The Accumulation of Nickel in Human Lungs

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Using data from published studies, lung concentrations of nickel were compared for persons with and without occupational exposure to nickel. As expected, the concentrations were much higher for persons with occupational exposure. To estimate the effects of nickel-containing tobacco smoke and nickel in the ambient air on the amount of nickel accumulated in lungs over time, a model was derived that took into account various variables related to the deposition of nickel in lungs. The model predicted nickel concentrations that were in the range of those of persons without known nickel exposure. Nickel is a suspected carcinogen and has been associated with an increased risk of respiratory tract cancer among nickel workers. However, before the nickel content of cigarettes can be implicated in the etiology of lung cancer, further studies are needed to evaluate the independent effects of smoking and exposure to nickel.

Introduction

Since the 1930s, epidemiologic data have implicated nickel and certain nickel compounds in the etiology of lung cancer among occupationally exposed workers (1,2). The research has focused on workers in nickel refining and processing operations and to a lesser extent on other groups of workers occupationally exposed to nickel, e.g., stainless-steel welders. Detectable accumulations of nickel in the lungs of persons without known occupational exposure have been reported (Table 1) and may result from nickel present in ambient air and cigarette smoke, or through unidentified occupational exposure. It has not been established whether the concentration of nickel in ambient air or cigarette smoke is sufficient to result in a significant accumulation in human lungs and present a health risk.

This paper reviews data on nickel concentrations found in the lungs of occupationally and nonoccupationally exposed persons. These concentrations are compared to those obtained from a model that estimates the amount of nickel accumulated in human lungs through nickel-contaminated ambient air and cigarette smoke.

Materials and Methods

The amount of nickel accumulated in lungs from breathing ambient air and from cigarette smoking was estimated using the following data. About 40 to 90% of nickel

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in ambient air is insoluble. One study found that an average of 41% of the nickel in ambient air was in an insoluble form (3). Other sources (2,4) indicate this percentage may be considerably higher.

Data on the biological half-life of nickel in human lungs are scarce. One study determined the half-life to be about 1 year in human lungs (5). An *in vitro* study (6) estimated the dissolution half-life of some nickel compounds (Ni, NiO, and others) to be over 11 years. Other sources (2) indicate that the clearance rate of nickel from lungs is slower for insoluble compounds such as nickel oxide. The International Commission on Radiological Protection (7) estimated the half-life of nickel in human tissues to be about 3.3 years.

The volume of air breathed per day is 20 m³ (10 m³ per 8-hr workday and 10 m³ for the remainder of the day) (7). The volume of human lungs is assumed to be 5000 cm³. About 35% of the nickel inhaled is deposited in the lungs (8). The average amount of inhaled particulate nickel per cigarette smoked is from 0.07 μg (5) to 0.2 μg (8). One cubic centimeter of fixed lung tissue is equivalent to 1 g wet weight.

Ambient air nickel concentrations in most United States cities range from 0.01 to 0.25 μg/m³ (Environmental Protection Agency, unpublished data, 1986).

The following model estimates the total amount (T) of nickel accumulated in lungs over time:

$$T = (365/12)PL[DM \sum_{i=1,S} \exp(-Ci) + BA \sum_{j=1,N} \exp(-Cj)],$$

where: P = % nickel deposited in lungs, L = % insoluble nickel, D = number cigarettes smoked per day, M = μg nickel per cigarette smoked, S = months of cigarette smoking, B = volume air breathed per day, A = ambient air nickel concentration (μg/m³), N = months of nickel accumulation from breathing ambient air, and C = decay constant.

Table 1. Nickel concentrations in lungs of persons with no known occupational exposure to nickel.

Reference	n	Mean nickel, μg/g wet weight[a]	Range, μg/g wet wt	Comments[b]
9	25	< 0.5		Coal miners
	25	< 0.5		Nonminers Lower detection limit = 0.5.
10	141	1.8–2.1	< 0.5–2.8	U.S. subjects. Nickel in lungs of 70 of 141 persons. 90th percentile = 2.8. Lower detection limit = 0.5
11	44	0.8–1.1	< 0.5–4.2	African subjects, ≥ 20 years of age. Nickel in lungs of 25 of 44. Lower detection limit = 0.5
	34	2.2–2.4	< 0.5–3.6	Near East subjects, ≥ 20 years of age. Nickel in lungs of 19 of 34. Lower detection limit = 0.5.
	69	1.4–1.6	< 0.5–7.4	Far East subjects, ≥ 20 years of age. Nickel in lungs of 44 of 69. Lower detection limit = 0.5.
	7	2.0 ± 0.34	0.7–3.5	Swiss subjects, ≥ 20 years of age
12	4	0.016	0.008–0.024	18–44 years of age.
5	25	0.23 ± 0.06		20–40 years of age. Autopsies. AAS.
13	30	0.16 ± 0.094	0.038–0.44	15 males, 15 females. Levels 2 times higher in males. 10–60+ years of age. FAAS. Autopsies.
14	2	1.65	0.3–3	1 case leukemia, 1 case lung cancer.
15	11	0.6	0.1–2.2	FAAS. Autopsies.
16	35	0.04 ± 0.025	< 0.01–0.12	PIXE.
17	12	0.085 ± 0.065	0.008–0.221	AAS. Autopsies. 18–72 years of age.
18	16	0.018	0.004–0.036	FAAS. Autopsies. About 27–85 years of age.
19	25	—	0.004–0.2	. FAAS. Autopsies. 4 cases lung cancer

[a]Concentrations given as μg/g dry weight were converted to μg/g wet weight by dividing by 10 (20); values given as parts per million (ppm) were taken to be equivalent to μg/g wet weight unless stated as ppm dry weight.

[b]Abbreviations: AAS, atomic absorption spectroscopy; FAAS, flame atomic absorption spectroscopy; PIXE, particle-induced X-ray emission.

The model assumes that the accumulation occurs at the beginning of each month, and the decay process occurs throughout the month. This approximation to a dynamic model has a negligible effect on the total amount of nickel accumulated. The model provides estimates of the average amount of nickel accumulated in lung tissue but does not take into account individual variations, the amounts of specific nickel compounds accumulated, or the amount of nickel accumulated at different sites within the lung. The information needed to include these parameters in the model was not available.

Results

Table 1 gives nickel concentrations in lung tissue for persons without occupational exposure to nickel, and Table 2 gives the concentrations for nickel workers. Excluded are studies that gave nickel concentrations that were at least an order of magnitude below those given in other studies (2,24). Not all studies provided data on occupational exposure to nickel, and Table 1 may include some persons with occupational exposure. Although there is some overlap between the lung concentrations of nickel

Table 2. Nickel concentrations in lungs of nickel workers.

Reference	n	Mean nickel, μg/g wet weight[a]	Range, μg/g wet wt	Comments
9	2	10.5	9–12	Lower limit of detection = 0.5; both cases had lung cancer
21	1	0.197		Smoked 20 years; < 1 pack/day
22	1	280		Lung cancer; lung removed 10 years after leaving refinery
14	4	36.3	6–116	All cases had lung cancer
15	1	210		Nasal cancer; smoker
	9	23	0.5–68	Lung cancer; eight cases were smokers
	12	10	0.5–27	Cancer other than lung cancer; 4 cases were postmortem specimens; flame atomic absorption spectroscopy
23			2–1350	Autopsy specimens; electrothermal atomic absorption spectroscopy

[a]See footnote a of Table 1 for an explanation of calculations.

of persons with or without known occupational exposure to nickel, the mean values for nickel workers are considerably higher than those of nonexposed persons.

Tables 1 and 2 give the analytical methods used for determining nickel concentrations or the lower detection limits if provided. All of the more recent technologies, e.g., atomic absorption spectroscopy, have lower detection limits in the range of 0.01 ppm nickel (25). Variations in the mean nickel content of lungs of persons without known occupational exposure to nickel are probably not due to the analytical techniques used. Most likely they reflect variations in the sampling methods used, the ages of the persons evaluated, and their accumulated exposures to environmental nickel.

Using the nickel accumulation model, nickel concentrations in the lungs of nonsmokers for nickel half-lives of 1 or 9 years, air concentrations of 0.01 or 0.25 $\mu g/m^3$, 40 or 90% insoluble nickel, and for 10 to 60 years of accumulation are given in Table 3, and nickel concentrations in the lungs of persons who smoked 1 or 3 packages of cigarettes per day for 10 to 50 years are given in Table 4. For short nickel half-lives (1 year) the nickel concentrations reach a steady state within about 10 years. For longer half-lives (9 years) nickel continues to accumulate throughout the entire period of exposure. To estimate the total lung concentration of nickel from ambient air exposure and smoking, the appropriate values from Tables 3 and 4 are added. For example, for a nickel half-life of 1 year, an air concentration of 0.25 $\mu g/m^3$, an insoluble fraction of 40%, smoked three packages of cigarettes (0.2 μg nickel/cigarette) per day for 30 years, the nickel concentration in the lungs after 40 years is 0.07 (Table 3) + 0.17 (Table 4) = 0.24 $\mu g/g$ wet tissue.

Table 3. Accumulation of nickel in lung tissue from ambient air.

Air conc., $\mu g/m^3$	Half-life, years	Insoluble, %	Years of nickel accumulation			
			10	20	40	60
0.01	1	40	< 0.01	< 0.01	< 0.01	< 0.01
		90	0.01	0.01	0.01	0.01
	9	40	0.01	0.03	0.03	0.03
		90	0.03	0.04	0.06	0.06
0.25	1	40	0.07	0.07	0.07	0.07
		90	0.17	0.17	0.17	0.17
	9	40	0.35	0.52	0.63	0.66
		90	0.80	1.18	1.41	1.47

Comment

The deposition and removal of particulate matter from lungs is a complex process, and the type of model used in this paper can only approximate this process. Nevertheless, the model appeared to provide reasonable estimates of nickel accumulation in lungs in that they were in the range of values obtained from the analyses of lung tissue among persons without occupational exposure to nickel. The model could be used to derive nickel accumulations from occupational exposures using time-weighted exposure data, which may be useful in assessing the nickel burden resulting from these exposures.

Lung concentrations of nickel were derived from the model using various assumptions and a range of values that probably include the upper and lower bounds of the relevant parameters. For some sets of model parameters lung concentrations increased over the durations of exposure/smoking evaluated. This is in agreement with the finding that nickel concentrations in human lungs increase with age (18).

Many of the persons included in the studies in Table 2 had respiratory tract cancer. These cases were probably selected for evaluation and do not represent a random sample of persons with either occupational exposure to nickel and/or lung cancer. Also, the lung concentrations of nickel given in Table 2 do not establish levels that might pose a carcinogenic risk.

The model derived in this paper shows that heavy cigarette smoking (three packages/day) significantly increases the amount of nickel accumulated. For the same sets of model parameters, smoking contributes more to the total nickel lung concentration than high ambient air levels (0.25 $\mu g/m^3$). But, the total amount of nickel accumulated in lungs of heavy smokers is considerably less than the amount accumulated by persons occupationally exposed to nickel.

Some epidemiologic studies have found elevated lung cancer risks for workers in the nickel mining and refining industries and industries using nickel (2). In 13 studies of nickel miners and refiners, the standardized mortality ratios (SMRs) for lung cancer ranged from 0.72 to 5.5 (median, 2.1). In nine studies of industries using nickel, the SMRs ranged from 0.59 to 2.0 (median 1.2). These studies did not take into account the smoking habits of the work-

Table 4. Accumulation of nickel in lung tissue from cigarette smoking.

			μg nickel per cigarette					
			0.07			0.2		
Half-life, years	Insoluble, %	Packs per day	Years of cigarette smoking					
			10	30	50	10	30	50
1	40	1	0.01	0.01	0.01	0.06	0.06	0.06
		3	0.06	0.06	0.06	0.17	0.17	0.17
	90	1	0.04	0.04	0.04	0.13	0.13	0.13
		3	0.14	0.14	0.14	0.39	0.39	0.39
9	40	1	0.10	0.17	0.18	0.28	0.48	0.52
		3	0.30	0.49	0.53	0.85	1.43	1.55
	90	1	0.22	0.36	0.39	0.64	1.07	1.17
		3	0.66	1.09	1.19	1.92	2.81	3.50

ers. Therefore, the SMRs may either underestimate or overestimate the risks of lung cancer if the smoking habits of the nickel workers differed from those of persons in the comparison populations. In contrast to the lung cancer SMRs for persons with occupational exposure to nickel, the lung cancer SMR for men who smoked over two packages of cigarettes per day is 16.6 (26). Before the nickel content of cigarettes can be implicated in the etiology of lung cancer, further work needs to be done to evaluate the separate effects of smoking and exposure to nickel.

The model derived in this paper did not consider the form of nickel accumulated or the concentration of nickel at different sites in the lung. Both of these variables may be important in the evaluation of nickel carcinogenesis. Some nickel compounds, e.g., nickel subsulfide, have been classified as known human carcinogens. The Environmental Protection Agency (2) has commented that there is a reasonable probability that the ultimate carcinogenic form of nickel is the nickel ion and that all forms of nickel might be regarded as potential human carcinogens.

The model used in this paper probably gives reasonable predictions of the amount of nickel accumulated in lungs over time from breathing ambient air and from cigarette smoking. The model cannot be used to make inferences about the carcinogenic risks resulting from the derived nickel accumulations.

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