, 1975

Table 4. Nickel Tissue Distribution in Animals After Ingestion Exposure

Species	Dose	Time after exposure	Nickel levels in tissues	Reference
Mouse	0.58 mg Ni/kg ($NiCl_2$) gastric intubation	5 to 24 hr	kidney > lung > liver, heart, serum, fat, pancreas, eyes, spinal cord, brain	Jasim and Tjalve, 1986
Pregnant mouse	0.58 mg Ni/kg ($NiCl_2$) gastric intubation on gd 18	24 hr	Placental and fetal tissues: placenta > kidney > heart > lung > liver > whole fetus > brain	
Rat	10 mg Ni [$NiSO_4$, $NiCl_2$, $Ni(NO_3)_2$] by gavage	24 hr	kidney > lung > liver, spleen, pancreas, heart, blood > brain	Ishimatsu et al., 1995
Mouse	0.58 mg Ni/kg ($NiCl_2$) by gastric intubation once daily for 7 days	24 hr	kidney > lung > peripheral nervous system, spinal cord, liver	Borg and Tjalve ,1989
Rats	100, 500, 1000 ppm Ni (nickel acetate) in food for 6 weeks	0	kidney > heart, liver, testes, plasma	Whanger, 1973
Mouse	Dose 3.0, 3.5 mg Ni/day/mouse in water for 180 days (5, 10 g/L nickel sulfate)	4 wk to 23 wk	kidney > liver, blood	Dieter et al. ,1988
Mouse	5 ppm Ni^{2+} (acetate or oxalate) in drinking water for life time	0	spleen > kidney, lung, liver, heart	Schroeder et al., 1964
Pregnant mouse	5 ppm Ni^{2+} (acetate or oxalate) in drinking water for life time	0	Increased nickel concentration in newborn mouse	
Rat	2500 ppm Ni ($NiSO_4$) in food for 2 years	0	kidney > fat > liver, bone	Ambrose et al., 1976

Table 5. Nickel Excretion from Rats After Intratracheal Instillation of Nickel Salts

Species	Dose (Ni)	Time after exposure (days)	Excretion in urine (%)	Half-Time for Excretion in urine (hours)	Excretion in feces (%)	Half-Time for Excretion in Feces (Hours)	Reference
Rat	1.27 Fg	1 3 21	72 78.5 96.5	N/R	 3.4	N/R	Carvalho and Ziemer, 1982
Rat	5.9 Fg	1 3 90	58 61 64	N/R	<5 <5 6.4	N/R	English et al.,1981
Rat	1 Fg 11 Fg 106 Fg	4	54 56 82	23 12 4.6	31 26 13	14 12 17	Medinsky et al., 1987

[1]N/R = Not reported

Table 6. Exposure Estimation in Epidemiology Studies Specifying Soluble Nickel

Source	Population	Selection criteria and exposure assessment	Estimated workplace levels, soluble Ni[1], mg/m^3	Estimated workplace levels, insoluble (mg/m^3)
Pang et al., 1996	Ni platers (U.K.)	Min employment 3 mos. in Ni plating; never worked with chromium.	0.010-0.080 [2]	None
Karjalainen et al., 1992	Ni refinery Finland Outokumpu Oy Harjavalta	Min employment 3 mos. Defined by period of employment and type of work. Primarily sol Ni, as sulfate in electrowinning; subsulfide form present when matte is ground. Oxides not present.	annual avg. <0.50 [0.26-0.76 tank house areas]	subsulfide, <0.20
Anderson et al., 1996	Ni refinery workers, Norway Kristianstad	Concentrations estimated by 'expert group', and measurements taken at one point in time (1973). Species assumed present in respirable air in proportion to presence in material in work area. Similar to Clydach process, but through 1978 handled some substances that Clydach handled only up to 1929. Smelter plant nearby.	0.50-2.0 in electrolysis areas	
ICNCM, 1990; Easton et al., 1992	Clydach Wales INCO Nickel refinery	Follow-up through 1985. Min 5 years employment. Based on process. Estimated concentrations extrapolated from recent conditions. Some percentage of nearly every department is soluble Ni; highest is 30-40% in Ni sulfate plant; also high oxidic but low sulfidic. Workers may have worked in other departments.	0.20-2.0 ["thru 1979"] Calciners, decrease over time, 0.25-0.75	1-2 in Ni plant; 10 in Cu plant
ICNCM, 1990	Ontario, Port Colborne electrolysis INCO Ontario Mining, smelting, and refining	Worked >=6 months. 1950 thru 1984. At electrolytic workplaces, exposed to sol Ni <0.3 mg and <1.0 mg/m^3 total. Recently sol as low as 0.20 mg Concentrations of soluble somewhat comparable to Kristiansand Norway but the later had 7 x higher insoluble, which dropped to 2.5 x after 1987	<0.30 >1.0 anode tasks None	<0.70 0.25-1.0

[1] Different methods were used to estimate exposures at different workplaces, so these levels are only roughly comparable. In addition, levels vary with changes in procedures over time.
[2] Estimated workplace concentrations based on contemporary exposure assessments, summarized in Table C-1. Concentrations in this study may be higher because they occurred during an earlier time period.

Table 7. Characteristics of Epidemiology Studies Specifying Soluble Nickel

Source	Population	Cohort size (Cases or Deaths)	Person years	Lung	Nasal	Stomach
Pang et al., 1996	Ni platers (U.K.)	284 (99)	6928.6	RR 1.25 (0.36-4.33)[1]	none observed (<1 expected)	2.61(0.60-11.33)
Karjalainen et al., 1992	Ni refinery workers, Finland	369 (6) in refinery [1339 (67) in smelter and refinery]	6089 [27,130]	RR 2.0 (0.3-7.4)	RR 53.8 (1.4-300)[2]	4.3(0.5-16)
Anderson et al., 1996	Ni refinery workers, Kristiansand Norway	4764 (1979)	125,000	RR 3.1(2.1-4.8)[3] [highest sol Ni] 1.5 (1.0-2.2) [highest oxide}	RR overall 18 (12.3-25.4)[4] RR soluble only 2.7 (0.3-9-8)	0.9(0.7-1.3)
ICNCM, 1990; Easton, et al., 1992	Clydach, Wales INCO [Ni sulfate plant]	[Total: 2524/1360] [#Ni sulfate plant: not given]	__	SMR[5] 333 (108-776) SMRs ~112 for entry after 1930	SMR 363 (99-931) 1 case post 1930 entry	SMR 71 (1930 entry, total cohort)
ICNCM, 1990	Ontario INCO Sinter, leaching, calcining	54,509 (298)	1950-1984	SMR 261 (220-336)	SMR 5073 (3282-7489)	114 (65-185)
ICNCM, 1990	Ontario. INCO Electrolysis	(1608)	NR	SMR 110 (101-120)	SMR 142 (52-309)	101 (84-121)

[1] Exposed to Ni > 1 yr. Relative risk (RR) for mortality (paper also reports SMR), controlled for age, start year, follow-up, and exposure duration. Internal comparison

[2] SIR, population of SW Finland as comparison. 1 case nasal cancer+2 cases after termination data; 2 lung cancer cases.

[3] RR incidence for sol Ni, >15 mg/m3 cumulative exposure, from multivariate regression, adjusted for smoking habits, age, and Ni oxides. Estimated RR for 1-4 mg/m3 cumulative exposure was 1.2 (0.8-1.9). Exposure estimate based on process, per Archibald (1962) and ICNCM (1990); expert judgement estimates for 82 work areas .

[4] SIR. Not adjusted for age, smoking, duration, or other exposures.

[5] SMR, (reference is 100) for "hydrometallurgy department >5 years exposed and <1 year in other high risk area. Before 1959. Copper plant risks were similar; plants had similar s exposure but greater oxide exposure Source ICNCM, 1990

Table 8. New Cases of Lung Cancer Among 4902 Male Nickel Refinery Workers by Cumulative Exposure to Nickel Compounds[1].

Soluble nickel compounds (mg/m^3)	Cumulative Exposure to Oxidic Nickel (mg/m^3)									
	<1		1-4		5-14		$15		Total	
	O[2]	SIR[3]	O	SIR	O	SIR	O	SIR	O	SIR
<1	40	1.8**	2	1.4	17	3.3**	33	2.9**	92	2.3**
1-4	15	2.6**	13	1.8	2	2.0	5	4.6*	35	2.3**
5-14	3	4.3	10	2.2*	8	6.5**	1	1.8	22	3.1**
$15	1	13.3	16	5.6**	27	8.2**	8	9.2**	52	7.3**
Total	59	2.0**	41	2.6**	54	5.0**	47	3.4**	201	2.9**

[1]Adapted from Andersen et al. (1996) and additional information provided by Andersen.
[2]O = Observed number of cases.
[3]SIR = Standardized incidence ratio.
* $p<0.05$
** $p<0.01$

Table 9. Cancer Incidence Among Smelter and Refinery Workers (Anttila et al., 1998)

	Overall Risk		Risk for 20 + Year Latency	
Cohort	Observed/ Exposed	SIR (95% CI)	Observed/Exposed	SIR (95% CI)
Lung Cancer				
Unexposed Workers	13/10.7	1.22 (0.65 - 2.08)	--	--
Exposed Nickel Workers	21/15.1	1.39 (0.86 - 2.13)	--	--
Smelter	15/10.8	1.39 (0.78 - 2.28)	13/6.5	2.00 (1.07 - 3.42)
Refinery*	6/2.3	2.61 (0.96 - 5.67)	6/1.8	3.38 (1.24 - 7.36)
Nose and Nasal Sinuses				
Unexposed Workers	0	0	--	--
Exposed Nickel Workers	2/0.2	8.79 (1.06 - 31.7)	--	--
Smelter	0	0	0	0
Refinery	2/0.05	41.1 (4.97 - 148)	2/0.03	67.1 (8.12 - 242)

*Two of the six cases had also worked in the smelter

Table 10. Comparison of Risk of Dying of Lung Cancer[1] at Different Levels of Cumulative Exposure to Soluble Nickel by Different Levels of Combined Cumulative Exposure to Sulfidic and Oxidic Nickel in the Mond/inco (Clydach) Nickel Refinery

Degree of exposure to sulfidic and oxidic nickel, respectively[2]	Low exposure to soluble nickel[3]			High exposure to soluble nickel[4]			Difference in the SMR values (P-value)
	O	E[5]	SMR	O	E[5]	SMR	
Low, low	51	26.01	196	7	4.16	168	0.931
Low, high	18	5.14	350	30	3.87	776	0.024
High, low	8	1.25	638	1	0.15	658	0.999
High, high	32	6.34	505	28	2.36	1187	0.003

[1] From ICNCM (1990), Table 33. Includes all men with 15 or more years since first employment except those who worked in general trades. O = observed number of deaths, E = expected number of deaths, SMR = standardized mortality ratio.
[2] Low sulfidic nickel exposure = < 15 (mg Ni/m^3) x years and high sulfidic nickel exposure = $\geq$15 (mg Ni/m^3) x years; low oxidic nickel exposure = < 50 (mg Ni/m^3) x years and high oxidic nickel exposure = $\geq$50 (mg Ni/m^3) x years
[3] Low soluble nickel exposure = <10 (mg Ni/m^3) x years.
[4] High soluble nickel exposure = $\geq$10 (mg Ni/m^3) x years.
[5] Based on the mortality rates for England and Wales.

Table 11. Comparison of Risk of Dying of Lung Cancer[1] at Different Levels of Cumulative Exposure to Sulfidic Nickel by Different Levels of Combined Cumulative Exposure to Oxidic and Soluble Nickel in the Mond/inco (Clydach) Nickel Refinery

Degree of exposure to oxidic and soluble nickel, respectively[2]	Low exposure to sulfidic nickel[3]			High exposure to sulfidic nickel[4]			Difference in the SMR values (P-value)
	O	E[5]	SMR	O	E[5]	SMR	
Low, low	51	26.01	196	8	1.25	638	0.004
Low, high	7	4.16	168	1	0.15	657	0.388
High, low	18	5.14	350	32	6.34	505	0.458
High, high	30	3.87	776	28	2.36	1187	0.265

[1] From ICNCM (1990), Table 34. Includes all men with 15 or more years since first employment except those who worked in general trades. O = observed number of deaths, E = expected number of deaths, SMR = standardized mortality ratio
[2] Low oxidic nickel exposure = < 50 (mg Ni/m^3) x years and high oxidic nickel exposure = $\geq$50 (mg Ni/m^3) x years; low soluble nickel exposure = < 10 (mg Ni/m^3) x years and high soluble nickel exposure = $\geq$10 (mg Ni/m^3) x years
[3] Low sufidic nickel exposure = <15 (mg Ni/m^3) x years.
[4] High sulfidic nickel exposure = $\geq$15 (mg Ni/m^3) x years.
[5] Based on the mortality rates for England and Wales.

Table 12. Comparison of Risk of Dying of Lung Cancer[1] at Different Levels of Cumulative Exposure to Oxidic Nickel by Different Levels of Combined Cumulative Exposure to Sulfidic and Soluble Nickel in the Mond/INCO(Clydach) Nickel Refinery

Degree of exposure to sulfidic and soluble nickel, respectively[2]	Low exposure to oxidic nickel[3]			High exposure to oxidic nickel[4]			Difference in the SMR values (P-value)
	O	E[5]	SMR	O	E[5]	SMR	
Low, low	51	26.01	196	18	5.14	350	0.100
Low, high	7	4.16	168	30	3.87	776	< 0.001
High, low	8	1.25	638	32	6.34	505	0.839
High, high	1	0.15	658	28	2.36	1187	0.841

[1] From ICNCM (1990), Table 35. Includes all men with 15 or more years since first employment except those who worked in general trades. O = observed number of deaths, E = expected number of deaths, SMR = standardized mortality ratio.
[2] Low sulfidic nickel exposure = < 15 (mg Ni/m^3) x years and high sulfidic nickel exposure = $ 15 (mg Ni/m^3) x years; low soluble nickel exposure = < 10 (mg Ni/m^3) x years and high soluble nickel exposure = $ 10 (mg Ni/m^3) x years
[3] Low oxidic nickel exposure = <50 (mg Ni/m^3) x years.
[4] High oxidic nickel exposure =$ 50 (mg Ni/m^3) x years.
[5] Based on the mortality rates for England and Wales.

Table 13. Comparison of Risk of Dying of Nasal Cancer[1] at Different Levels of Cumulative Exposure to Soluble Nickel by Different Levels of Combined Cumulative Exposure to Sulfidic and Oxidic Nickel in the Mond/INCO (Clydach) Nickel Refinery.

Degree of exposure to sulfidic and oxidic nickel, respectively[2]	Low exposure to soluble nickel[3]			High exposure to soluble nickel[4]			Difference in the O/E values (p-value)
	0	E[5]	O/E	O	E[5]	O/E	
Low, low	7	0.166	42	3	0.025	120	0.284
Low, high	5	0.045	112	16	0.048	339	0.079
High, low	3	0.009	345	--	--	--	--
High, high	11	0.051	214	22	0.025	865	<0.001

[1] Includes all men with 15 or more years since first employment except those who worked in general trades. O = observed number of deaths, E = expected number of deaths, SMR = standardized mortality ratio.
[2] Low sulfidic nickel exposure = < 15 (mg Ni/m^3) x years and high sulfidic nickel exposure = $\geq$15 (mg Ni/m^3) x years; low oxidic nickel exposure = < 50 (mg Ni/m^3) x years and high oxidic nickel exposure = $\geq$50 (mg Ni/m^3) x years.
[3] Low soluble nickel exposure = < 10 (mg Ni/m3) x years.
[4] High soluble nickel exposure = $\geq$ 10 (mg Ni/m^3) x years.
[5] Based on the mortality rates for England and Wales

Table 14. Comparison of Risk of Dying of Nasal Cancer[1] at Different Levels of Cumulative Exposure to Sulfidic Nickel by Different Levels of Combined Cumulative Exposure to Oxidic and Soluble Nickel in the Mond/INCO (Clydach) Nickel Refinery.

Degree of exposure to oxidic and soluble nickel, respectively[2]	Low exposure to sulfidic nickel[3]			High exposure to sulfidic nickel[4]			Difference in the O/E values (p-value)
	0	E[5]	O/E	O	E[5]	O/E	
Low, low	7	0.166	42	3	0.009	345	0.001
Low, high	3	0.025	120	-	-	-	-
High, low	5	0.045	112	11	0.051	214	0.472
High, high	16	0.048	336	22	0.025	865	0.011

[1] From ICNCM (1990), Table 38. Includes all men with 15 or more years since first employment except those who worked in general trades. O = observed number of deaths, E = expected number of deaths, SMR = standardized mortality ratio.

[2] Low oxidic nickel exposure = < 50 (mg Ni/m^3) x years and high oxidic nickel exposure = $\geq$50 (mg Ni/m^3) x years; low soluble nickel exposure = < 10 (mg Ni/m^3) x years and high soluble nickel exposure = $\geq$10 (mg Ni/m^3) x years.

[3] Low sulfidic nickel exposure = < 15 (mg Ni/m3) x years.

[4] High sulfidic nickel exposure = $\geq$ 15 (mg Ni/m^3) x years.

[5] Based on the mortality rates for England and Wales

Table 15. Effect of Exposure to 100 mg/L Nickel in Drinking Water on the Urinary Excretion of Albumin, ß$_2$-m, and Kidney Weight in Male and Female Rats[1]

Sex	Exposure Duration	Condition	Albumin[3] (Fg/24 hr)	ß$_2$m[3] (Fg/24hr)	Relative Kidney Weight[4] (g/kg)
Males	3 months	Control	622 (216-2970)	5.15 (2.1-15.4)	5.93 ± 0.08
		Nickel	720 (132-2406)	4.59 (1.7-15.1)	6.08 ± 0.13
	6 months	Control	989 (194-11200)	3.02 (0.2-24.7)	5.43 ± 0.10
		Nickel	2065 (448-5600)	4.91 (0.6-17.4)	5.91 ± 0.16*
Females	3 months	Control	202 (88-326)	0.52 (0.05-14.4)	6.12 ± 0.23
		Nickel	329 (115-1162)	1.11 (0.23-6.60)	6.47 ± 0.12
	6 months	Control	354 (114-1575)	0.55 (0.05-1.93)	6.52 ± 0.12
		Nickel	1319* (209-9600)	0.87 (0.06-3.90)	6.78 ± 0.11

[1] Adapted from Vyskocil et al., 1994
[2] Data were evaluated by two way variance analysis and Bonferroni test
[3] Geometric mean (range) of ten animals
[4] Arithmetic mean ± SEM of ten animals
*$p<0.05$ with respect to the matched controls

Table 16. Concentrations and Aerosol Sizes of Nickel Compounds Tested by NTP (1996a, 1996b, 1996c)

Compound/ Reference	Species	Concentration (mg/m^3)		Aerosol Size (Fm)	
		Compound	Ni	MMAD	GSD
Nickel Sulfate Hexahydrate $NiSO_4"6H_2O$/ NTP, 1996a	Rat	0.12	0.03	2.50 ± 0.38	2.38 ± 0.27
		0.25	0.06	2.24 ± 0.26	2.21 ± 0.26
		0.5	0.11	2.25 ± 0.16	2.08 ± 0.17
	Mouse	0.25	0.06	2.34 ± 0.21	2.24 ± 0.17
		0.5	0.11	2.27 ± 0.18	2.07 ± 0.13
		1	0.22	2.53 ± 0.20	2.02 ± 0.15
Nickel Oxide NiO/NTP, 1996b	Rat	0.62	0.5	2.21 ± 0.14	1.97 ± 0.08
		1.25	1.0	2.23 ± 0.17	1.89 ± 0.36
		2.5	2.0	2.21 ± 0.16	1.80 ± 0.11
	Mouse	1.25	1.0	2.46 ± 0.22	1.87 ± 0.09
		2.5	2.0	2.42 ± 0.13	1.81 ± 0.08
		5	3.9	2.55 ± 0.16	1.76 ± 0.10
Nickel Subsulfide Ni_3S_2/NTP, 1996c	Rat	0.15	0.11	2.17 ± 0.34	2.34 ± 0.39
		1	0.73	2.18 ± 0.22	1.91 ± 0.12
	Mouse	0.6	0.44	2.24 ± 0.31	1.98 ± 0.16
		1.2	0.88	2.25 ± 0.16	2.08 ± 0.17

Table 17. NonNeoplastic Lesions in the NTP (1996a) Chronic Inhalation Bioassay of Nickel Sulfate Hexahydrate

Species, Sex	Exposure Conc. (mg Ni/m^3)	Lung Lesions						Bronchial Lymph Node		Olfactory Epithelium
		Chronic active inflammation	Macrophage hyperplasia	Fibrosis	Alveolar Proteinosis	Bronchial-ization	Interstitial Infiltration	Lymphoid hyperplasia	Macrophage hyperplasia	Atrophy
Rat, Male	0	14/54	7/54	3/54	0/54	---	---	0/51	0/51	0/54
	0.027	11/53	9/53	6/53	0/53	---	---	0/49	0/49	0/52
	0.056	42/53**	35/53**	35/53**	12/53**	---	---	3/47	0/47	3/53
	0.11	46/53**	48/53**	43/53**	41/53**	---	---	10/52**	0/52	7/53**
Rat, female	0	14/52	9/52	8/52	1/52	---	---	2/50	0/50	0/51
	0.027	13/53	10/53	7/53	0/53	---	---	1/52	0/52	1/52
	0.056	49/53**	32/53**	45/53**	22/53**	---	---	0/51	0/51	1/53
	0.11	52/54**	45/54**	49/54**	49/54**	---	---	11/49**	0/49	7/54**
Mouse, male	0	1/61	6/61	---	0/61	1/61	1/61	2/46	0/46	0/61
	0.056	2/61	9/61	---	0/61	4/61	0/61	4/49	0/49	0/61
	0.11	8/62*	35/62*	---	0/62	19/62**	3/62	2/45	8/45**	12/61**
	0.22	29/61**	59/61**	---	42/61**	39/61**	17/61**	17/54**	39/54**	37/60**
Mouse, female	0	1/61	7/61	---	0/61	0/61	0/61	15/50	2/50	3/61
	0.056	7/60*	24/60*	---	0/60	9/60**	4/60	9/54	0/54	2/59
	0.11	14/60**	53/60**	---	11/60**	32/60**	16/60**	16/58	14/58**	1/60
	0.22	40/60**	59/60**	---	45/60**	45/60**	39/60**	26/56**	37/56**	17/60**

* Significantly different (p#0.05) from the control group by the logistic regression test.
** Significantly different (p#0.01) from the control group by the logistic regression test.

Table 18. Nonneoplastic Lesions of the Lung at the 7- and 15-Month Interim Sacrifices in NTP (1996a)

Species, Sex	Exposure Conc. (mg Ni/m^3)	Chronic active inflammation		Macrophage hyperplasia		Fibrosis		Alveolar Proteinosis	
		7 mo	15 mo	7 mo	15 mo	7 mo	15 mo	7 mo	15 mo
Rat, Male	0	0/5	0/5	0/5	0/5	--	0/5	--	0/5
	0.027	4/5*	1/5	1/5	0/5	--	0/5	--	0/5
	0.056	4/5*	1/5	5/5**	2/5	--	0/5	--	1/5
	0.11	5/5**	5/5**	5/5**	5/5**	--	2/5	--	4/5*
Rat, female	0	0/5	2/5	0/5	1/5	--	0/5	0/5	0/5
	0.027	2/5	0/5	2/5	1/5	--	0/5	0/5	0/5
	0.056	4/5*	4/5	4/5*	3/5	--	1/5	0/5	3/5
	0.11	5/5**	5/5	5/5**	5/5*	--	3/5	2/5	5/5**
Mouse, male	0	0/5	0/5	0/5	0/5	--	--	0/5	0/5
	0.056	0/5	0/5	0/5	1/5	--	--	0/5	0/5
	0.11	0/5	0/5	1/5	4/5*	--	--	0/5	0/5
	0.22	0/5	4/5*	5/5**	5/5**	--	--	0/5	3/5
Mouse, female	0	0/5	0/5	0/5	0/5	--	--	0/5	0/5
	0.056	0/5	0/5	0/5	1/5	--	--	0/5	0/5
	0.11	0/5	0/5	1/5	2/5	--	--	0/5	0/5
	0.22	2/5	5/5**	5/5**	5/5**	--	--	0/5	5/5**

Table 19. Neoplastic Lesions in the NTP (1996a) Chronic Inhalation Bioassay of Nickel Sulfate Hexahydrate

Species, Sex	Exposure Conc. (mg Ni/m^3)	Lung Alveolar/Bronchiolar Tumors		
		Adenoma	Carcinoma	Adenoma or carcinoma
Rat, male	0	0/54	1/54	2/54[2]
	0.03	0/53	0/53	0/53
	0.06	0/53	1/53	1/53
	0.11	2/53	1/53	3/53
Rat, female	0	0/52	0/52	0/52
	0.03	0/53	0/53	0/53
	0.06	0/53	0/53	0/53
	0.11	1/54	0/54	1/54
Mouse, male	0	5/61	9/61	13/61
	0.06	5/61	13/61	18/61
	0.11	3/62	4/62	7/62
	0.22	5/61	3/61	8/61
Mouse, female	0	3/61	4/61	7/61
	0.06	3/60	3/60	6/60
	0.11	2/60	9/60	10/60
	0.22	0/60	2/60	2/60

Table 20. Results of NTP (1996b) Chronic Inhalation Bioassay of Nickel Oxide

Species, Sex	Exposure Conc. (mg Ni/m^3)	Nonneoplastic Lung Lesions[1]		Lung Alveolar/Bronchiolar Tumors			Bronchial Lymph Node		Adrenal Medulla Pheochromocytoma		
		Chronic inflammation	Alveolar pigment	Adenoma	Carcinoma	Adenoma or carcinoma[4]	Lymphoid hyperplasia	Pigment	Benign	Malignant	Benign or malignant
Rat, male	0	28/54	1/54	0/54	0/54	1/54[5] (p=0.062)	0/52	0/52	27/54 (p=0.041)	0/54 (p<0.001)	27/54 (p=0.008)
	0.5	53/53[2]	53/53[2]	1/53	0/53	1/53	7/51[3]	45/51[2]	24/52	0/52	24/52
	1.0	53/53[2]	53/53[2]	3/53	3/53	6/53 (p=0.054)	10/53[2]	51/53[2]	26/53	1/53	27/53
	2.0	52/52[2]	52/52[2]	2/52	2/52	4/52	18/52[4]	51/52[2]	32/52	6/52 (p=0.015)	35/52 (p=0.027)
Rat, female	0	18/53	0/53	1/53	0/53	1/53 (p=0.022)	1/49	0/49	4/51 (p<0.001)	---	---
	0.5	52/53[2]	52/53[2]	0/53	0/53	0/53	5/50	43/50[2]	7/52	---	---
	1.0	53/53[2]	53/53[2]	1/53	5/53[3]	6/53 (p=0.053)	20/53[2]	52/53[2]	6/53	---	---
	2.0	54/54[2]	54/54[2]	4/54	1/54	5/54	13/52[2]	47/52[2]	18/53 (p=0.001)	---	---
Mouse, male	0	0/57	0/57	7/57	4/57	9/57	5/45	0/45	---	---	---
	1.0	21/67[2]	65/67[2]	5/67	10/67	14/67	18/56[3]	55/56[2]	---	---	---
	2.0	34/66[2]	66/66[2]	6/66	9/66	15/66	28/61[2]	61/61[2]	---	---	---
	3.9	55/69[2]	68/69[2]	11/69	6/69	14/69	33/62[2]	60/62[2]	---	---	---
Mouse, female	0	7/64	0/64	2/64	4/64	6/64	14/54	0/54	---	---	---
	1.0	43/66[2]	64/66[2]	4/66	11/66	15/66 (p=0.043)	37/63[2]	58/63[2]	---	---	---
	2.0	53/63[2]	61/63[2]	10/63[3]	4/63	12/63	40/59[2]	56/59[2]	---	---	---
	3.9	52/64[2]	64/64[2]	3/64	5/64	8/64	44/62[2]	60/62[2]	---	---	---

[1] Nonneoplastic lung lesions that were significantly (p#0.05 or #0.01) increased in addition to chronic active inflammation included alveolar proteinosis, bronchialization and proteinosis (alveolus) in mice (both sexes) $1.25 mg Ni/m^3.
[2] Significantly different (p#0.01) from the control group by the logistic regression test.
[3] Significantly different (p#0.05) from the control group by the logistic regression test.
[4] P-values for trend test given in parentheses next to control incidences if p#0.05. P-values for pairwise comparison between an exposure group and controls given in parentheses next to the exposure group if p#0.05.
[5] Incidence of adenoma or carcinoma or squamous cell carcinoma.

Table 21. Results of NTP (1996c) Chronic Inhalation Bioassay of Nickel Subsulfide

Species, Sex	ExposureConc. (mg Ni /m^3)	Nonneoplastic Lung Lesions[1]	Lung Alveolar/Bronchiolar Tumors			Bronchial Lymph Node Hyperplasia		Olfactory Epithelium[6]	Adrenal Medulla Pheochromocytoma[4]		
		Chronic active inflammation	Adenoma	Carcinoma	Adenoma or carcinoma[4]	Lym-phoid	Macro-phage	Atrophy	Benign	Malignant	Benign or malignant
Rat, male	0	9/53	0/53	0/53	0/53 (p=0.003)	5/52	1/52	2/53	13/53 (p<0.001)	0/53 (p<0.001)	14/53 (p<0.001)
	0.11	53/53[2]	3/53	3/53	6/53 (p=0.020)	29/51[2]	14/51[2]	1/53	30/52 (p=0.002)	2/52 (p=0.242)	30/52 (p=0.003)
	0.73	51/53[2]	6/53[3]	7/53[3]	11/53 (p=0.001)	34/53[2]	28/53[2]	9/52[3]	37/53 (p<0.001)	11/53 (p=0.002)	42/53 (p<0.001)
Rat, female	0	7/53	2/53	0/53	2/53 (p=0.030)	11/50	0/50	0/53	2/53 (p<0.001)	1/53	3/53 (p<0.001)
	0.11	51/53[2]	5/53	0/53	6/53[5] (p=0.142)	36/49[2]	16/49[2]	0/53	7/53 (p=0.083)	0/53	7/53 (p=0.166)
	0.73	51/53[2]	5/53	4/53	9/53 (p=0.031)	36/50[2]	24/50[2]	16/52[2]	36/53 (p<0.001)	1/53	36/53 (p<0.001)
Mouse, male	0	1/61	6/61	7/61	13/61	4/40	1/40	1/61	---	---	---
	0.44	52/59[2]	3/59	2/59	5/59	40/53[2]	47/53[2]	27/59[2]	---	---	---
	0.88	53/58[2]	2/58	4/58	6/58	49/54[2]	50/54[2]	55/59[2]	---	---	---
Mouse, female	0	1/58	3/58	7/58	9/58	10/50	0/50	1/58	---	---	---
	0.44	46/59[2]	1/59	1/59	2/59	46/57[2]	44/57[2]	11/59[2]	---	---	---
	0.88	58/60[2]	1/60	2/60	3/60	52/59[2]	47/59[2]	41/60[2]	---	---	---

[1] Nonneoplastic lung lesions in addition to chronic inflammation that were significantly (p#0.01) increased included macrophage hyperplasia in rats (both sexes) at $0.11 mg Ni/m^3 and mice (both sexes) at $0.44 mg Ni/m3; fibrosis in rats (both sexes) at $0.11 mg Ni/m^3, male mice at 0.88 mg Ni/m^3 and female mice at $0.44 mg Ni/m^3; alveolar proteinosis in rats (both sexes) at $0.11 mg/m^3 and mice (both sexes) at $0.44 mg/m^3; and bronchialization in mice (both sexes) at $0.44 mg Ni/m^3.

[2] Significantly different (p#0.01) from the control group by the logistic regression test.

[3] Significantly different (p#0.05) from the control group by the logistic regression test.

[4] P-values for trend test given in parentheses next to control incidences if p#0.05. P-values for pairwise comparison between an exposure group and controls given in parentheses next to the exposure group if p#0.05.

[5] Incidence of adenoma or carcinoma or squamous cell carcinoma.

[6] Other nasal lesions included significantly (p#0.01) increased chronic active inflammation in female rats at 0.73 mg Ni/m^3; and acute inflammation and olfactory epithelium degeneration in female mice at $0.44 mg Ni/m^3.

Table 22. Aerosol Size Measurements for the Rat and Mouse Chambers in the Subchronic NTP (1996a) Study with Nickel Sulfate Hexahydrate

Target Concentration (mg $NiSO_4 \cdot 6H_2O/m^3$)	Target Concentration (mg Ni/m^3)	Mass Median Aerodynamic Diameter (Fm)	Geometric Standard Deviation
0.12	0.027	2.31	2.1
0.25	0.056	2.11	2.7
0.5	0.11	3.08	2.9
1.0	0.22	1.81	2.2
2.0	0.45	2.01	2.0

Table 23. Relative Solubility and Injection-Site Tumorigenicity of Nickel Compounds in Rats (Gilman, 1966)

Nickel Compound[1]	Number of Tumors/Number of Sites[2]	Tumor-bearing Animals (%)
Sulfate	0/54	0
Fluoride	3/36	17
Hydroxide	19/40	75
Monosulfide	0/28	0
Oxide	2/40	10
Subsulfide	22/40	85

[1] Compounds listed in order of decreasing water solubility.
[2] Total number of tumors and total number of injection sites (combined animal data).

Table 24. Local Tumor Responses in Rats Exposed to Soluble Nickel Compounds and Metallic Nickel by Intraperitoneal Injection (Pott et al., 1989, 1990)

Compound	Exposure Schedule[1]	Total Dose (mg Ni)	Tumor Incidence[2]
Saline	1 ml x 3	0	1/33
	1 ml x 50	0	0/34
Nickel chloride"$6H_2O$	1 mg x 50	50	4/32[3]
Nickel sulfate"$7H_2O$	1 mg x 50	50	6/30[3]
Nickel acetate"$4H_2O$	1 mg x 25	25	3/35
	1 mg x 50	50	5/31[4]
Nickel carbonate"$4H_2O$	1 mg x 25	25	1/35
Nickel hydroxide"$2H_2O$	1 mg x 50	50	3/33
Metallic nickel	6 mg x 1	6	4/34[5]
	6 mg x 2	12	5/34[5]
	1 mg x 25	25	25/35[5]

[1] mg Ni x number of injections; compounds listed in order of decreasing water solubility
[2] Combined incidences of abdominal mesotheliomas and sarcomas (incidences not reported for separate tumor types).
[3] Significantly increased ($p<0.05$) compared to control group.
[4] $p<0.05$ for positive dose-related trend.
[5] P values not reported for tumor incidences for metallic nickel and nickel alloys.

Table 25. Lung Tumor Response in Strain A Mouse Intraperitoneal Bioassay of Nickel Acetate (Stoner et al., 1976)

Total Dose[1] (mg Ni/kg)	Lung Tumor Incidence in Surviving Mice	Mean No. Lung Tumors/Mouse ± S.E.
0	7/19 (37%)	0.42 ± 0.10
17	8/18 (44%)	0.67 ± 0.16
42	7/14 (50%)	0.71 ± 0.19
85	12/19 (63%)[2]	1.26 ± 0.29
Positive Control[3]	18/18 (100%)	21.6 ± 2.81

[1] Total dose administered in study, assuming doses were reported as nickel acetate tetrahydrate
[2] Significantly increased ($p<0.01$) compared to vehicle control group.
[3] Single dose of 20 mg urethane/mouse.

Table 26. Kidney Tumor Incidences in Rats Following Initiation with Nickel Acetate and Promotion with Sodium Barbital (Kasprzak et al., 1990)

Group	Treatment	Incidences of Renal Cortical Tumors[1]		
		Adenoma	Adenocarcinoma	Adenoma or Adenocarcinoma
1	Nickel Acetate	1/23 (1)	0/23	1/23 (1)
2	Nickel Acetate + Sodium Barbital	13/24[2] (21)	4/24 (4)	16/24[2] (25)
3	Sodium Barbital	6/24 (9)	0/24	6/24 (9)
4	Saline	0/24	0/24	0/24

[1] Incidences in rats surviving until first tumor was observed. Total number of tumors in parentheses.
[2] Significantly ($P<0.002$) higher incidence than Group 1 or combined Groups 1 and 3 using Fisher's Exact Test.

Table 27. Tumor Incidences in Offspring of Rats Following Prenatal Exposure to Nickel Acetate via Maternal Intraperitoneal Injection and Postnatal Exposure to Sodium Barbital (Diwan et al., 1992)

Treatment Group[1]	Sex	Adenomas or Carcinomas	
		Kidney[2]	Pituitary
Group 1A,Nickel Acetate	M	0/17	9/17
	F	0/16	5/16
	M+F	0/33	14/33 (p=0.012)[6]
Group 1B, Nickel Acetate + Sodium Barbital	M	8/15 (p=0.007)[3,4]	6/15
	F	0/15	5/15
Group 2A, Nickel Acetate	M	0/15	6/15
	F	0/16	8/16
	M+F	0/31	14/31 (p=0.008)[6]
Group 2B, Nickel Acetate + Sodium Barbital	M	7/15 (p=0.012)[3,5]	7/15
	F	0/15	6/15
Group 4A, Sodium Acetate	M	0/15	1/15
	F	0/16	3/16
	M+F	0/31	4/31
Group 4B, Sodium Acetate + Sodium Barbital	M	1/15	2/15
	F	0/14	4/14

[1] See text for specific information on experimental design.
[2] Adenomas or carcinomas of the renal cortex or pelvis.
[3] Significant as compared with Group 4B males, Fisher's Exact Test.
[4] Group 1B had 15 tumors in 8 affected males.
[4] Group 2B had 10 tumors in 7 affected males.
[5] Significant as compared with Group 4A M+F, Fisher's Exact Test.

Table 28. Summary of Studies Investigating Asthmagenic Effects of Nickel

Cases	Occupational exposure	Historical features	Response to bronchial challenge	Specific skin prick test	Nickel-specific IgE	Reference
1	Nickel electroplating	Dermatitis Asthma	Sustained immediate FEV1 fall	Positive	N/A	McConnell et al., 1973
1	Nickel electroplating	Urticaria Asthma	Immediate FEV1 fall	Positive	Positive	Malo et al., 1982
1	Nickel/Chromium electroplating	Asthma	Immediate and delayed (3.5 hr) FEV1 fall	Negative	Positive	Novey et al., 1983
1	Nickel electroplating	Asthma	Late (3 hr) FEV1 fall	Negative	negative	Malo et al., 1985
3	Nickel catalyst plant	Asthma	N/A	N/A	N/A	Davies, 1986
1	Nickel/Zinc electroplating	Asthma	Immediate and delayed (6 hr) FEV1 fall	Positive	N/A	Hong et al., 1986

N/A = Not applicable; test not conducted.

Table 29. Studies and Endpoints Considered as the Basis for the Nickel RfD

Study/ Nickel Species	Species/ Strain/ Sex	Route	Duration	Endpoint	NOAEL/ LOAEL (mg/kg/day)	$BMDL_{10}$ (mg/kg/day)
Vyskocil et al., 1994/ $NiSO_4$	Rat/ Wistar/ M&F	Drinking water	6 months	Decreased glomerular function	None/ 6.9 (males)	–[1]
Ambrose et al., 1976/ $NiSO_4$	Rat/ Wistar/ M&F	Feed	2 years	Decreased body weight	8[2] / 80	11 - 58
American Biogenics Corporation, 1988/ $NiCl_2$	Rat/ Sprague Dawley/ M&F	Gavage/ water	92 days	Decreased body weight in males, pneumonitis in both sexes	5[3] (2.7) 35 (19)	1.5-17 (Based on decreased BW)
Dieter et al., 1988/$NiSO_4$	Mouse/B6C3F1/F	Drinking water	180 days	Thymic atrophy, decreased thymus weight	None/ 44	–[1]
Smith et al., 1993/$NiCl_2$	Rat/Long-Evans/ M&F	Drinking water	2-gen repro	Increased pup death	None/ 1.3 (equivocal)	–[1]

[1] No appropriate BMD was calculated for this study.

[2]The NOAEL and LOAEL were reported as 5 mg/kg/day and 50 mg/kg/day in the nickel RfD verified on 07/16/87, due to the use of a generic food factor of 0.05, rather than the strain-specific value used for this assessment.

[3] Assuming doses were reported in terms of nickel dose. The doses in parentheses are the nickel doses if the doses were reported in terms of nickel chloride hexahydrate.

Table 30. Endpoints Considered as the Basis for the Nickel RfC

Sex/Species	Duration	Endpoint	Region[1]	NOAEL/ LOAEL (mg Ni/m^3)	NOAEL(HEC)/ LOAEL(HEC) (mg Ni/m^3)	$BMCL_{10}$(HEC) (mg Ni/m^3)
M rat	Chronic	Lung fibrosis	PU	0.027/0.056	0.0021/0.0046	0.0017[2]
F rat	Chronic	Lung fibrosis	PU	0.027/0.056	0.0024/0.0052	0.0024
F rat	Chronic	Alveolar proteinosis	PU	0.027/0.056	0.0024/0.0052	0.0028
F rat	Chronic	Atrophy of olfactory epithelium	ET	0.056/0.11	0.0019/0.0039	0.0025-0.0026
M rat	Chronic	Atrophy of olfactory epithelium	ET	0.056/0.11	0.0033/0.0068	0.0038-0.0043
M rat	Chronic	Chronic active inflammation	PU	0.027/0.056	0.0021/0.0046	0.0020
F rat	Chronic	Chronic active inflammation	PU	0.027/0.056	0.0024/0.0052	0.0021
M rat	Chronic	Macrophage hyperplasia	PU	0.027/0.056	0.0021/0.0046	0.0012-0.0016
F rat	Chronic	Macrophage hyperplasia	PU	0.027/0.056	0.0024/0.0052	0.0013-0.0019
F rat	Subchronic	Atrophy of olfactory epithelium	ET	0.11/0.22	0.0016/0.0036	0.00048
F rat	Subchronic	Macrophage hyperplasia	PU	None/0.027	None/0.0027	–[3]

All data from NTP 1996a
[1]PU = pulmonary, ET = extrathoracic; TH = thoracic (pulmonary plus tracheobronchial)
[2]Used as the basis for the RfC
[3]Data not amenable to modeling because no information available on the shape of the concentration-response curve available