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SCIENTIFIC AND TECHNICAL ASSESSMENT REPORT

ON

NICKEL

NOTICE

This document is a preliminary draft. It has not been formally released by EPA and should not at this stage be construed to represent Agency policy. It is being circulated for comment on its technical accuracy and policy implications.

U.S. ENVIRONMENTAL PROTECTION AGENCY

OFFICE OF RESEARCH AND DEVELOPMENT

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PREFACE

Although this report is issued in the Scientific and Technical Assessment Report Series, it differs in several respects from the comprehensive multi-media format that the Series will usually have because it was nearly completed prior to the creation of the STAR series in August 1974.

This document was prepared by a task force convened at the direction of Dr. John F. Finklea, Director, U. S. Environmental Protection Agency, National Environmental Research Center (NERC), Research Triangle Park (RTP), N. C. Assembly, integration, and production of the report was directed by the Special Studies Staff, NERC/RTP. The objective of the task force was to review and evaluate the current knowledge of nickel in the environment as related to possible deleterious effects upon human health and welfare

Information from the literature and other sources has been considered generally through March 1974.

A report prepared for the U. S. Environmental Protection Agency (EPA) by a National Academy of Sciences' Panel on Nickel of the Committee on Medical and Biological Effects of Environmental Pollutants served as a primary reference for this report.

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1. INTRODUCTION

The purpose of this document is to summarize our current knowledge of nickel in the environment, and the effects of nickel compounds upon human health and welfare; and to assess this knowledge base with a view toward the need for control of the activities of man which impact upon the nature and distribution of nickel in the environment. It was not intended that this document constitute an in-depth scientific summary of biological effects. Such an in-depth summary has been prepared by the National Academy of Science Panel on Nickel and was used as a basic reference for this report. Primary emphasis is placed on those aspects of the problem which are considered most important relative to the decision making processes which are the responsibility of the Environmental Protection Agency. The major concerns of this document are the transformation and distribution processes which govern spatial and temporal changes in the concentration of various nickel compounds in air, water, soil, and biota. Particular attention is given to those processes and interface problems which may provide the insight necessary for prudent decisions regarding management and control. These include measurement and analytical techniques necessary for monitoring environmental loading and man's contribution thereto, transport and removal processes within and between environmental media, mechanisms and risks of exposure and response, undesirable effects, and control technology and remedial action. An attempt is made to establish a set of decision-making criteria and a systematic framework for evaluating alternative control actions.

2.0 SUMMARY AND CONCLUSIONS

2.1 SUMMARY

Nickel is a natural component of the earth's crust where it is found in igneous rock and in shale. Large nodule deposits with a high nickel content have been found on the ocean floor. The average farm soil contains 0.003 percent or more of nickel although concentrations vary widely from area to area.

Nickel is found in all coals and is also found in crude oil.

Sea water has a nickel content ranging from 0.1 to 0.5 μg/liter, while the mean concentrations in the waters of the major river basins of the United States range from 3 to 56 μg/liter.

Little is known concerning natural atmospheric sources of nickel. The forms of nickel in air and their reactions have not been extensively studied. It would be expected that nickel would be present predominately in particulate form.

Nickel has been found in material filtered from the air throughout the United States. Urban values are generally higher than nonurban with the highest values generally being in the industrialized cities of the East. The highest nonurban values in the East exceed some urban values found in the western parts of the nation.

Clear annual average trends are not apparent in the data presented. Seasonal variations are observed at some but not all sites.

Limited data on particle sizes associated with nickel are available. They suggest that less than half of the nickel is to be found in the smaller particulates, 1 micrometer or less in diameter.

The largest source of nickel emissions to the air is the combustion of fossil fuel; mining and metallurgical nickel products are additional sources. Nickel emissions from power generating plants using pulverized coal is concentrated in particulate matter of less than one micrometer in diameter and, therefore, is respirable. Use of oil presents a similar hazard since 90 percent of such particulate emissions are less than one micrometer.

Diesel engine exhausts and exhausts from cars with catalysts are possible mobile sources of nickel emissions.

The average nickel concentration in drinking water obtained from a survey of community water supplies was 4.8 µg/liter. Among the common foods for which the nickel content has been ascertained, the following have relatively high levels of Ni: baking powder, 13.4 µg/g; orange pekoe tea, 7.6 µg/g; buckwheat seed, 6.5 µg/g; cocoa, 5.0 µg/g; gelatin, 4.5 µg/g; black pepper, 3.9 µg/g; mushrooms, 3.5 µg/g; cabbage, 3.3 µg/g; red kidney beans, 2.6 µg/g; oats, 2.4 µg/g; and shortening, from 2.0 to 6.0 µg/g.

The nickel content of plants is usually less than 1 ppm. Plants whether they are used for food or not, may be exposed to nickel from the air, in the water or in the soil. Aerial exposure occurs largely due to nickel dust from industrial processes and motor vehicles being deposited on vegetation and the soil.

Nickel concentrations in soil in industrial areas were 1.4 times higher than soil in residential zones and levels around airports were

higher than either the industrial or residential soils. Agricultural soils were found to have concentrations slightly above residential levels.

Phosphate fertilizers and sewage sludge may raise soil concentrations of nickel when added to the soil. Fertilizers have shown nickel concentration ranges from 3.0 to 38.0 µg/g; sewage sludge <32 to 2900 µg/g dry weight.

Fallout from automobiles may increase the nickel content of soil along highways

Exposure of terrestrial plants to nickel occurs chiefly through the roots. Nickel can only enter the plant when in soluble form and is dependent on soil moisture, pH, the solubility and chemistry of nickel, chemical binding, and the presence and competition of other elements.

Routes of exposure of man and other animals to nickel are essentially the same, with differences, perhaps, in relative magnitude of importance. The routes of exposure of animals in order of importance are: ingestion, inhalation, absorption through the skin, and parenteral administration.

Exposure of animals other than humans to nickel is dependent on their choice of food plants. In the case of domestic animals, it will be principally through the nickel present in pasture grasses and feed grains.

It has been suggested that mammals possess mechanisms that limit intestinal absorption of nickel. Feeding experiments using dogs suggest that 10 percent of soluble nickel is absorbed. Higher absorption in dogs than in man might be expected due to the relatively low pH of the canine gastric juices.

It has been estimated that the nickel content of food and water ingested by human beings ranges from 300 to 600 μg per day; however, most of the nickel content of the diet passes through the gastrointestinal system unabsorbed.

The highest concentration of nickel in the body is in the skin. The estimated quantity of nickel inhaled by a resident of one of the cities having the highest measurements of nickel in ambient air are 2.36 μg/day in New York City, or 13.8 μg/day in East Chicago. The average daily intake of nickel by urban residents is 2 to 14 μg/per day, depending upon the season and the location.

The amount of nickel inhaled by smokers of cigarettes has been estimated: A smoker who consumes 40 cigarettes per day inhales a maximum of 14.8 μg of nickel per day from this source.

Nickel is found in normal human serum and in rabbit serum in three forms; bound to albumin, bound to an α-macroglobulin termed "nickeloplasmin," and in ultrafilterable complexes. The latter complexes may function as carriers for the extracellular transport and renal excretion of nickel, since certain of them are also present in urine.

Nickel has also been shown to bind to isolated DNA, RNA, and protein as well as to their monomeric subunits.

Nickel is known to inhibit a number of enzymes, notably 5-nucleotidase and ATPase, the latter being an essential enzyme in energy transfer reactions.

In its effect on nervous and contractil

In its effect on nervous and contractile tissue, nickel appears to compete with and to imitate the effects of calcium, causing essentially a prolonged action potential and an uncoupling between membrane activation and muscle contraction. Few effects of nickel on the central nervous system have been reported.

Nickel meets certain criteria for essentiality as a micronutrient by virtue of its: demonstration in the fetus or newborn, homeostatically regulated concentration, pathophysiologically altered metabolic pool, presence as an integral part of an enzyme, and prevention or reversal of a deficiency state. With regard to these criteria, it has been demonstrated that nickel can cross the placenta (man), that the kidney processes an active excretory mechanism for nickel (man), that nickel concentrations in serum are significantly increased following myocardial infarction and after stroke and burns (man), and that perimitochondrial dilation of rough endoplasmic reticulum may be an early sign of hepatocyte degeneration in nickel deficiency (chicks).

Nickel salts are relatively non-toxic by the oral route but quite toxic when administered intravenously. Less information is available regarding toxicity by inhalation, except for nickel carbonyl which is extremely toxic. It is known, however, that nickel oxide displays moderate retention in the hamster lung. The pulmonary parenchyma is the target tissue for nickel carbonyl regardless of the route of exposure. Interstitial edema and epithelial hyperplasia proceed severe intra-alveolar edema and death. Pathologic findings in other organs are generally less severe.

It has been suggested that the acute toxicity of nickel carbonyl may result, in part, from inhibition of the utilization of ATP as previously mentioned. The principal concern over nickel carbonyl is related to its carcinogenicity rather than its toxicity.

The carcinogenicity of nickel compounds, in general, appears to be inversely correlated with their solubility in aqueous media. The stronger carcinogens, Ni_3S_2 and NiO, are practically insoluble in aqueous solutions, while the non-carcinogens, $NiSO_4$, $NiCl_2$, and $NiNH_4SO_4$ are highly soluble. NiS, which has low solubility, is an exception, exhibiting low carcinogenicity, as is $Ni(C_2H_3O_2)_2$, which is relatively soluble, in showing moderate carcinogenicity. Although there has been considerable speculation, the exact mechanisms whereby nickel compounds exert their carcinogenic actions are incompletely understood. The mechanisms whereby nickel enters target cells are undoubtedly important in the etiology of nickel carcinogenesis. In the cases of nickel carbonyl and nickelocene, it appears that the intact compounds pass across the cell membrane without metabolic alteration. With other, rather insoluble inorganic nickel compounds, such as nickel subsulfide, a diffusible intermediate complex appears to be involved in the intracellular transport of the metal. Once entry into the cell is gained, the biochemical effects of the Ni^{2+} ions may become an important aspect of nickel carcinogenesis. The inhibitory effects of nickel compounds, particularly nickel carbonyl, on RNA synthesis are particularly noteworthy.

There is some evidence that nickel compounds may interact synergistically with polynuclear aromatic hydrocarbons in reducing the time required for tumor production.

Nickel dermatitis, "nickel itch," occurs among nickel miners and workers in smelters, refiners and the nickel-plating industry. Currently, nickel dermatitis is being reported by non-industrial populations who came in contact with the metal in their every day activities.

Nickel has not been demonstrated to be an essential element for plant growth. Lack of nickel in the soil does not appear to be detrimental, while an overabundance is.

Dwarfing or growth repression, chlorosis and death all occur from overabundance of nickel.

Toxicity of nickel usually appears in plants when concentrations are 3 ppm or higher.

Tolerance mechanisms may be "external" or "internal" in nature. Tolerant plants are metabolically different from normal plants. They also have mechanisms which concentrate nickel in the epidermis and sclerenchymatous tissue.

Most microorganisms are sensitive to nickel compounds; however, a few exist which are capable of oxidizing nickel sulfides. These bacteria are found on mine drainage areas.

Inorganic nickel salts have been used as fungicides. Landfill leachates contain varying amounts of nickel, and have the porential for contaminating drinking water supplies. Nickel can also enter the environment through the incineration of municipal solid wastes, but the quantities reported are small. The nickel content of composts made from such wastes is also relatively small. Continued recycling of municipal incinerator residue for scrap steel may result in a buildup of nickel (and other metallic impurities.

Control technology for the disposal of nickel-bearing materials in landfills involves detailed site planning and engineering.

2.2 CONCLUSIONS

The following are the more significant conclusions derived from the currently available information regarding nickel in the environment:

o Nickel has been found in air throughout the country. Urban concentrations are generally higher than nonurban with the highest values generally being found in the industrialized cities of the East. Some season variations have been noted at some sites, but annual trends are not obvious.

o It appears that less than half of the atmospheric nickel is associated with fine particulates; however, data on particle size is limited.

o The chemical reactions, chemical forms, residence time, ultimate fate and the transformation and transport of nickel-containing particles are not known.

o By far the largest source of atmospheric nickel is the combustion of fossil fuels. Particulate matter in the respirable range (>/μg) is emitted from the burning of pulverized coal and from the combustion of oil.

o The use of nickel-containing catalysts may add to the atmospheric loading of nickel.

o The extent to which the nickel concentrations present in ambient air pose a hazard for human health is at present unknown.

o Ingestion is the chief route of exposure to nickel for humans not exposed occupationally. Most of the ingested nickel is excreted in the feces.

o Food from plants growing in normal agricultural soils do not constitute an important source of nickel exposure to humans.

o The nickel-containing stainless steels used for food processing equipment are thought to dissolve only minute amounts of metal, "trace quantities having no pharmacological significance."

o Except for the potential toxicity to crop producing plants, there is little evidence available to indicate that nickel contamination of soils is a critical problem. There are many published accounts of nickel toxicity to selected crops. Soils near nickel mining areas can be expected to contain toxic levels of nickel. Sewage sludge is also a potential significant source for nickel contamination of soils, as are industrial sludges containing nickel.

o The movement of nickel through biological food chains has not been well documented.

o Landfill leachates have the potential for contaminating drinking water supplies with nickel, therefore good landfill management is important.

o The incineration or composting of municipal solid waste does not constitute a major nickel pollution problem.

o Very little is known about the chemistry of nickel and its compounds in seawater, however, it appears that the concentration factor of nickel is among the lowest in the transition metal groups.

o The probability of exposure to nickel carbonyl, the most toxic of all known organic nickel compounds, is limited primarily to cases of occupational exposure.

ô A smoker who consumes two packages of cigarettes per day may inhale 1-5 μg of nickel per year, 84 percent of which may be nickel carbonyl.

o The principal concern over nickel carbonyl is over its carcinogenicity rather than its toxicity. The exact mechanisms whereby nickel compounds exert their carcinogenic actions are incompletely understood.

o There is no evidence to indicate that the risk of the general population to exposure to nickel through inhalation of ambient air or oral intake through food and water is cause for concern.

o Nickel hypersensitivity due to contact with the metal is quite common among the nonindustrial population, particularly women; however the true incidence among the general population is unknown. The capacity of nickel to act as a skin sensitizer is also unknown.

3. CHEMICAL AND PHYSICAL PROPERTIES

Nickel is a silvery-white metal that is hard, malleable, and ductile. It has an atomic weight of 58.71, a specific gravity of 8.9, a melting point of 1455°C, and a boiling point of 2900°C. It is insoluble in both hot and cold water but soluble in dilute acids. There are five isotopes of nickel, 58, 60, 61, 62, and 64 which occur in natural abundance of 67.88, 26.23, 1.19, 3.66, and 1.08 percent respectively. The most common valences of nickel are 0 and 2^+, but the element may form compounds with more uncommon valences as 1^-, 1^+, 3^+, and 4^-. Nickel is highly magnetic and is not oxidized under ordinary conditions.

Nickel is not found in the free state in nature. It occurs, along with iron, as an alloy. The most important ores are pentlandite, a sulfide of iron and nickel, and garnierite, a hydrated magnesium-nickel silicate of variable composition. A major producing area for nickel is Ontario, Canada. Other producing areas include Cuba, New Caledonia, the Scandinavian countries, South Africa, and Russia.

The process used most extensively for obtaining pure metallic nickel involves separation of the sulfides of nickel, copper, and iron by selective flotation. After separation, the nickel sulfide is converted to the oxide by roasting, and the oxide is reduced with carbon affording approximately 96 percent pure metallic nickel. It is then cast into huge anodes and refined electrolytically in a nickel (II) sulfate bath. The nickel which deposits on the cathode is 99.98 percent pure.

In combination, nickel exhibits an oxidation state of +2 almost exclusively. One notable exception is tetravalent nickel in the dioxide, NiO_2 a black anhydrous substance formed by the oxidation of nickel (II) salts in alkaline solution. Soluble nickel salts are prepared from nickel (II) oxide (NiO). Nickel (II) sulfide is produced as a black precipitate by the action of ammonical sulfide solutions upon nickel (II) salts. This compound exists in at least two crystalline modifications of different degrees of solubility in mineral acids; this property is of value in the analytical separation of the element.

Because of its hardness, resistance to corrosion, and high reflectivity when polished, nickel is widely used in the plating of iron, steel, and copper. It is also a constituent of many important alloys. Monel metal, (Ni, Cu and a little Fe), is used as a corrosive resistant alloy. Permalloy, (Ni and Fe), is remarkably permeable to the magnetic field. It is used in instruments for the electrical transmission and reproduction of sound. German silver is a nickel-zinc-copper alloy. Nickelchrome and chromel are alloys containing nickel, iron, and chromium; they are resistant to oxidation at high temperatures and show high electrical resistance at high temperatures, so are used in electrical heating units such as stoves, pressing irons, and toasters. Alnico contains aluminum, nickel, iron, and cobalt. Platinite and invar are nickel alloys which have the same coefficient of expansion for "seal in" wires through glass, such as those in electric light bulbs. Nickel coins contain 75 percent copper. Finely divided nickel is used as a catalyst in the hydrogenation of oils.

4. MEASUREMENT TECHNIQUES

4.1 AIR

4.1.1 Air Sampling

Air pollutants containing nickel are usually in particulate form. Samples can be collected by means of high volume samplers, sequential tape samplers, electrostatic precipitators, scrubbers, impingers, or impactors. The selection of filter material is made to minimize probable interference with the method of measurement.

4.1.2 Preparation of Sample

Particulate nickel collected on paper, fiberglass, or Teflon filters as well as on impingers can be dissolved with nitric acid, the excess nitrogen oxides removed by boiling, and the solution made up to volume. Three of the methods to be described require no prior chemical preparation of the sample.

The available analytical methods for nickel are based upon the techniques listed below:

- o Atomic Absorption Spectrometry
- o Spectrophotometry with dimethylglyoxime or other color regeants
- o Polarography
- o Anodic Stripping Voltammetry
- o Optical Emission Spectroscopy
- o Ring Oven
- o X-Ray induced Fluorescence
- o Neutron Activation Analysis

The last two require virtually no chemical separation nor preparation of the sample prior to measurement. Economic considerations,

calls for multiple elements and many samples. The ring oven is a simple, inexpensive device whose use requires no prior treatment of the collected sample.

4.1.3 Analysis

4.1.3.1 Atomic Absorption--Atomic absorption (AA) spectroscopy is the most popular technique for metals analysis and serves well for the determination of nickel in solution. In order to adapt it to the increased sensitivity demand of water samples and some biological samples, concentration techniques (either solvent or chelation) are used. AA spectroscopy, involves dissociating the element of interest into an un-ionized, unexcited ground state. In this condition, the element can absorb radiation at discrete narrow emission lines provided by a hollow cathode lamp, which contains neon or argon at low pressure and has a cathode of the element sought. The intensity of absorption measures the element present. The resonance line for nickel is 232 nm.

Background absorption is a problem when nickel is measured by AA. The absorption occurs when appreciable concentrations of sample solvent, such as ethyl propionate or methyl isobutyl ketone, are aspirated into the flame. This background is measurable at 232 nm.

The nickel analysis will fit into the scope of the AA technique with a modicum of effort. Fifteen elements can be analyzed in about 30 minutes, not including sample preparation. A tentative method of analysis for nickel in atmospheric particles has been proposed by Kneip et al.[1]

A solvent-extraction method by Sachdev and West[2] can be used to isolate nickel from interferences in aqueous solution and concentrate it as well. A mixed ligand system containing 0.1 percent dithizone, 0.75 percent 8-quinolinol, and 20 percent acethyl acetone in ethyl

propionate is used. The extraction is carried out at pH 6 ± 0.05 with ammonium tartrate. The organic extract is aspirated into the air-acetylene flame. It is claimed that concentrations as low as 0.004 ppm can be determined.

The above method has been modified by Dharamarajan and West[3] to apply directly to air samples collected on membrane or fiberglass filters. In this modified method a portion of the filter with sample is moistened with 2 ml of 15 percent ammonium acetate solution, then ten milliliters of ligand mixture are added, and the organic extract is aspirated.

4.1.3.2 Spectrophotometry--Spectrophotometry with color forming reagents is a technique with a long history. It is used most frequently in water analysis and is not as fast as AA even on a routine basis. The spectrophotometric method for measuring nickel is based upon the formation of dimethylglyoxime complex. It is one of the best known colorimetric methods. The nickel compound is formed in citrate solution. Oxidation with bromine water intensifies the color. The complex is extracted from aqueous solution with chloroform. Cobalt or copper interference is removed with an ammonia wash and manganese interference is thwarted with hydroxylamine hydrochloride. The absorbance is measured at 445 nm. Sensitivity of the procedure is estimated to be 0.0042 mg/cm^3.

Forester and Jones[4] report that α-furil dioxime forms a sensitive, stable color with nickel at 535 nm. The color can be extracted with chloroform to enhance sensitivity and improve selectivity. However, oxidation of nickel furil dioxime with bromine or iodine to increase color intensity does not work as in the case of nickel dimethylglyoxime.

4.1.3.3 Polarography--The polarographic method relies on the diffusion current produced from the oxidation or reduction process which occurs at an electrode with renewable surface. A dropping mercury electrode is typical of the type used. The potential required for the process is characteristic of the species in solution. This makes it possible to resolve several ions in solutuion by varying the applied potential. The principle underlying the use of polarography for quantitative analysis is that the diffusion current is directly proportional to the concentration of sample ions if other pertinent variables are kept constant.

A polarographic method for nickel reported by West and Dean[5] uses sodium fluoride as the background electrolyte. Sodium fluoride eliminates interference by forming stable complexes with iron, cobalt, and copper. Evaluation of the measurement can be made from a standard curve of current versus concentration or by adding a nickel standard to a second aliquot of sample and testing it with the polarographic procedure.

Although the above method is an example of the classic polarographic technique, it falls short of the sensitivities obtainable by the spectrometric methods. Polarographic techniques can be improved by the use of pulse polarography.

D. D. Gilbert[6] described a pulse method for measuring nickel and vanadium, that used the differential mode of operation. Good agreement with colorimetric and emission spectroscopic procedures was demonstrated. Concentrations of 0.045 µg/ml could be determined.

Pulse polarography compares favorably with atomic absorption in sensitivity limits but is not as fast if only one or two elements are to be determined.

4.1.3.4 Anodic Stripping Voltammetry--Anodic stripping voltammetry (ASV) is recommended for its sensitivity. Pulse techniques are known and sample volumes as small as 2 ml are sufficient. The desired metals are plated out of solution onto an electrode. Then, the electrode potential is varied linearly in the anodic direction. This causes the metals to be stripped off in turn from the electrode. The dissolution curve, amperage versus voltage, shows a current peak as each metal species goes into solution. As long as the voltage is changed at a fixed rate, the curve is also amperage versus time. Thus, the area under the peak is a measure of nickel content. If the peak is sharp, its height can be the measure. Calibration is made with standards.

The kinds of electrodes used are mercury pool and drop, mercury film on inert metal, or inert metal, either platinum or gold. Nicholson[7] described a study which produced a set of analytical conditions for ASV of nickel at solid electrodes. The solution contained nickel in a complex ion (thiocyanate) in order to bring plating and stripping reactions within a reasonable range of potential. Even under such favorable conditions, mercury is oxidized at the stripping voltage, masking the nickel current. Because of this, inert electrodes of gold or platinum were used. Nickel concentrations as low as 5×10^{-8} M (3 ppb) were determined. In order to produce measurable currents, the plating-stripping times were increased for increasingly lower concentrations.

4.1.3.5 Optical Emission Spectrometry--In this technique, the sample in solution is dispensed by rotating an electrode into the region of a high voltage A.C. spark. The emission is analyzed, usually by diffraction grating. The metal concentration is determined by comparing intensity of sample emission to intensity of emission for standard solution at a selected wavelength.

R. J. Thompson[8] has described the procedure which is used in EPA for the spectroscopic determination of metals in atmospheric particulate matter. The sample collection phase is carried out with glass fiber or membrane filters. The sample is treated successively by low temperature ashing and solution in a mixture of nitric and hydrochloric acid. For the spectroscopic step, a Quantometer is set to read out a number of metals.

Generally, atomic absorption is more precise, accurate, and manipulatively simpler than optical emission spectrometry. The detection limits of the two methods are not too far apart for nickel. For atomic absorption it is 0.004 $\mu g/m^3$ compared to 0.006 $\mu g/m^3$ for optical emission spectroscopy. Thompson[8] states that, for routine analysis involving more than six metals, the use of emission spectroscopy becomes efficient.

4.1.3.6 Ring Oven Method--The ring oven is suited for the identification and quantification of airborne particulate material. The apparatus is simple and convenient for field use. The sample can be collected by tape sampler or simply on filter paper. The dust spot sample is centered on the heated ring of the oven. If the spot is less than 22 mm in diameter it can be analyzed without prior sample preparation. The procedure is reviewed by West.[9]

The lower limit of identification is 0.08 μg and the range of determination is 0.1 to 1.0 μg nickel. There are no potential interferences. When the ring zone is exposed to formaldehyde, the tetracyanonickelate complex, which is formed during preliminary treatment of the spot with potassium cyanide is broken, thereby freeing the nickel to react with dimethyl-glyoxime.

4.1.3.7 X-Ray Fluorescence Spectrometry--X-ray fluorescence spectrometry consists of irradiating the filter medium or impactor film containing the collected particulate matter with X-rays. The method appears to be rapid, sensitive, and capable of doing multicomponent analysis on a routine basis. However, large numbers of samples are needed to justify the costs. Photons of sufficient energy produce vacancies in the inner shells of the atoms of the specimen and X-ray fluorescence results. These X-rays are detected, sorted with respect to their energies, and elemental concentrations are determined from intensity measurements.

Dzubay and Stevens[10] described a new X-ray fluorescence spectrometer system that incorporates secondary fluorescers of copper, molybdenum, and terbium. A high resolution-low background silicon detector was used. This system permits scanning for the elements in the periodic system from aluminum and beyond. The analysis time was about fifteen minutes.

The method is non-destructive but, in the case of particulates, it is imperative that the particles be uniformly deposited on the collection surface. The filter collector that is used should be very low in impurity.

Giauque et al.[11] have described the application of X-ray fluorescence analysis to the characterization of aerosols. Hammerle et al.[12] studied X-ray fluorescence as a method for measuring elements in atmospheric aerosols. They compared this method with neutron-activation analysis and found greater sensitivity and precision with

X-ray fluorescence. A comparison of their results for nickel show 0.47 ± .03 μg when using X-ray fluorescence; 0.40 ± .24 μg when using neutron-activation; and at lower concentrations; 0.06 ± .02 with X-ray, and an undetectable amount with NAA. Either method is best applied to scanning for groups of elements.

4.1.3.8 Neutron Activation Analysis--Neutron-activation analysis (NAA) has found wide application for a number of years. In the past it was necessary to separate the elements of interest to remove the interferences of other elements. The field of instrument neutron-activation analysis (INAA), in which no chemical separations are performed, has been greatly extended by the development of lithium-drifted Ge γ-ray detectors. Ge (Li) detectors have much better resolution than the sodium iodide (Tl) scintillation counters previously used for X-ray spectrometry. This means that it is now possible to resolve γ-rays of many radioactive nuclides from complex mixtures of activities.

The nuclides are identified by γ-ray spectrometry. Gamma-ray energies of most products of reasonable half life including nickel, have been accurately determined.

The value of the technique lies in the ability to measure the concentrations of a group of elements in one sample. The same sample can then be used to measure additional elements by other methods.

The analysis can be largely automated and computerized for species emitting strong γ-rays. If a computer is not available, manual computation for long run irradiations as required for Ni would take 2 hours per sample for the group of elements.

4.2 WATER

The techniques of atomic absorption spectrophotometry, polarography, anodic stripping voltammetry, and ring oven are applicable to the determination of nickel in water. The nickel concentration, however, may be less than for air samples by a factor of a thousand. If sample enrichment is necessary, the solvent extraction method of Sachdev and West[2] can be used or the chelation method of Malissa and Schoeffman.[13] The literature describes the chelation method as auxiliary to atomic absorption spectrometry. Reference to use with other methods has not been found.

X-Ray fluorescence analysis requires that the sample be dry-deposited on plastic film. No reference has been found to the evaporation of samples of water for deposition. Vassos et al.[14] describe a technique for preconcentration by electrodeposition of nickel on pyrolytic graphite. After deposition, a thin disk was cleaved from the electrode surface and analyzed by X-ray fluorescence. Quantities determined were in the low ppm range. Since the recommended deposition times exceed one hour, the method appears to be cumbersome.

4.3 BIOLOGICAL MATERIALS

4.3.1 Sample Preparation

The initial step with plant or animal tissue is often blending, homogenizing, or grinding. In view of the very low concentrations of nickel anticipated, however, use of the above apparatus with stainless steel and nickel-plated parts is to be avoided. Pestles of glass and teflon are available for grinding.

It will be noted that with some techniques serum and urine samples can be analyzed without chemical pretreatment.

Methods for the destruction of sample organic matter are of two kinds; dry ashing and wet digestion. In dry ashing, the sample is ignited in a furnace at about 500°C and the ash then dissolved in acid.

Other dry ashing methods are the Schoeniger flash and the Parr bomb. These techniques use oxygen under pressure in place of air as oxidant. The dried sample is combusted in a closed system. A newer technique has been developed by Gleit and Holland.[15,16] A radio frequency discharge is used to produce an oxygen plasma which attacks organic matter at temperatures below 100°C. Biological tissues have been ashed in this way. A commercial model is available, but it is reported that ashing times exceed twenty-four hours. Hopefully, later design will improve upon this undesirable characteristic.

In wet digestion, hot acids and oxidizing agents are used. Frequently used mixtures for the wet treatment are sulfuric, nitric, and perchloric acids. The simpler mixture of nitric acid and hydrogen peroxide is better suited for the analysis of tissues.

Dry ashing is recommended for its simplicity and because large samples can be handled. Wet digestion is considered to be superior in terms of speed, the low temperatures employed, and freedom from loss by retention on container wall.

Because lower amounts of nickel are expected in biological samples than in air samples, concentration may be needed to exploit the methods of analysis described under air.

Additionally, separation from the sample matrix may be necessary to eliminate interferences. The extraction method of Sachdev and West,[2] which has been described earlier, can be used. Malissa and Schoeffman[13] have shown that ammonium pyrrolidine dithiocarbonate (APDC) can be used to chelate with metallic elements at controlled pH. At pH 2 through 4, nickel can be extracted with APDC into methylisobutyl ketone along with cobalt. This technique is well suited for samples that are intended for AA.

4.3.2 Analysis

Techniques applicable to nickel in biological samples are AA spectrophotometry, pulse polarography, and anodic stripping voltammetry.

X-ray fluorescence could be used, but sample preparation is a problem. Walter et al.[17] reported on the analysis of biological, clinical, and environmental samples using X-ray fluorescence. They used a 3-Mev beam of protons from a Van de Graff accelerator to excite X-ray fluorescence rather than use primary X-rays as described under air analysis. A wide range of elements including nickel was determined.

Of interest at this point is their preparation of the sample targets for analysis. Self-supporting materials, such as leaves or insect wings, were attached to the sample holder with adhesive. Non-selfsupporting samples, such as urine, blood, aqueous solutions, or tissue sections, were deposited on plastic material which was stretched over a graphite ring. The deposited liquid samples were dried in a vacuum desiccator. Deposits, such as whole blood or ashed substances,

tended to flake if not packaged with a cover of polyethylene or polystyrene.

4.4 NICKEL CARBONYL

Because nickel carbonyl [$Ni(CO)_4$] is a highly toxic gas, it has received special attention with respect to sample handling and analysis. At 60°C nickel carbonyl decomposes into carbon monoxide and nickel. The nickel can be collected as particles. Nickel carbonyl can be trapped in absolute ethanol and be kept at -78°C.

The summary to be found in the National Academy of Sciences' report[18] highlights the analytical problems of nickel carbonyl and describes a gas chromatographic procedure for its determination. The procedure is useful for monitoring industrial atmospheres, and is an aid in diagnosing nickel carbonyl poisoning.

Brief et al.[19] described a field method in which air samples were collected in dilute hydrochloric acid. A yellow complex was developed with α-furil dioxime. After extraction with chloroform, the color was determined spectrophotometrically. The limit of detection was estimated to be 0.002 ppm $Ni(CO)_4$.

Brief et al.[1] reviewed five other methods which are in use. In one method the $Ni(CO)_4$ is bubbled into a saturated solution of sulfur in trifluoroethylene. The precipitated nickel sulfide is analyzed by spectrograph in the ultraviolet region. The sensitivity limit is 0.0003 ppm $Ni(CO)_4$. In the second method, the sample is passed over red mercuric oxide at 200°C. The mercury is determined spectrographically. A parallel sample stream is oxidized to carbon dioxide and passed over red mercuric oxide to liberate mercury.

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5. ENVIRONMENTAL APPRAISAL

5.1 ORIGIN AND ABUNDANCE

5.1.1 Natural Sources

Nickel is a natural component of the earth's crust (0.008 percent) -- the major portion being found in igneous rock (0.01 percent) with shale (0.005 percent)containing the next largest amount . The earth's core contains 8.5 percent nickel. Meteorites may contain 5 to 50 percent nickel. Large nodule deposits with high nickel content have been found on the ocean floor. Cobalt usually occurs with nickel, its presence varying from a trace to ratios of one to ten.

The average farm soil in the United States contains 0.003 percent or more of nickel, although the concentration in surface and subsurface soils varies widely from area to area. This variability must be taken into account when sampling to determine contamination from man-made sources.

Nickel is found in all coals, but the content varies widely. The average nickel content of coal from the United States is about 0.025 kg/MT in the mid-western states, 0.016 kg/MT in the eastern states, and 0.004 kg/MT in the western states. The average nickel concentration in coal in the eastern and mid-western sections exceeds that found in the earth's crust, hence coal could be considered as a source of nickel.

Nickel is also found in crude oil. The nickel content of crude oil ranges from 0.000003 to 0.0064 percent. The nickel content of commercial residual fuels ranges from nil to 0.00002 percent.

In the weathering process of rocks, nickel goes into the insoluble minerals of the hydrolysates. Therefore, the nickel content of surface or ground water is likely to be small unless it is due to man-made

pollution. Nickel has been found in U. S. waters with a frequency of 16 percent and a mean concentration of 19 µg/liter. The nickel content of sea water ranges from 0.1 to 0.5 µg/l.[1]

Little is known concerning natural sources of nickel found in the atmosphere. Nickel has been identified in volcanic gases and condensates in a few instances. Nickel is found in detectable quantities in air in both urban and non-urban areas. The data are not sufficient to determine the contributions of natural sources to nickel in the non-urban atmosphere.

5.1.2 Man-Made Sources

5.1.2.1 Stationary Sources

The possible sources from which nickel may be emitted into the atmosphere can be separated into four groups: mining, metallurgical nickel products, and combustion.

Ontario, Canada is a major producer of nickel. Other producing areas include Cuba, New Caledonia, the Scandinavian countries, South Africa, Russia, Australia, and Indonesia. Mining is of minimal impact in the United States since nickel mining and ore processing plants in this country are few in number. One such plant is located in Huntington, West Virginia. Air monitoring in 1968 to assess nickel concentrations in Huntington and two other communities showed that ambient nickel concentrations at the air sampling stations near the plant measured 1.2 $\mu g/m^3$ of air, compared with an average nickel concentration of 0.04 $\mu g/m^3$ at the six other sampling sites.[2] No information is available regarding health consequences in relation to these levels of nickel. It is estimated that nickel mining operations emit about 2 MT of

nickel per year.[3]

Air monitoring in Sudbury, Ontario, a major nickel mining and processing center, indicated ambient nickel concentrations ranged from 0.035 to 2.009 $\mu g/m^3$, depending upon the date of measurement. The nickel concentrations in the Canadian cities of Toronto, Simcoe, and St. Catherines had much lower ranges for the same dates of measurement (every two weeks, January through August): Toronto - 0.006 to 0.107 $\mu g/m^3$; Simcoe - 0.004 to 0.066 $\mu g/m^3$;[1] and St. Catherines - 0.007 to 0.043 $\mu g/m^3$.[1] There was no evidence presented which would indicate whether nickel was hazardous to human health in Sudbury at the concentrations reported.

Most of the nickel reaching the atmosphere from ore processing is particulate with the possibility that some gaseous nickel carbonyl escapes from plants using the Mond process. The metallurgical processing of ore to produce metallic nickel results in an estimated emission to the atmosphere of 225 MT per year.[4]

Most nickel is produced from sulfide ores. The process used most extensively for obtaining pure metallic nickel involves separation of the sulfides of nickel, copper, and iron by selective flotation. After separation, the nickel sulfide is converted to the oxide by roasting, and the oxide is reduced with carbon affording approximately 96 percent pure metallic nickel. It is then cast into huge anodes and refined electrolytically in a nickel (II) sulfate bath. The nickel which deposits on the cathode is 99.98 percent pure.

The primary use of nickel is by the metallurgical products industry as an alloying or plating material. Some loss of nickel

is expected during alloying operations. Where melting at high temperatures is necessary, a metallic fume containing compounds of the melt is usually evolved. In straight melting operations without oxygen lancing, nickel preferentially remains in the melt since it is chemically negative relative to iron and, thus, stays out of the slag surface. Oxygen blows stir up the melt and provide more opportunities for nickel to be lost. Product sources have an estimated emission of 756 MT per year.[4] Nickel emissions from plating operations are more localized and constitute an occupational health problem rather than an atmospheric load.

By far the largest source of nickel in the atmosphere is the combustion of fossil fuels. Recent data[4] estimate total nickel emissions from coal use (primarily large power generating stations) at 3500 MT per year and oil consumption (residential and commercial heating and power generating stations) at 7300 MT per year. It has been reported[5] that the nickel emissions from power generating plants using pulverized coal is concentrated in particulate matter of less than one micrometer in diameter and, is therefore, respirable. Oil emissions present a similar hazard since 90 percent of such particulate emissions are less than one μm.

The emission of nickel by stationary sources is summarized in Table 5.1.

5.1.2.2 Mobile sources--Nickel can be emitted from mobile sources by a variety of mechanisms. Gas turbine high temperature components are fabricated from nickel or high-nickel alloys and the spallation of these materials can cause emission of nickel particles.[6] Nickel and vanadium

Table 5.1. EMISSION OF NICKEL TO THE ATMOSPHERE FROM STATIONARY SOURCES,[17]

Source	Amount emitted, MT	Percengage of total nickel emissions
Nickel mining	2	0.02
Iron and Steel		
Blast Furnace	91	0.79
Gray Iron Foundary Cupola	72	0.62
Ferro-Alloys		
Blast Furnace	445	3.84
Electric Furnace	89	0.77
Non-Ferrous Alloys		
Furnaces	58	0.50
Power Plant Boilers[a]		
Coal[a]	3,447	29.76
Oil	4,105	35.44
Industrial Boilers		
Coal	30	0.26
Oil	1,033	8.92
Residential/Commercial		
Coal	3	0.03
Oil	2,209	19.07
	11,584	100.25

[a]EPA data

are the principal metallic components in crude oil where these metals are bound as porphyrin derivatives.[7] Concentrations of these elements vary greatly with crude oil source but common levels for these elements are 400 to 1000 ppm for vanadium and 10 to 100 ppm for nickel.[8] Both elements are increased in concentration in residuum because the metallo-porphyrins are very stable, low vapor pressure components; typical concentrations of nickel in the residuum are in the 100 to 1000 ppm range.[9] The concentration of nickel in fuel oil and gasoline is lower than that in crude oil by at least two orders of magnitude[9] and, consequently, the nickel emissions from engines fueled by such products are very low. However, catalytic converters frequently include nickel in their casing materials or in the catalyst itself.[10] Thus, the potential for nickel emissions from catalyst equipped cars is greater than from older cars.

In the mid 1960's several nickel-containing compounds were developed by a petroleum company as deposit modifiers and preignition control agents in gasoline engines. One of these compounds was used in gasoline over a brief period at concentrations of 10^{-2} to 10^{-3} grams/gallon, but its use was discontinued because of fear of nickel carbonyl emissions. At present, there are no nickel compounds registered for use as gasoline additives in the United States.

Nickel emissions from gas turbine engines have been estimated in several recent studies.[6,11] Development of automotive engines, tested by Dow[12] have given emission rates of 0.002 to 0.0034 grams/mile depending on the cycle driven. Table 5.2 presents literature data for one gas

Table 5.2. NICKEL EMISSIONS FROM SELECTED VEHICLES[6,11,12,13]

Vehicle and equipment	Nickel emissions, gram/mile
WR-26 Gas Turbine car	0.003
1974 Chevrolet, unleaded gas	0.00006
1974 Chevrolet, Engelhard catalyst	0.00023
1974 Chevrolet, AC catalyst	0.00029
1974 Chevrolet, UOP catalyst	0.00024
1974 Chevrolet, Mathey-Bishop catalyst	0.00048
1974 Chevrolet, Gould reduction catalyst	0.001
Mercedes Diesel	0.003
1974 Pontiac, unleaded gas	<0.0001
1972 Pontiac, base metal catalyst	<0.001
1971 Chevrolet, Engelhard catalyst	0.003
1971 Chevrolet, leaded gasoline	0.0001
1972 Chevrolet, Gould reduction catalyst[b]	0.003

[a]Tests performed according to the 1975 Federal Test Procedure.[14]

[b]Test performed according to the 1972 Federal Test Procedure (hot start).[15]

turbine powered automobile, a Mercedes diesel, a non-catalyst equipped car operated on lead-free and on leaded fuel, and several catalyst equipped cars. In general, nickel emissions from non-catalyst equipped cars are approximately $4X10^{-5}$ grams/mile over the Federal urban driving cycle. Gas turbine emissions are about 100 times greater than baseline while emissions from catalyst cars are characteristically in the 10^{-4} grams/mile range. Nickel-bearing catalysts seem to have somewhat higher emissions in a few tests.

Nickel levels in distillate products, such as gasoline or diesel fuel, range from 0.001 to a maximum of about 0.1 ppm. At worst this nickel level would correspond to an emission rate of $3X10^{-5}$ grams/mile, which is in fair agreement with the observed values. Most marketed fuels have nickel levels much below the maximum value, however, and it appears that the observed nickel emissions are higher by a factor of ten than can be accounted for by typical fuel nickel concentrations. It is likely that engine wear products may account for this difference.

Table 5.3 presents nickel emission rates for aircraft turbine engines determined in the EPA in-house programs. Although spallation may occur in such engines, only traces of nickel were found in the overall particulate from these particular engines.

"Worst case" exposures for non-catalyst equipped car occupants or nearby pedestrians to nickel oxide aerosol are, thus estimated at 0.1 $\mu g/m^3$ for one hour peak exposures. Twenty-four/average exposures for this "worst case" are estimated to be 0.015 $\mu g/m^3$. This case with

Table 5.3. ELEMENTAL ANALYSIS OF PARTICULATE EMITTED FROM AIRCRAFT TURBINE ENGINES[a]

Substance	Concentration in particulate, percent by weight	
	JT-8-D engin	J-57 engin
Nickel	0.19	0.3
Chromium	1.4	Trace
Magnesium	0.008	0.3
Aluminum	0.62	0.5
Silicon	0.08	5.0
Sulfur	0.4	1.0

[a]Engines run at 90 percent of rated power. Particulate concentration in exhaust was: 11.7 mg/liter in the JT-8-D engin and 44.0 mg/liter in the J-57 engin.

catalyst equipped cars would raise these exposures by about one order of magnitude.

5.2 CONCENTRATIONS

5.2.1 Air

Although there have been several studies concerned with nickel in the air, only the National Air Surveillance Networks (NASN) data are extensive enough in geographical and temporal dimensions to provide a national index.[16]

Table 5.4 contains annual average concentrations for those urban NASN sites where all data were available for 1965 through 1969. Table 5.4 has been arranged in order of decreasing five-year average concentrations. Overall averages for these sites are to be found in the last line of the table. The overall averages in this table were selected for the sites having the most complete data. These averages are therefore not identical with the "best" overall averages for the nation for the years shown. However, such "best" averages should not be very different from the values given.

Table 5.5 presents data for the nonurban NASN sites, also selected on the basis of data completeness, and arranged in order of decreasing five-year averages.

Simple inspection of these tables will reveal the following:

- Urban concentrations are generally higher than nonurban with the higher values being found in the industrialized cities of the Northeast.

Table 5.4. ANNUAL AVERAGE NICKEL CONCENTRATIONS AT NASN URBAN SITES[16]
(ng/m^3)

Location	1965	1966	1967	1968	1969	5-year average
New Haven, CT	85	79	92	84	139	96
Philadelphia, PA	122	36	62	84	96	80
E. Chicago, IN	154	35	35	55	103	76
Reading, PA	61	38	38	92	122	70
Jersey City, NJ	69	52	75	69	64	66
Newark, NJ	73	49	77	61	55	63
Providence, RI	41	58	37	64	112	62
Portland, OR	59	37	41	80	70	57
Baltimore, MD	33	70	42	56	75	55
Wilmington, DE	38	37	40	66	93	55
Perth Amboy, NJ	59	43	68	31	44	49
Honolulu, HI	39	29	26	94	44	46
New Orleans, LA	16	8	12	100	73	42
Seattle, WA	39	36	27	43	49	39
Chicago, IL	37	29	31	33	50	36
Los Angeles, CA	18	39	23	42	30	34
Pittsburgh, PA	23	22	27	52	42	33
Louisville, KY	40	30	29	25	29	31
Oakland, CA	23	21	31	34	34	29
Youngstown, OH	16	26	19	40	45	29
Detroit, MI	18	24	26	49	25	28
Washington, DC	28	17	28	22	42	27

Table 5.4 (Con't.)

Location	1965	1966	1967	1968	1969	5-year average
Camden, NJ	23	44	23	15	23	26
San Diego, CA	20	23	21	23	40	25
San Francisco, CA	16	28	19	24	28	23
Bayamon, PR	20	13	33	20	22	22
Hammond, IN	22	14	26	20	29	22
Columbus, OH	25	16	14	18	30	21
Warminster, PA	18	21	20	27	18	21
South Bend, IN	40	17	9	13	20	20
Indianapolis, IN	18	18	18	26	22	19
Norfolk, VA	19	10	15	18	27	18
Charleston, WV	15	12	12	19	21	16
Cleveland, OH	17	10	14	17	20	16
Glassboro, NJ	16	11	11	13	25	15
Cincinnati, OH	14	12	14	10	19	14
Akron, OH	17	11	13	13	12	13
Chattanooga, TN	14	11	11	12	15	13
Concord, NH	ϕ[a]	11	18	17	16	13
Milwaukee, WI	13	9	10	7	11	10
Toledo, OH	11	8	12	11	8	10
Charlotte, NC	8	9	ϕ	10	11	9
Kansas City, MO	14	ϕ	8	8	9	9
Phoenix, AZ	11	13	11	7	ϕ	10

Table 5.4 (Con't.)

Location	1965	1966	1967	1968	1969	5-year average
St. Paul, MN	ϕ	ϕ	10	12	12	9
Minneapolis, MN	ϕ	ϕ	ϕ	11	10	8
Atlanta, GA	7	ϕ	9	ϕ	9	7
Des Moines, IA	8	ϕ	7	8	7	7
Salt Lake City, UT	12	ϕ	ϕ	ϕ	ϕ	7
Nashville, TN	ϕ	ϕ	ϕ	ϕ	9	7
Albuquerque, NM	ϕ	ϕ	ϕ	ϕ	ϕ	ϕ
Boise City, ID	ϕ	ϕ	ϕ	ϕ	ϕ	ϕ
Helena, MT	ϕ	ϕ	ϕ	ϕ	ϕ	ϕ
Las Vegas, NV	ϕ	ϕ	ϕ	ϕ	ϕ	ϕ
Maricopa Co., AZ	ϕ	ϕ	ϕ	ϕ	ϕ	ϕ
Memphis, TN	ϕ	ϕ	ϕ	ϕ	ϕ	ϕ
Oklahoma City, OK	ϕ	ϕ	ϕ	ϕ	ϕ	ϕ
Omaha, NE	ϕ	ϕ	ϕ	ϕ	ϕ	ϕ
San Antonio, TX	ϕ	ϕ	ϕ	ϕ	ϕ	ϕ
Tucson, AZ	ϕ	ϕ	ϕ	ϕ	ϕ	ϕ
Tulsa, OK	ϕ	ϕ	ϕ	ϕ	ϕ	ϕ
Wichita, KS	ϕ	ϕ	ϕ	ϕ	ϕ	ϕ
Averages	25.5	20.2	21.6	28.5	32.3	25.6

[a] ϕ implies minimum detectable concentration or less = 6 ng/m^3 or less. Averages computed using ϕ = 6 ng/m^3.

Table 5.5. ANNUAL AVERAGE NICKEL CONCENTRATIONS AT NASN NONURBAN SITES[16] (ng/m^3)

Location	1965	1966	1967	1968	1969	5-year average
Cape Hatteras, NC	Θ[a]	5	Θ	4	35	9
Calvert Co., MD	Θ	6	13	4	17	8
Orange Co., VT	4	6	9	6	11	7
Jefferson Co., NY	3	5	4	Θ	9	5
Clarion Co., PA	Θ	4	5	Θ	5	4
Coos Co., NH	Θ	6	Θ	Θ	Θ	3
Parke Co., IN	Θ	5	3	Θ	Θ	3
Shenandoah Nat. Pk., VA	Θ	3	Θ	Θ	4	3
Blk. Hills Frst., SD	Θ	Θ	Θ	Θ	Θ	Θ
Cherokee Co., OK	Θ	3	Θ	Θ	Θ	Θ
Curry Co., OR	Θ	3	Θ	Θ	Θ	Θ
Glacier Nat. Pk., MT	3	Θ	Θ	Θ	Θ	Θ
Grand Canyon Pk., AZ	Θ	3	Θ	Θ	Θ	Θ
Humboldt Co., CA	Θ	4	Θ	Θ	Θ	Θ
Matagorda Co., TX	Θ	Θ	Θ	Θ	Θ	Θ
Thomas Co., NE	Θ	Θ	Θ	Θ	Θ	Θ
White Pine Co., NV	Θ	Θ	Θ	Θ	Θ	Θ
Averages	Θ	4	3	Θ	6	4

[a] Θ implies minimum detectable concentration or less = 2 ng/m^3 or less. Averages computed using Θ = 2.

- Higher nonurban concentrations are found at the eastern sites. These higher nonurban concentrations exceed some urban values found in the western parts of the nation.
- There are no striking trends shown by the annual averages in these tables.

Seasonal variation in concentration seems common although it is not universal. In an attempt to assess this, the quarterly averages for the cold months (quarters 1 and 4) have been compared to the quarterly average concentrations for the warm months (quarters 2 and 3) by forming a ratio. These ratios should have values consistently different from one if a seasonal affect is observed. Data of this kind are presented in Table 5.6 for selected urban sites and in Table 5.7 for some nonurban sites. Only sites with the higher quarterly averages were used in this exercise. This was done because as concentrations approach the minimum detectable the numbers become small and the ratio becomes extremely sensitive to normal analytical errors. Interpretation then becomes difficult. Such difficulty is apparent in Table 5.7 where all available concentrations were small and some ratios are, in fact, indeterminate because the actual concentrations were smaller than could be measured.

With these limitations in mind, the data in Table 5.7 suggest the presence of a seasonal nonurban variation with the higher nickel concentrations occurring in the cold months. Note, however, that all of the sites in this table are in the eastern part of the country. Nearly all values from the nonurban Midwest and West are so low that the ratios are indeterminate. No conclusions may be drawn about those sites.

The first ten entries in Table 5.6 are the ten urban sites with

Table 5.6. SEASONAL VARIATION IN NICKEL CONCENTRATIONS AT SOME NASN SITES[a,16]

	1965	1966	1967	1969
New Haven, CT	1.6	1.3	2.7	3.3
Philadelphia, PA	3.8	1.7	1.3	1.3
E. Chicago, IN	7.8	1.2	1.5	8.7
Reading, PA	1.6	1.7	3.2	6.4
Jersey City, NJ	2.2	1.9	6.1	1.3
Newark, NJ	1.6	1.3	1.2	1.6
Providence, RI	2.2	2.3	1.4	5.4
Portland, OR	1.9	1.5	0.5	1.6
Baltimore, MD	1.7	2.3	1.6	1.6
Wilmington, DE	1.4	1.9	1.6	2.6
Honolulu, HI	1.0	1.9	1.3	1.1
New Orleans, LA	2.5	2.1	[b]	2.8
Houston, TX	1.2	1.1	-	0.98

[a]Ratio of quarterly concentration for the colder six months (quarters 1 and 4) compared to warmer six months (quarters 2 and 3).

[b]Data not available.

Table 5.7. SEASONAL VARIATION IN NICKEL CONCENTRATIONS AT SOME NASN NONURBAN SITES[a]

	1965	1966	1967	1969
Cape Hatteras, NC	ρ[b]	3.8	1.8	0.5
Calvert Co., MD	ρ	1.6	1.2	2.6
Orange Co., VT	ρ	1.2	1.6	1.6
Jefferson Co., NY	1.8	0.9	1.0	1.6
Clarion Co., PA	ρ	1.2	1.3	2.8

[a]Ratio of quarterly concentrations for the colder six months (quarters 1 and 4) compared to warmer six months (quarters 2 and 3).

[b]ρ implies an indefinite ratio caused by a value of Θ for the denominator or numerator and denominator. Θ implies the minimum detectable concentration or less.

the highest 5-year average concentrations. Those ratios are (with one exception) greater than one which also indicates generally higher nickel concentrations in the cold months than in the warm months. All of these sites except one are in the industrialized Northeast.

This seasonal variation is usually attributed to the increased burning of fossil fuels during the cold weather. Such sweeping, one parameter explanations may be inadequate and merely glib if applied indiscriminately. For example, the last three entries of Table 5.6 have been chosen for site locations in warm climates. If the usual explanation for seasonal variation is valid it would probably be absent at such sites. In the case of Houston, that consideration seems correct since all ratios are near one. For New Orleans, geographically near Houston, seasonal variation is marked and sustained. For Honolulu the situation seems mixed.

In 1970 the nickel content of various particle size fractions was measured at six urban NASN sites.[19] Less than half (31 to 49 percent) of the mass of nickel-associated aerosol was found to be in particles with mass median diameters of less than 1 micrometer.

5.2.2 Water

The amount of nickel in seawater ranges from 0.1 to 0.5 µg/liter. Nickel rarely occurs in ground water; when it does occur, it is usually in the insoluble minerals of the hydrolysates. Thus, nickel in surface water is likely to be in small amounts unless it is from industrial waste.

Nickel was identified in U. S. waters with a frequency of 16 percent. The Missouri and Western Gulf basins had the lowest frequency of nickel detection, and were among the lowest mean concentration levels (Table 5.8. The highest mean concentrations was 130 µg/liter in the Cuyahoga River at Cleveland, Ohio.[20]

5.2.3 Soils

Soils are formed from rocks, therefore, the composition of a soil depends upon the composition of the parent rock from which it originated. Variations in the nickel concentration of the parent rock means that variations in soil will occur from region to region. Continental glaciation also had an effect upon the soil levels of nickel and chromium.[21]

Mitchell [22] divided soils into two groups: those originating from sandstones, limestones or acid igneous rocks and containing less than 50 µg/g of nickel; and those derived from clayey sediments or basic igneous rocks and containing from 5 to 500 µg/g of nickel. Bowen[23] lists the nickel content of igneous rocks as 75 µg/g, shales 68 µg/g, limestones 20 µg/g with soils averaging 40 µg/g unless they are derived from serpentine soils. Serpentine soils commonly contain a high percentage of nickel, iron, and chromium. Nickel is concentrated with iron in laterite, a hard, red soil which is found in tropico and is low in silica and high in iron and aluminum. Nickel concentrations in serpentine soils ranges from 5 to 6000 µg/g with an average of 3000 µg/g.[21]

Table 5.8. NICKEL IN WATER FROM MAJOR RIVER BASINS OF THE UNITED STATES[20]

River basin	Mean nickel concentration, µg/liter	Frequency of detection, %
Northeast	8	22.0
North Atlantic	8	28.1
Southeast	4	20.9
Tennessee River	4	8.8
Ohio River	31	25.2
Lake Erie	56	53.2
Upper Mississippi	15	15.2
Western Great Lakes	10	9.1
Missouri River	5	2.0
Southwest-Lower Mississippi	17	9.7
Colorado River	12	8.0
Western Gulf	3	2.1
Pacific Northwest	10	10.5
California	10	13.8
Great Basin	4	15.8
Alaska	5	11.1

Vanselow[23] cites the studies of a number of workers from around the world. Concentrations of nickel in the soils listed by these workers vary from 1 to 730µg/g for non-serpentine soils. Levels in soils in the U. S. were listed as ranging from 1 to 100 µg/g.

Klein[24] studied surface soils from industrial, agricultural, and residential areas. He analyzed the soils to determine the presence of calci cadmium, cobalt, chromium, copper, iron, nickel, lead, silver and zinc. An analysis of 264 soil samples from a 300 sq. mile area indicated that metal concentrations were higher in industrial soils than in residential or urban areas. The enrichment for nickel was approximately 1.4 times that found in the residential zones. Airport soils were significantly enriched. Agricultural soils tended to run a little higher than the concentrations in residential zones (Table 5.9).

The addition of sewage sludge or phosphate fertilizers can also raise the concentrations of nickel in soil. Studies by Yost et al.[25] showed tha the amount of nickel in fertilizers ranged from 3.0 - 38.0 µg/g. The nickel content of sludge varied from <32 to 2900 µg/g dry weight.

The concentrations of nickel in the soil along highways may be increased by fallout from automobiles.[26] Lagerwerff and Specht[26] have shown that the concentrations of nickel are higher along highly traveled throughways and decrease the farther one gets from the highways. The range was from 7400 µg/g near the highway to 2220 µg/g 32 meters away.

Table 5.9 METAL CONCENTRATIONS RELATED TO LAND USE PATTERNS, µg/g [24]

		Ag	Ca	Cd	Co	Cr	Cu	Fe	Hg	Ni	Pb	Zn
Residential	median	0	1,000	0.4	2	1.6	7.5	2,000	0.07	4	15	17
N = 70	mean	0.13	2,300	0.41	2.3	3.2	8.0	2,200	0.10	5.4	17.9	21.1
	std dev	0.19	2,600	0.44	1.5	3.3	4.5	1,100	0.10	4.1	12.6	12.5
Agricultural	median	0	800	0.4	2.5	3.9	5.6	2,200	0.09	6	11	17
N = 91	mean	0.19	1,400	0.57	2.7	4.6	8.8	2,600	0.11	5.6	15.4	22.1
	std dev	0.25	1,900	0.52	1.5	3.6	6.0	1,600	0.09	4.4	14.9	12.9
Industrial	median	0.4	1,900	0.7	2	6.0	11.2	3,200	0.11	7	22	32
N = 86	mean	0.37	3,200	0.66	2.8	8.5	16.3	3,100	0.14	8.3	47.7	56.6
	std dev	0.33	3,000	0.54	1.8	9.0	14.3	1,400	0.10	5.2	59.6	63.1
Airport	median	0.4	3,700	0.7	8	22	9.4	7,000	0.17	11	14	36
N = 7	mean	0.29	4,100	0.77	7.9	17.6	10.4	6,200	0.33	12.3	17.9	36.6
	std dev	0.30	3,800	0.56	2.7	8.9	2.1	1,600	0.18	5.9	8.4	15.0
Industrial/residential		2.85	1.39	1.61	1.22	2.66	2.04	1.41	1.40	1.54	2.62	2.68
Airport/residential		2.24	1.78	1.88	3.43	5.50	1.30	2.82	3.30	2.28	1.00	1.74

5.2.4 Plants

The nickel content of plants is usually less than 1 µg/g.[23] Only plants growing on serpentine soils have higher levels. Table 5.10 shows the concentrations of nickel found in a wide variety of plants. It may be noted that many of the plants listed in the table are used by man as food.

Plants exist which are capable of concentrating nickel in their tissues.[27] Alyssum bertolonii, which grows in Italy and the Western Balkans usually contains up to 5-10 percent (ash weight) of nickel. Pimilea suteri, from New Zealand, accumulates not only nickel (2.5 percent ash weight) but also chromium. Species of Hybanthus, particularly H. floribundus, from Australia, have been shown to accumulate nickel and cobalt. Growing in soils containing in excess of 400 µg/g, these plants were shown to be capable of concentrating nickel at levels up to 3,665µg/g in leaf tissue. The maximum nickel concentration in leaf tissue was 26 percent (ash weight).

Knobcone pine, Pinus attenuata, and tanoak, Lithocarpus densiflora, growing on serpentine soils near Curry, Oregon, were reported to have a maximum nickel content of 300 µg/g and 630 µg/g respectively.[21]

5.2.5 Microorganisms

Nickel is not a constituent of microorganisms as far as is presently known, but is toxic to a majority of them.

Millerite (NiS) is oxidized by the Thiobacillus - Ferrobacillus group. In general, the bacterial oxidation of this mineral results the formation of nickel sulfate and hydrogen sulfide. The process occurs only under an acid pH.[28,29]

Table 5.10. TISSUE ANALYSIS VALUES USEFUL IN INDICATING NICKEL STATUS [23]

µg/g

Plant	Type of culture	Tissue sampled	Age, stage, condition or date of sample	Range in dry matter (ppm.)				
				Showing deficiency symptoms	Low range	Intermediate range	High range	Showing toxicity symptoms
Alfalfa (*Medicago sativa*)	Field	Tops	Mature	...	...	1.00–4.00	...	...
Alyssum (*Alyssum bertholonii*)	Field	Leaves	Mature	...	...	...	4,000.00	...
	Field	Seeds	Mature	...	...	...	2,500.00	...
Apricot (*Prunus armeniaca*)	Field	Fruit	Mature	...	...	0.65	...	...
Barley (*Hordeum vulgare*)	Field	Leaves	May, 1955	...	...	...	4.00–6.00	...
Bean (*Phaseolus* spp.)	Field	Seeds	Mature	...	...	0.59	...	...
Bog asphodel (*Narthecium* spp.)	Field	Leaves and stems	Mature	...	...	0.40–5.30	...	...
Buckwheat (*Fagopyrum* spp.)	Field	Seeds	Mature	...	...	1.34	...	...
Bulrush (*Scirpus caespitosus*)	Field	Leaves and stems	Mature	...	...	0.30–3.00	...	...
Cabbage (*Brassica oleracea capitata*)	Field	Tops	Edible	...	...	3.30	...	...
Carrot (*Daucus carota sativa*)	Field	Roots	Mature	...	...	0.30	...	...
	Field	Leaves	Mature	...	...	1.80	...	...
Cherry (*Prunus cerasus*)	Field	Fruit	Mature	...	...	0.50	...	...
Citrus fruits (*Citrus* spp.)	Greenhouse	Leaves	Young	...	...	0.40	...	55.00
	Greenhouse	Leaves	Mature	...	...	1.00	...	140.00
	Field	Leaves	Mature	...	...	2.00–4.00	...	...
	Pots	Leaves	Mature	...	...	0.70–1.80	...	...
	Field	Leaves	Mature	...	...	0.40–1.00	...	...
Clover, bur (*Medicago hispida*)	Field	Tops	Mature	...	...	1.00–2.00	...	...
Clover, red (*Trifolium pratense*)	Field	Tops	Mature	...	...	1.90	...	...
Coffee (*Coffea* spp.)	Field	Beans	Mature	...	...	0.40	...	...

Table 5.10 (continued). TISSUE ANALYSIS VALUES USEFUL IN INDICATING NICKEL STATUS (µg/g)

Plant	Type of culture	Tissue sampled	Age, stage, condition or date of sample	Range in dry matter (ppm)				
				Showing deficiency symptoms	Low range	Intermediate range	High range	Showing toxicity symptoms
Corn (*Zea mays*)	Field	Grain	Mature	...	...	0.14	...	...
Cress, water (*Rorippa nasturtium-aquaticum*)	Field	Tops	Mature	...	...	0.50	...	...
	Field	Leaves	Mature	...	...	0.13	...	...
Fig (*Ficus carica*)	Field	Fruit	Mature	...	...	1.20	...	...
GRASSES Sweet vernal grass (*Anthoxanthum odoratum*)	Field	Tops	Mature	...	...	0.70–1.70	...	...
Various grass spp.	Field	Tops	Mature	...	...	0.20–0.80	...	...
	Field	Tops	Mature	...	...	...	9.00–56.00	...
	Field	Tops	Mature	...	...	0.60–3.00	...	...
Heather and Heath (*Calluna vulgaris*)	Field	Tops	Mature	...	...	0.60–2.60	...	...
(*Erica cinerea*)	Field	Tops	Mature	...	...	1.50–1.70	...	...
(*Erica tetralix*)	Field	Tops	Mature	...	...	1.10–1.50	...	...
Mushroom (*Cantharellus cibarius*)	Field	Buttons	Edible	...	...	3.50	...	...
Oats* (*Avena sativa*)	Field	Grain	Mature	...	...	0.45	...	...
	Field	Leaves	June	...	...	16.00–51.00	134.00	...
	Field	Leaves	Mature	...	...	7.00	32.00	...
	Pots	Tops	Mature	...	...	...	84.00–340.00	...
Onion (*Allium cepa*)	Field	Bulbs	Mature	...	...	0.16	...	...
Pea (*Pisum sativum*)	Field	Seeds	Mature	...	...	2.00	...	...
Pear (*Pyrus communis*)	Field	Fruit	Mature	...	...	1.30	...	...
Potato (*Solanum tuberosum*)	Field	Tubers	Mature	...	...	0.25	...	...
	Field	Tubers	Mature	...	...	0.08–0.37	...	...
Rice (*Oryza sativa*)	Field	Grain	Polished	...	...	0.02	...	...
Sedge (*Carex* spp.)	Field	Tops	Mature	...	...	0.20–3.20	...	...
Soybean (*Glycine soja*)	Field	Seeds	Mature	...	...	3.90	...	...

Table 5.10 (continued). TISSUE ANALYSIS VALUES USEFUL IN INDICATING NICKEL STATUS[23]
(µg/g)

Plant	Type of culture	Tissue sampled	Age, stage, condition or date of sample	Range in dry matter (ppm.)					Reference
				Showing deficiency symptoms	Low range	Intermediate range	High range	Showing toxicity symptoms	
Spinach (*Spinacia oleracea*)	Field	Tops	Mature	...	...	2.40	...	...	Bertrand and Mokragnatz (1930c)
Squash (*Cucurbita* spp.)	Field	Fruit	Mature	...	...	4.60	...	...	Beristein (1945)
Tea (*Camellia sinensis*)	Field	Leaves	Mature	...	...	3.00-5.00	...	...	Laycock (1954)
Timothy (*Phleum pratense*)	Field	Tops	Mature	...	...	0.46	...	...	Mitchell (1945)
Tomato (*Lycopersicon esculentum*)	Field	Fruit	Mature	...	...	0.15	...	...	Bertrand and Mokragnatz (1930c)
	Field	Fruit	Mature	...	...	0.01	...	...	Bertrand and Mokragnatz (1930a)
Walnut (*Juglans regia*)	Field	Leaves	Mature	...	...	0.90-5.00	...	...	Vanselow (1945)
	Field	Meats	Mature	...	...	0.60	...	...	Bertrand and Mokragnatz (1930c)
Wheat (*Triticum* spp.)	Field	Grain	Mature	...	...	0.35	...	...	Bertrand and Mokragnatz (1930c)
	Field	Grain	Mature	...	...	...	35.00	...	Sullivan (1933)
	Field	Grain	Mature	...	...	4.00	16.00	...	Vergnano (1959)

5.2.6 Animals

Among the first transition series of elements, chromium, manganese, iron, cobalt, copper, and zinc have been shown to be essential to the health and life of animals. It is highly probable that nickel, located in the midst of that series, is also an essential element in animals.

5.2.6.1 Sea Animals--The average concentration of nickel in sea water is about 0.1 to 0.5 μg/liter. Nickel is concentrated in a variety of fish and crustaceans as illustrated in Table 5.11. The concentrations represent enrichment of up to several orders of magnitude over sea water levels.

5.2.6.2 Land Animals--Analyses for the presence of nickel, primarily in serum, have been made in a variety of animals. Table 5.12 summarizes serum nickel levels in healthy adults of a variety of species. Measurements are made by atomic absorption spectrometry, using the standard pyrrolidone dithiocarbomate complexation, methylisobutylketone extraction procedure.[30] Conclusions about these values reached by Sunderman et al.[31] indicate no significant difference between sexes for any of these species. Dietary studies on cattle receiving up to 250μg/g nickel for an 8-week period showed that no increase of nickel was apparent in liver or kidney, although there was some increase in the lung. Another feeding supplement study, with cows receiving up to 1750μg/g nickel salts, resulted in no increase in the nickel levels of the milk produced.

Table 5.11. NICKEL CONCENTRATIONS IN FISH AND CRUSTACEANS[1]

Seafood	Nickel concentration, µg/g (fresh wt)
Oysters, fresh	1.50
Mollusks (Puget Sound)	0.74
Clams, Fresh	0.58
Shellfish (Japanese)	0.14
Scallops, fresh-frozen	0.04
Lobster, claw meat	0.66
Shrimp, fresh-frozen	0.03
Crabmeat, canned	0.03
Anchovies, canned	0.72
Sardines, canned	0.21
Haddock, frozen	0.05
Swordfish, frozen	0.02
Salmon flesh	1.70
Dressed-fish samples:	
whitefish, Moose Lake	0.2
northern pike, Moose Lake	0.2
whitefish, Lake Ontario	0.2
northern pike, Lac St. Pierre	0.2
northern pike, Lake Erie	0.2
smelt, Lake Erie	0.2
yellow perch, Lake Erie	0.2

Table 5.12. NICKEL IN THE SERUM OF HEALTHY ADULT ANIMALS OF SEVERAL SPECIES[31]

Species, and number of animals tested	Nickel Conc. (µg/l)	
	Mean	Range
Domestic horses (4)	2.0	1.3 - 2.5
Man (47)	2.6	1.1 - 4.6
Jersey cattle (4)	2.6	1.7 - 4.4
Beagle dogs (4)	2.7	1.8 - 4.2
Fischer rats (11)	2.7	0.9 - 4.1
British goats (3)	3.5	2.7 - 4.4
New Hampshire chickens (4)	3.6	3.3 - 3.8
Domestic cats (3)	3.7	1.5 - 6.4
Guinea pigs (3)	4.1	2.4 - 7.1
Syrian hamsters (3)	5.0	4.2 - 5.6
Yorkshire pigs (7)	5.3	3.5 - 8.3
New Zealand rabbits (24)	9.3	6.5 - 14.0

5.2.6.3 Humans--The normal human has within his body approximately 10 mg of nickel; however, wide individual variations exist.[55] Extensive studies have been conducted to determine the distribution of nickel in tissues of the human body, liver and excretion. Much of the work on the tissue distribution has been done by Tipton and her colleagues.[32-34] They performed autopsies on: 1) apparently healthy Americans who died suddenly, with no apparent disease at the time of death, and, 2) on foreign adults from the eastern hemisphere, many of whom had chronic illnesses at the time of death. The nickel content of 29 tissues from 150 adults was determined by emission spectrography. Nickel was observed in only about one third of all the samples analyzed, although it was observed in every tissue, the greatest frequency and the highest concentration occurred in skin.

The body does not readily retain nickel; retention seems to be around only 3.6 percent. Studies of lungs of selected groups, ranging from victims of nickel carbonyl poisoning to normal subjects, show a gradient in nickel levels. (Table 5.13). Miners showed a small but significant increase in nickel content over the general population,while victims of nickel carbonyl poisoning had very high nickel levels.

Nickel has been measured in hair, excreta, and blood. Hair measurements have produced varied results, presumably because of differences in sampling the hair, and in the work techniques used before the analysis. Nechay and Sunderman[35] reported average nickel levels of 0.22 μg/g (range, 0.13-0.51; S.D.+0.08) in hair segments taken not more than 5 cm from the scalp, with no significant difference between men and women.

Table 5.13. NICKEL IN LUNG TISSUE OF ONTARIO SUBJECTS[1]

Subject	Age	Nickel content of lung, μg/100g		
		Wet tissue	Dry tissue	Ash
Normal lungs				
Male	50	0.018	0.091	4.0
Male	52	0.021	0.119	2.0
Male	71	0.021	0.175	5.0
Male	75	0.017	0.116	4.8
Female	23	0.009	0.060	4.0
Female	35	0.010	0.102	5.0
Female	48	0.014	0.083	5.0
Ore miners				
Male	--(27)[a]		0.86	8
Male	--(19)		0.25	6
Male	--(20)		0.22	7
Male	--(21)		0.49	12
Male	--(17)		1.36	13
Male	--(39)		0.48	10
Victims of $Ni(CO)_4$ poisoning:				
Male	--[b]	7.2	39	975
Male	--[b]	9.7	63	1,450
Male	--[b]	10.9	67	1,550
Male	--[b]	16.1	97	1,950

[a]Age not available, years as miners given in parentheses.

[b]Age not available, years of work experience given as 10 to 25 years.

Schroeder and Nason[36] reported nickel levels of 0.97 µg/g [S.E.M. = ± .15] for men's hair and 3.98 µg/g [S.E.M. = ± 1.06] for women (significant differences at p <0.0001).

Most orally ingested nickel is excreted in the feces. In a limited study, Horak[37] found that nickel levels in the feces of healthy subjects averaged 3.3 ± 0.8 µg/g net weight. Average levels of nickel in urine have been measured in many laboratories (Table 5.14). Variability among them is great, with means ranging from 0.20 µg/100 ml to 9.3 µg/100 ml. Sweat appears to have significantly higher levels of nickel than urine, with 52 ± 36 µg/liter in men, and 131 ± µg/liter for women,[38] and has been identified as an important route for the excretion of absorbed nickel from the body.

Investigation in Sunderman's laboratory has demonstrated that nickel exists in three forms in human blood: (1) as ultrafilterable nickel, bound up in some as yet unidentified complex form, (2) as albumin bond nickel, and (3) as a nickel metalloprotein that has been named "nickelplasma". Many studies of nickel levels in whole blood, serum and plasma have been made. Variability in the reported results is great, but as sensitive atomic absorption methods have developed, reproducibility has improved. A study[39] measuring the serum nickel levels among groups of adult residents of Hartford, Connecticut, a city with relatively low environmental nickel concentrations, and comparing them with levels from a group of adult residents of Sudbury, Ontario, Canada, the site of the largest open-pit nickel mine in North America, indicated that measurements of nickel in serum could be used to reflect environmental exposure to nickel. In the Hartford population, serum nickel concentrations averaged 2.6 ± 1.0 µg/liter, while the Sudbury

Table 5.14. CONCENTRATIONS OF NICKEL IN HUMAN URINE[1]

Method	Area	No. subjects	Nickel concentrations, g/100 ml[a] Mean	Range
Spectrophotometry	England	12	2.9	0.0 - 5.5
Spectrophotometry	Pennsylvania	69	1.1	0.0 - 3.0
Emission spectrography	Missouri	24	2.0	1.0 - 7.0
Spectrophotometry	Wales	?	4.0 ± 0.2	--
Emission spectrography	b	154	1.0	0.1 - 2.5
Atomic absorption	Pennsylvania	17	1.8 (19.8)	0.4 - 3.1
Atomic absorption	Connecticut	26	0.23 (2.4)	0.10 - 0. (1.0-5.6)
Atomic absorption	Germany	15	9.3	(5.7 - 12
Spectrophotometry	Yugoslavia	10	2.7	1.4 - 6.3
Atomic absorption	Connecticut	20	0.20 (2.5)	0.07 - 0. (0.05 - 6
	Canada[c]	19	0.72	0.21 - 1.

[a] Numbers in parentheses are concentrations in micrograms per day.

[b] Industrial workers from Ohio, New York, Florida, Colorado, and Oregon.

[c] Sudbury, Ontario.

population serum nickel concentrations averaged 4.6 ± 1.4 µg/liter. The differences were significant at $p < .001$. One caveat appeared in connection with the study: there was no evidence that the environmental exposure to nickel in Sudbury, Ontario was associated with adverse effects in man or animals.

5.3 TRANSFORMATION AND TRANSPORT MECHANISMS

5.3.1 Natural Mechanisms

In general, the atmospheric loading of particulates is determined by the rate of input of primary particulate and gases, the rate of transformation of pollutant gases into particles, the transport of primary and secondary pollutants through the atmosphere and the removal processes. Nickel-containing particulates will enter the atmosphere as primary particulate emission. Details concerning the transformation and transport of nickel-containing particles are not known. This is unfortunate because in order to relate the quality of the environment to the sources of pollution and in order to predict the control needed under present and future conditions, an accurate assessment of the inpact of these processes upon the atmospheric loading is essential. At the present time we cannot even make an estimate of the residence time of nickel in the atmosphere nor do we know the ultimate fate of nickel.

Transformation and transport processes can be divided according to the type of mechanism involved, that is, chemical mechanisms, physical and dynamic mechanisms, and biological mechanisms.

Figure 5.1 depicts the transformation and transport of nickel in the ecological system. The discussion in the following paragraphs shows that much additional study needs to be undertaken in order to assess the importance of the various mechanisms depicted in Figure 5.1.

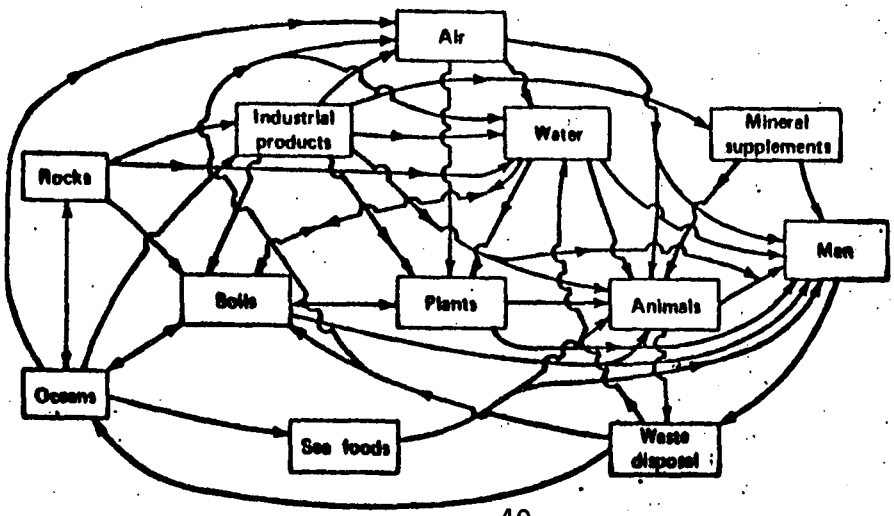

Fig. 5.1. **The cycling of microelements.**

5.3.1.1 Chemical Mechanisms--The forms of nickel in air and their reactions have not been extensively studied. It would be expected that nickel would be present predominantly in particles. However, owing to the industrial importance and widespread usage of nickel carbonyl, the possibility of nickel enetering the atmosphere as nickel carbonyl should not be overlooked. For example, the regeneration of fluid catalysts used in petroleum refining involves burning coke and carbon off zeolite catalysts. Nickel carbonyl is formed in the process. Although this compound is recognized as a hazard in industrial hygiene there seems to be little information available as to the amount of nickel carbonyl which escapes to the atmosphere.

Little, if anything, is known about chemical transformations of metallic elements in the atmosphere. There is a need to know whether nickel is present as a nitrate, sulfate, or some other compound, and whether these compounds undergo further reaction, either catalytically or directly. Particles in the atmosphere are believed to participate in some of the reactions associated with photochemical smog. Laboratory results have suggested that the oxidation of gases, such as sulfur dioxide, is accelerated when particles are present. However, the involvement of nickel-containing particles in such heterogeneous reactions has not been assessed.

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The soil chemistry of nickel is a crucial factor in physical and biological transport but there is no chemical transport per se. Soil pH is highly significant. In acid soils, nickel compounds are more soluble and, consequently, more available for transport in soil solution or uptake by plants.[41-44] Liming soil to increase the pH decreases the solubility and is an established treatment for plant toxicity due to excess nickel.[41,44,45] As the pH moves toward neutrality, nickel probably precipitates with the calcium supplied by lime or limestone and there is evidence to suggest that in slightly acid to neutral soils nickel will precipitate with available phosphorous.[41,44,46] Formation of complexes and chelates between nickel and the degradation products of soil organic matter may increase, depending on pH solubility and mobility of nickel in soils.[43,44,47,48] Adsorption at exchange sites on soil clay minerals and soil organic matter will remove cationic forms of nickel from solution.[41,43,44] This mechanism will be more significant in soils with a high organic content or a high content of silicate clay minerals and particularly for those soils with a clay fraction dominated by montmorillonite or illite. In neutral and alkaline soils, only small amounts of nickel will be adsorbed on exchange sites because precipitation reactions will lower the concentration in solution below that of other exchangeable cations.[43]

5.3.1.2 Physical and Dynamic Mechanisms--Those physical and dynamic processes which affect the physical properties of particles in the atmosphere[49] are:

- Gain or loss of particles entering an air mass by diffusion or convection from neighboring air masses.
- Net change in particle concentration by thermal (Brownian) coagulation.

- Net change in particle concentration by scavenging of smaller particles by larger ones during their fall.
- Net change of particle concentrations by collisions between particles resulting from turbulent velocity gradients.
- Loss of particles by gravitational sedimentation.
- Loss of particles by impaction on obstacles at the earth's surface.
- Loss of particles by diffusional diposition on surfaces
- Loss of particles by washout and rainout

The degree to which these processes are important is a function of particle size and altitude of the air mass.[50] Little information is available on the detailed mechanisms by which airborne nickel-containing particles participate in these processes.

The transport of particles in the atmosphere is controlled primarily by wind. Brownian motion diffusion will be insignificant when compared to the convective diffusion produced by turbulent air motion.

Large sized nickel-containing particles would be expected to fallout in the near vicinity of their source by gravitational sedimentation. Particles can also be deposited on surfaces by diffusional deposition and by impaction on obstacles at the earth's surface. Precipitational removal processes such as rain-out and wash-out are also important factors.

Particles deposited on ground surfaces may be further transported by ground water, probably eventually ending up in the oceans. No estimate is available on the amount of nickel added to the ocean each year.

Most of the nickel in surface and ground waters is believed to be due to industrial pollution.

Both the chemical and physical processes occurring within an air mass will affect the size distribution of the aerosol. Nucleation, condensation, coagulation, and gas-particle reactions all play a role in determining the size-composition distribution.

Condensation upon existing nuclei and the generation of new particles by nucleation and condensation processes are other important mechanisms affecting the size distribution. Specifics of the agglomeration of particles are unclear and much work is needed in this area.

Important physical transport mechanisms in soils are the downward movement in solution and the erosion of solid material from the soil surface. Quantitative data on movement down through different types of soil and on the extent of erosion transport are not available, but some qualitative estimates can be made.

Other things being equal, downward transport will be more rapid in coarse textured soils than in fine textured soils because of the larger pores and faster movement of the soil water. Similarly, transport through the soil will be faster in higher rainfall areas because of the potential for more water entering the soil.[44] Transport in solution will be affected not only by the amount and rate of flow of soil water but also by the previously discussed chemical mechanisms which control the concentration of nickel in the soil solution.

For soils in which added nickel remains near the surface because chemical mechanisms limit the concentration in soil solution, there is the possibility that soil particles with adsorbed nickel or

precipitates of nickel will be eroded from the surface by irrigation and/or rainfall and carried into surface waters.[44] This would be a particularly significant addition and should be considered when designing disposal sites for sewage or industrial sludges where the soil has been selected or treated to maximize heavy metal retention in the surface layers such as soils which have naturally high pH and calcium content or soils which have been treated to produce these conditions.

5.3.1.3 Biological Mechanisms

The principal biological mechanism for transport of nickel is plant uptake. Although nickel is not an essential plant nutrient it is absorbed by plants from the soil solution. The extent of such uptake is influenced by the concentration in the soil solution, soil temperature, pH, nutritional status of the plant, and by the formation of organic complexes and chelates which increase the solubility and mobility of nickel in soil but reduce its availability for uptake by plants.[41-48,51] In some cases, plant toxicity due to excess nickel in solution has been alleviated by application of sewage sludge which is of high organic content and contains significant amounts of nickel.[35] The organic matter forms complexes and chelates making nickel unavailable to plants. If the applications were not continued, the

nickel-organic compounds eventually break down by microbial action and the nickel again becomes available for plant uptake or participation in soil chemical processes. There are differences in uptake due to the type of plant, and within the same plant there will be differences in nickel concentration between leaves, stems, fruit, and roots.[41]

After uptake by a plant, nickel may be distributed to humans and animals as food or returned to the soil in unused plant parts. In soils where nickel is relatively immobile, plants can extract nickel from deeper soil horizons and concentrated the nickel in the surface layer of the soil by the decay of the plant parts. Emission transport can carry this nickel to surface waters.

Microbiological transformations of organic matter in the soil are important in binding nickel to and releasing it from organic complexes and chelates.

Earthworms living in soil with a high nickel content have been shown to contain high concentrations of nickel[52]

Airborne nickel may be deposited on vegetation and may enter the plants through the leaves, unless carefully washed, the nickel dust adhering to the vegetation may enter the digestive tract of organisms eating it. If the vegetation is not eaten, the nickel returns to the soil during the decay process.

Mosses and lichens tend to accumulate heavy metals largely through deposition. Moss tissues have a great capacity for sorbing heavy metals,[53,54] Negatively charged organic groups in moss tissues sorb the cations of the heavy metals selectively from dilute solutions. Nickel, along with copper, lead, chromium, cobalt, cadmium, zinc and manganese, is sorbed by the moss tissues and eventually incorporated into the moss carpet. The capacity for capturing heavy metals is not unique to mosses and lichens.[55] An increase in the above listed heavy metals is seen in most plant material as it begins to decompose. Dead organic matter prior to decomposition is usually much richer in heavy metals than the living plant material of the same type. This increase in heavy metal content of litter is due chiefly to its ability to sorb the metal ions.[55]

Very little is known about the chemistry of nickel and its compounds in seawater. The chemistry of nickel and its compounds in solution, especially in the presence of carbonate and sulfide ions, is largely that of bivalent nickel (Ni^{2+}). Calculated according to Liebig's Law of the Minimum, which states that the growth of a plant is dependent on the amount of nutrient which is present in the least quantity, the concentration factor of nickel, is among the lowest in the transition metal groups.[42]

Goldberg et al.[57] report the concentration of divalent nickel (Ni^{+2}) in seawater as 7 µg/liter and in streams as 0.3 µg/liter. Residence time in the oceans is listed as being 90,000 years. Ranges of element concentrations in marine organisms at various trophic levels are listed in Table 5.15.

Table 5.15. RANGES OF NICKEL CONCENTRATION[a] FACTORS IN MARINE ORGANISMS AT VARIOUS TROPHIC LEVELS[58]

Algae		Grazes		Predators		
Sessile	Plankton (Phytoplankton and Sargassum)	Plankton (Copepods, Pteropods, Salps, Doliolid)	Shellfish	Plankton [Euphausiids, Planktonic Amphipods, Shrimp (Acanthephyra, Paleomonetes)]	Fish	Squid
50 to 1,000	25 to 300	2 to 1,000	4,000 to 40,000	17-190	---	30-80

[a]Concentration in whole, fresh organisms versus concentrations in seawater.

5.3.2 Man-made

The disposal of municipal solid waste presents one mechanism for the reentry of nickel into the environment, the disposal routes normally encountered are incineration and landfilling. In municipal solid waste, small amounts of nickel are found in its ferrous fraction, a fraction that varies from 7-10 percent of the total weight, depending on geographic location and other variables.

Nickel can leach into nearby ground water supplies from landfills. Chain and DeWalle[59] have recently analyzed various landfill leachates for a vareity of constituents, including nickel, and report a range of nickel values from <0.05 to 13.0µg/g. These results were from nine different sources and represented a wide variety of conditions. The high value was obtained from a newly-established lysimeter maintained under controlled conditions so that leachates would be generated for a subsequent treatability study. The low value was obtained from a simulated landfill in which the leachate was recycled in order to study the attenuation of pollutants through a landfill.[60] Certain other conditions such as temperature, pH, amount of moisture, and the ferrous content of the refuse itself play a vital role in the amount of nickel in landfill leachates. Thus, there is a rather wide range of values possible. Since landfill leachate has the potential for contaminating a drinking water supply, good landfill management is extremely important.

An alternate disposal procedure is incineration, commonly practiced in many heavily populated areas of the U.S., particularly in the Northeast. Here nickel can enter the environment by several paths: volatilization through the stack effluent, entrainment in the fly ash, or collection with the incinerator residue. Jens and Rehn[61] reported on the analysis of samples taken from several incinerators (Table 5.16).

A more recent study by Achinger and Daniels[62] cites the nickel concentration of impinger-water residues as being < 0.5 ppm for sample number one and 0.5 ppm for sample number two. Sample one was from particulates caught after the filter; it includes the residue left after evaporation of the acetone used to rinse the sampling train after the filter and before the impinger. Sample two was from the residue left after evaporation of the chloroform and ether used to extract organic materials from the impinger water wash.

Table 5.16. NICKEL IN INCINERATOR ASH[61]

Source	Concentration, percent
Stack dust	1 to 10+
Collector catch	0.001 to 0.01
Residue	0.001 to 0.01

Buttermore, et al.[63] recently reported the nickel content for eight different municipal incinerator fly ashes. Reported as percentage nickel by weight, the range of values was 0.04 to 0.01 with the majority being 0.02 percent or less. From these reported low quantities, it appears that, at this time, nickel does not constitute a major pollution problem. Further, it is assumed that modern air pollution abatement equipment effectively removes most of the nickel and its compounds, if they are present, in the gaseous effluents of incineration.

In addition to entering the environment from disposal practices, nickel is also observed in processes involving the recycling of solid waste. Ostrowski[64] reports that induction and electric arc furnace heats made with scrap from municipal incinerator residue showed that this scrap contained considerable copper, tin, and nickel. Furthermore, he maintains that use of incinerated ferrous scrap from solid waste should be restricted to those steels whose specifications can accommodate these critical impurities. Additionally, he states that consideration must be given to the effect of the buildup of these residuals in the system through recycling of domestic scrap. The nickel percentage is reported at 0.100 for incinerated scrap, with upper and lower confidence limits being 0.134 and 0.065 for the 95 percent confidence band. This compares favorably to the 0.11 percent Ni determined for auto scrap by Carlson and Schmidt.[65]

Composting municipal solid waste has received much attention in the past, and even today has some residual interest. Because of the ferrous content and the accompanying shredding and grinding operations, some metals are dispersed throughout the compost itself. Recently, the United States Department of Agriculture[66] analyzed three compost samples for the presence of four heavy metal constituents; zinc, cadmium, copper, and nickel. On a μg Ni/g dry weight basis, the three analyses yielded 16 24, and 25, respectively. By comparison, digested sewage sludge has showed a range of 25 to 8,000 μg/g. presumably measured on a dry solids basis. Therefore, it can be readily observed that the nickel content of the compost was at the low end of sludge values, and should not present any major toxicity problems.

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6. ENVIRONMENTAL EXPOSURE

6.1 MULTI-MEDIA EXPOSURE

6.1.1 Ambient Air

Nickel is emitted into the ambient air from a variety of sources. Emission factors for a number of source types are presented in Tables 6.1 to 6.4. An emission factor is an estimated average of the rate at which a pollutant is released to the atmosphere as a result of some activity, divided by the level of that activity.[1] The nickel emission factors can be used to estimate emissions for a given community. The extent to which the nickel concentrations present in ambient air pose a hazard for human health is at present unknown.

As previously discussed, nickel mining and ore processing plants are major sources of nickel emissions to the atmosphere. Another source of nickel in ambient air is the combustion of fuel oil for space heating. In densely populated urban areas during winter months, fuel with the latter concentration level could produce considerable quantities of airborne nickel. It has been estimated that in Manhattan, where 14.8 million liters of fuel oil are used per year, allowing a nickel content of 10 ppm and an emission rate of 25 percent, the daily release rate of nickel into the atmosphere would be 156 kg during the cold weather months.

Coal-fired power plants are another stationary source of nickel. The content of nickel in coal varies according to the region in which the coal was produced: midwestern states, 0.025 kg/MT; eastern states, 0.016 kg/MT and western states 0.004 kg/MT.[3] Not all of the nickel

content of coal is emitted to the atmosphere; however, evidence does indicate that nickel is present in increasing proportions as the size of the coal ash decreases. Thus, the finely divided ash has a higher percentage of nickel present and is more likely to reach the human respiratory tract.[4] Certain types of boilers in coal-fired power plants (the spreader stoker, the cyclone fired unit, and the horizontally opposed types)[5] produce a higher nickel content in ash than others.

The National Air Surveillance Networks (NASN) monitored air quality in thirty cities in the United States.[7] From 1957 to 1968, the average nickel concentrations declined slightly from 0.047 $\mu g/m^3$ to 0.026 $\mu g/m^3$ among the NASN monitored cities. Cities having the highest airborne nickel concentrations were East Chicago, Indiana (0.132 $\mu g/m^3$); Boston, Massachusetts (0.112 $\mu g/m^3$); and New York City (0.118 $\mu g/m^3$). The cleanest cities, having no detectable nickel present in the air, were: Boise, Idaho; Albuquerque, New Mexico; and Moorhead, Minnesota.

Both urban-rural differences and seasonal differences in airborne nickel concentrations exist; the urban areas have the most nickel in the air during fall and winter months.[7]

6.1.2 Water

As indicated previously, the nickel concentration in U. S. surface and ground water is quite low. Data regarding the nickel concentration in drinking water actually consumed by man are limited. Samples collected at water plants do not reflect the pickup of metals from the distribution system. The EPA National Environmental Research Center at Cincinnati, Ohio conducted an extensive study of metal pickup in distribution within the Chicago supply. When the distribution samples were compared with samples collected at the treatment plant, it was noted that 34 percent showed an increase in the nickel content of the water. A Community Water Supply Survey was conducted in eight metropolitan areas in 1969-70. These included samples from 969 water supplies. The average nickel concentration in the water samples taken at the consumer's tap was 4.8 µg/liter. With an estimated consumption of two liters per day, the nickel intake via water for an adult would be approximately 10 µg/day.

Nickel was found in 78 percent of the samples with a minimum level of 1 µg/liter Using these data, Table 6.1 shows the frequency distribution of nickel in drinking water. [2]

Table 6.1. NICKEL IN DRINKING WATER,[2] COMMUNITY WATER SUPPLY SURVEY

Milligrams per Liter	Number of Samples	Percent of Samples
.000	543	21.69
.001 - .005	1082	43.22
.006 - .010	640	25.57
.011 - .015	167	6.68
.016 - .020	46	1.84
.021 - .025	14	.56
.026 - .030	4	.16
.031 - .035	2	.08
.036 - .040	1	.04
.041 - .045	1	.04
.046 - .050	1	.04
.051 - .055	1	.04
.075	1	.04
	2503	100.00

McNeely et al.[8] examined the tap water in two communities to determine the nickel concentration. The communities were Hartford, Connecticut, an area free from nickel industries; and Sudbury, Ontario, a center for nickel mining and processing. The mean concentration of nickel in five samples from Hartford was 1.1 $\pm$ 0.3 µg/liter. The mean nickel concentration in Sudbury was 200. $\pm$ µg/liter.

6.1.3 Food

The information available indicates that the concentration of nickel in foods is low and does not pose a toxicity problem.

Among the common foods for which the nickel content has been ascertained, the following have relatively high levels of Ni: baking powder, 13.4 µg/g; orange pekoe tea, 7.6 µg/g; buckwheat seed, 6.5 µg/g; cocoa, 5.0 µg/g, gelatin, 4.5 µg/g; black pepper, 3.9 µg/g; mushrooms, 3.5 µg/g; cabbage, 3.3 µg/g; red kidney beans, 2.6 µg/g; oats, 2.4 µg/g; and shortening, from 2.0 to 6.0 µg/g.[9]

The nickel-containing stainless steels used for food processing equipment are thought to contribute only minute amounts of metal; "trace quantities having no pharmacological significance."[10]

Exposure of animals other than humans to nickel is also dependent on their choice of food plants. In the case of domestic animals it will be principally through the nickel present in pasture grasses and feed grains.

Plants, whether they are used for food or not, may be exposed to nickel in air, water or soil. Aerial exposure

is principally caused by nickel dust from industrial processes and motor vehicles being deposited on vegetation and soil.[11,12] or entering aquatic habitats. The extent to which plant exposure to nickel may occur is dependent on the extent to which nickel deposition increases the concentration in the specific medium, such as, the soil. Applications of sewage sludge to soil may increase the nickel levels and therefore, plant exposure. Phosphate fertilizers also contain nickel as do certain pesticides. Applications of either of these substances may increase the possibility of exposure to nickel.

6.1.4 Soils

As indicated in other sections of this document, the nickel content of soils varies considerably from one area to another. The amount depends upon several factors and has been reported by a number of investigators to range from less than 50 g/g to 500 µg/g.[13] The higher concentrations usually occur in soils derived from serpentine rocks where concentrations as high as 5000 µg/g have been reported, whereas 50 µg/g or less is normal for soils derived from sandstones, limestones, and acid, igneous rocks.

Any discussion of trace metals in soils should probably distinguish between native trace metals and those that are added to soils. Pollution effects from trace metals in soils are more often associated with the added metals rather than the native ones. An exception, of course, has been the toxicity of nickel to plants growing on high nickel-containing serpentine soils.[13,14] This circumstance arises because the form in which the trace metals are added is different from the native metals which have normally reached a state of equilibrium with the surrounding soil and associated conditions.

Lagerwerff and Specht found[12] detectable amounts of nickel at sites near dense automative traffic areas, presumably from the use of nickeled gasoline and atmospheric abrasion of nickel-containing automobile parts. The concentration gradient of the nickel and other trace metals studied in the soils and vegetation decreased with distance from the road, indicating that the road traffic was the source of the pollution. The nickel concentrations, however, were extremely small and probably not significant with regard to pollution of the soils. Nickel has been used in selected fungicides[13] and is usually present in pulverized serpentine, which may be used as a source of available manganese.[15] Although these two uses may represent potential sources for nickel contamination of soils, there is little available evidence to suggest that these must be considered as important sources of nickel contamination of soils. However, soils near nickel mining areas can be expected to contain toxic levels of nickel. The ash from coal-fired power generating plants may contain significant quantities of nickel. Depending upon the technique used to manage the fly ash, some pollution of surrounding soils and associated ground waters could occur. Little evidence has been developed, however, to permit proper assessment of the situation. More than 200 ppm of water soluble nickel was reported in soils three miles from smelters located in the Sudbury Basin in Ontario.[16]

Although the mechanisms mentioned are potential sources for nickel contamination of soils, available evidence suggests that these are not significant, except perhaps in the localized areas in close proximity to the source.

The application of urban waste to lands for reasons of land and crop management and for waste management is not new. Since one of the most pressing problems facing metropolitan areas is disposal of large volumes of liquid and solid wastes, this technique is receiving widespread attention as a disposal method.[17] Many materials added to soils may contain toxic heavy metals. Sewage sludge contains zinc, copper, nickel, and cadmium in excess of soil levels.[18] The sludge and effluent are applied to soil with the intent that the toxic elements be retained by the soil. Since these elements will accumulate and persist, they are a potential long term environmental hazard with regard to the land application of urban wastes. Thus this appears to be potentially the greatest source for nickel contamination of soils. Sludges from several different areas were found to contain relatively high concentrations of nickel.[17,18] Chaney[18] suggests that because of the amounts of toxic metals, including nickel, contained in sludges from many large treatment plants treating municipal and industrial wastewater, from small plants serving only a few unregulated metal industries, and even from a few serving domestic sources, many sludges would be prohibited from being applied to soils. This

was based upon his review of available sludge analysis data, results of his own analysis of sludges from several areas, and the application of certain assumptions and factors with regard to soil conditions, metal content, etc. Sludges from the operating digestors of several cities ranged from < 50 mg/kg dry sludge in cities with little or no heavy metal producing industries to as high as 1100 mg/kg dry sludge in cities with moderate to relatively large amounts of heavy metals producing industries.

6.1.5 Occupational

Though the safety of the work environment is much better today than it was previously, there are still some industries for which sufficient monitoring of the workroom air has not been undertaken.[19]

6.2 RECEPTOR RISKS

Since nickel is present in natural waters, soils, and foods, man is inevitably subject to oral, inhalation and cutaneous exposures to trace amounts of nickel. The probability of exposure to nickel carbonyl, the most toxic of all known organic nickel compounds, is limited primarily to cases of occupational exposure. There is no evidence to indicate that the risk of the general population to exposure to nickel through inhalation of ambient air or oral intake through food and water is cause for concern.. Risk of nickel poisoning in the general population is minimal.

The possibility that plants and terrestrial organisms will be exposed to concentrations of nickel which may be detrimental is dependent largely on their proximity to industrial installations, urban centers or highly travelled highways, mining activities, or large deposits of mine wastes.

The addition of sewage sludge to agricultural soil may increase the risk of exposure of plants to nickel. Based upon Chaney's recommendations, a sludge containing only 300 mg/kg dry sludge of nickel would be a conditional sludge for application to soils of a cation exchange capacity equal to 10.[18] This suggests that as many as 30 to 60 percent of the sludge for which data is available could not be applied to soils based upon metal content and today's knowledge of the ultimate fate of the metals in the soils and plants. Only 25 to 50 percent would be recommended.

There have been numerous examples of metal toxicity in agriculture crops, some directly related to the application of sludge and effluent.[20,22] Much of this has already been related to poor land management. In the case of the application of typical domestic sludge to land, it would appear that mercury, cadmium, zinc, and copper, in that order, may become limiting relative to potential toxic concentrations before nickel and chromium cause problems. Sludges from metropolitan areas with large industrial inputs may contain concentrations of nickel and chromium that are so large that these elements may become the controlling factor with regard to soil toxicity and resulting toxicity to sensitive plants.

Since selected factors such as organic matter, phosphate, and other factors control the accumulation of toxic metals, including nickel, in soils and crops, proper management of the receiving soils and observance of certain application techniques will play an important role in controlling the application of sludges, effluents, compost and other wastes to the soils so that toxicity to the soils and crops will be manageable. Chaney[18] discussed this and suggested that two bases be used for formulating

recommendations for the addition of toxic metals (in sludges, effluent, compost, etc.) to agricultural soils. These are: a benefit: risk ratio, and a limitation of metal additions to permit contained general farming. Since nickel has been found in sludges, effluents, and compost in quantities sufficient to cause toxicity problems in soils and plants, caution must be exercised in applying these wastes to the soils. In order that this caution be properly exercised, studies must continue to provide knowledge and data not now available with regard to such factors as crop species and varietal differences in tolerance and accumulation of toxic metals; reversion of toxic metals in different soils; effects of organic matter, phosphate, etc.; basic knowledge on crop and management effects on soil organic matter as it relates to control of excess copper, nickel, and zinc. Further, almost nothing is known about toxic metal interactions and the importance and mechanisms of phosphate interaction with zinc, copper, nickel, cadmium, lead, and mercury. to alleviate toxicity and prevent plant transport of these toxic elements.[20]

Exposure of aquatic plants and animals to detrimental levels of nickel will depend on the concentrations in the water where they exist.

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7. MECHANISMS OF EXPOSURE

7.1 ANIMAL

7.1.1 Routes of Intake and Absorption

7.1.1.1 Routes of Animal Exposure--Routes of exposure of man and other animals to nickel are essentially the same with differences, perhaps, in relative magnitude of importance. The routes of exposure of animals in order of importance are: ingestion, inhalation, absorption, and parenteral administration.

7.1.1.1.1 Ingestion--Tedeschi and Sunderman[1] have determined that nickel ingestion averages 373 µg/day in dogs fed a major brand of dog food ad libitum. Except in unusual circumstances, intake of nickel by domestic animals by any means other than ingestion would be negligible.

7.1.1.1.2 Absorption--Schroeder et al.[2] have suggested that mammals possess mechanisms that limit intestinal absorption of nickel. Feeding experiments using dogs suggest that 10 percent of soluble nickel is absorbed. Higher absorption in dogs than in man might be expected due to the relatively low pH of the canine gastric juices.

7.2 HUMAN

7.2.1 Oral Intake

It has been estimated that the nickel content of food and water ingested by human beings ranges from 300 to 600 µg per day.[2] However, most of the nickel content of the diet passes through the gastro-intestinal system unabsorbed.

7.2.2 Percutaneous Absorption

The quantity of nickel absorbed through the skin is probably negligible. This route is of clinical significance because of nickel dermatitis.[3]

7.2.3 Parenteral Administration

The nickel content of stainless steel prostheses and implants has become a problem in terms of incurring hypersensitivity to the metal.[4] Here, again, the quantities of nickel leached from the items by body fluids are negligible.

7.2.4 Inhalation

The estimated quantities of nickel inhaled by a resident of one of the cities having the highest measurements of nickel in ambient air are 2,36 µg/day in New York City, or 13.8 µg/day in East Chicago. The average daily intake of nickel by urban residents is 2-14 µg/ per day, depending upon the season and the location.[5]

The production of nickel -cadmium batteries, and nickel electroplating are industries which may involve hazards from nickel dust. Steel mills are also potential sources of nickel emissions but have not been evaluated in this report.

7.2.5 Special Categories

7.2.5.1 Smoking--The mean nickel content of cigarettes has been found to range from 2.0 to 6.2 µg/cigarette.[6,7] Studies have demonstrated that 10 to 20 percent of the nickel in cigarettes is released in mainstream smoke. Of the nickel present in smoke, 84% is in gaseous phase, and 16 percent is in particulate phase.[6] There is some evidence that the gaseous nickel in cigarette smoke is in the form of nickel carbonyl. Thus, a smoker who consumes two packages of cigarettes per day will inhale a maximum of 14.8 µg of nickel per year.[8]

American pipe tobacco, cigars, and snuff have been found to contain 2-3 µg of nickel per gram of tobacco.[9] Cigars and snuff from other countries have even higher nickel content. The wrappings around the cheaper brands of cigars are made from tobacco leaves treated in such a way that the content of inorganic particles is high, though the amount of nickel present has not been ascertained.

7.2.6.2 Medical Appliances--Nickel bearing surgical implants and specially designed prosthetic devices in direct contact with the human body for long periods of time may corrode at rates sufficient to produce toxicity.[10]

7.2.5.3 Other Environmental Sources--Among other possible sources of nickel contact exposure are inexpensive jewelry, coinage, clothing fasterners, tools, cooking utensils, stainless steel kitchen equipment, and detergents.

7.3 PLANTS AND ORGANISMS

Exposure of terrestrial plants to nickel occurs chiefly through the roots. The root hairs are the avenue through which nickel enters the plant, and then only when in solution. When in solution, nickel may move across the cell membranes in the root hairs and then move into the root proper. From there it can be translocated throughout the plant in the xylem sap. Uptake of nickel by plants depends on the concentration of nickel in the soil, the type and nutritional status of the plant, and even more importantly the availability of nickel. The pH, chemical binding, solubility, presence and composition of other elements and the organic composition of the soil all are important in determining the availability of nickel. The organic composition of soil and litter is an important factor because it affects ion exchange. The negatively charged organic ions are capable of binding metallic ions and holding them in a form which is not readily available. Microbial action and the importance of Eh in nickel uptake seems not to have been studied.

Exposure of plants to nickel in urban industrial areas and along highly traveled highways may occur through the deposition of airborne nickel on the plant surfaces. The extent to which the nickel bearing dust is retained on plant surfaces is dependent to a great extent on the growth form of the plant and leaf morphology. Foliar penetration of the leaf by nickel may occur if it is in solution. Studies showing foliar penetration by nickel in solution are few and deal chiefly with nickel containing pesticides. Studies exist which indicate that trace elements,

such as iron, manganese, zinc, copper, molybdenum, and cobalt, are rapidly absorbed from the leaf surface.[11] After foliar absorption, the element may be moved about the plant or remain in the leaf.

Deposition of nickel onto the surface of mosses results in its being taken up through ion exchange.[12,13] The degree of sorption between the simple cations of heavy metals and negatively charged organic groups in most moss tisues is: calcium and lead> nickel> cobalt> cadmium> zinc and> manganese.[12] The sorption of nickel by mosses and lichens does not necessarily mean that it is taken into the moss or lichen tissues, but it does favor an accumulation in dead organic matter, litter and humus.[14] Table 7.1 shows the concentrations of nickel in a spruce forest in Sweden.

Microorganisms growing on the leaves, other plant surfaces, and in the soil may be exposed to nickel in particulate form when it is deposited on the plant and soil surfaces. For exposure to occur, the nickel solution must come into contact with the cell membrane of the microorganisms.

Aquatic plant species are exposed to nickel either through their cell membranes or in the case of higher plants through their root systems.

Exposure of aquatic animals may occur either through the ingestion of vegetable matter or through the circulation of water through their systems.

Table 7.1. CONCENTRATION OF NICKEL IN A SPRUCE FOREST IN CENTRAL SWEDEN (mg/kg dry weight)[13]

	Nickel	
Spruce (*Picea abies*)		
roots <5 mm diam	7.6	(25) [a]
≥5 mm »	5.8	(15)
wood	0.5	
bark	2.5	(2.3)
twigs, 1st year	14	(4.4)
2nd »	13	(5.4)
3rd »	13	(4.5)
4th »	10	(3.1)
5th—7th year	6.1	(3.6)
needles, 1st year	3.8	(2.3)
2nd »	3.4	(2.3)
3rd »	2.5	(1.7)
4th »	3.0	(2.1)
5th—7th year	3.2	(2.0)
needle litter	26	(9.3)
Cowberry (*Vaccinium vitis idaea*)		
above ground biomass	6.2	(5.6)
Bilberry (*Vaccinium myrtillus*)		
above ground biomass	4.8	(4.2)
Hairgrass (*Deschampsia flexuosa*)		
leaves	12	(2.8)
leaf litter	14	(3.0)
roots+rhizomes	13	(3.1)
Epiphytic lichens (*Parmelia physodes*)	18	(16)
Mosses (*Hypnum cupressiforme*)	52	(9)
Humus layer (*raw humus*)	36	(5.4)

[a] **Figures in brackets are enrichment ratios, calculated as the quotient between the metal concentration of the component in this site and of the same component in a similar site with no local deposition.**

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8. MECHANISMS OF RESPONSE

8.1 ANIMAL METABOLISM

8.1.1 Transport

Ultrafilterable nickel complexes may function as carriers for the extracellular transport and renal excretion of nickel.[2] Estimates of total serum nickel and ultrafilterable fractions for several species are shown in Table 8.1 .

Table 8.1. SERUM NICKEL IN SEVERAL SPECIES

Specie	Concentration, μg/100 ml	
	Serum	Ultrafilterable
Men	0.23	0.09
Dogs	0.23	0.20
Rabbits	0.90	0.14
Rats	0.66	0.18
Lobsters	0.88	0.33

Species differences in nickel-binding properties of serum albumin may account for the variations in partitioning of serum nickel. Callan and Sunderman[1] reported the first association constants of serum albumin for divalent nickel-63 as follows: man - 300,000; dog - 25,000; rabbit - >300,000; rat - 200,000; and pig - 80,000 liters/mole.

"Nickeloplasmin" has been identified as an alpha-macroglobulin which binds a portion of the nickel in normal serum of man and rabbits.[3] It is apparently a glycoprotein with esterase activity[4] and a molecular weight of 700,000.[5] It resembles, but is not identical to the zinc-containing

macroglobulin isolated from human serum.[7] The physiologic significance of nickeloplasmin is not known.

8.1.2 Excretion

Nickel that is ingested in food is for the most part unabsorbed and excreted in the feces. The same holds true for soluble nickel in drinking water. In dogs, Tedeschi and Sunderman[8] demonstrated that 90 percent of ingested nickel was recovered in feces and only 10 percent in urine

In rats fed nickel soaps or nickel catalyst of 250, 500 or 1000 µg/g nickel in their diets, approximately 90 percent of the nickel was found in the feces and less than 1 percent was excreted in the urine.[9] When nickel was given as nickel carbonate, 74 percent was excreted in the feces and 1.6 percent in the urine.[10] Nickel that enters the body via the pulmonary route or by parenteral administration is excreted predominately in the urine.

With injection of small doses of nickel-63 in the rat, 61 percent was excreted in the urine and only 5.9 percent in the feces within 72 hours.[11] Additional studies on parenterally administered nickel will be discussed under Undesirable Effects.

8.1.3 Binding to Biological Substances

The biological activity of nickel depends upon the nature and location of its intra- and extracellular binding sites. In general, nickel is similar in binding properties to other metals of the first transition series. It is unique in its divalent state, however, in that it exists in three interconvertible geometric structures--square planar, octahedral, and tetrahedral. Possible structure-function relationships have not been routinely considered in studies on the biological activity of divalent nickel.

8.1.3.1 Binding to Nucleic Acids--Divalent nickel has been shown to bind to phosphates, purines and pyrimidines of DNA and RNA, providing conformational stabilization of the nucleic acids.[12,13] Heating of RNA in the presence of nickel results in breakage of phosphodiester linkages and depolymerization.[14-16] Binding of nickel to nucleic acids may have adverse implications for the regulation of cell growth and division and for the transfer of hereditary information.

8.1.3.2 Binding to Nucleotides--Divalent nickel binds to the separate monomeric components of nucleic acids through the same functional groups as in the polymerized forms. Adenosine triphosphate (ATP),which is required in nucleic acid synthesis and in energy transfer for many biosynthetic reactions, binds nickel as does the pyrmidine base of the coenzyme,thiamine pyrophosphate.

8.1.3.3 Binding to Proteins--It has been determined that nickel binds to carboxyl[17] and imidazole[18] groups of bovine and human serum albumin. The alpha-amino group of aspartic acid,[19] a sulfhydryl group, and between the terminal amino group and the adjacent peptide[20] have also been implicated as nickel binding sites. The later mode of binding has been postulated for vasopressin, alpha-chymotrypsin, ribonuclease,[20] and myoglobin.[21] Divalent nickel binding has also been demonstrated with casein, gelatin, pseudoglobulin, and keratin.

8.1.3.4 Binding to Peptides--The binding of nickel to oligopeptides has served as a simplified model for the interaction of the metal with proteins. Di- and triglycine form complexes with nickel with binding of the metal to

carboxyl, peptide nitrogen, and amino groups.[22] With triglycine, chelation involves the peptide nitrogen and the amino group.[22] Peptides with amino acids containing sulfur or heterocyclic nitrogens also coordinate with nickel through these electron donor atoms.[23] Titration of nickel-oligopeptide complexes can result in rearrangement of coordination sites around nickel with concomitant conversion of the paramagnetic octahedral complexes to diamagnetic square planar complexes. Whether these transitions alter biological activity is not known. At least one case is known in which the formation of a complex catalyses cleavage of a synthetic octapeptide.[24]

8.1.3.5 Binding to Amino Acids--Amino acids that contain unique functional groups, as for example, sulfhydryl groups or heterocyclic nitrogens, readily form coordination complexes of these groups with nickel and the alpha-amino groups.[25] Amino acids that possess only carboxyl and alpha-amino groups chelate with nickel through these groups. Proline also forms such complexes even though only one hydrogen is present on the available nitrogen atom.[27]

8.1.3.6 Other Divalent Nickel Complexes--Nickel has been shown to form complexes with porphyrins,[28] including uroporphyrins[28] and bilirubin.[29] It has been postulated that nickel could thus interfere with biosynthesis of porphyrin containing compounds such as hemoglobin and chlorophyll.

Nickel also binds to triphosphoinositide and phosphatidylserine[30] as well as to dihydrolipoic acid.[31] The later chelation could interfere with the ultilization of pyruvate in the formation of coenzyme A.[31] Divalent nickel binds to coenzyme A itself,[32] to citric acid,[33] and to phytic acid.[34]

Whether the affinity of nickel for these or any of the substances previously mentioned has significance in terms of mechanisms of physiologic effects, remains to be clarified.

8.1.4 Effects on Enzyme Activities

Nickel has not been shown to be an integral component of any enzyme except nickeloplasmin,[4] but it does activate and/or inhibit certain enzyme systems (Table 8.2). In interpreting enzyme activation and inhibition data, it must be remembered that many factors influence enzyme determinations such as enzyme and substrate concentrations, pH, and ionic strengths. Experiments employing different assay conditions or enzymes of different sources or purities are, therefore, not directly comparable.

Of the enzymes known to be inhibited by divalent nickel perhaps 5'-nucleotidase and adenosine triphosphatase are most important.[58] The former enzyme catalyzes the hydrolysis of the 5'-nucleotide phosphate. The later catalyzes the dephosphorylation of ATP, is extremely important in energy transfer reactions.

8.1.5 Alterations in Nickel Metabolism in Disease

Ryabova[61-63] has determined that artificially induced myocardial ischemia produces a significant increase in myocardial nickel concentration in dogs. However, there is no significant alteration in mean serum nickel as is observed with myocardial infarction in man.

8.1.6 Effects on Excitable Tissues

In general, nickel competes with and imitates the effects of calcium on excitable tissues--nerves, myoneural junctions, and muscles. Nickel binds to the reactive groups of proteins such as the ammonium, carboxyl, hydroxyl, and sulfhydryl, and to

8.2. ACTIVATION AND INHIBITION OF ENZYME ACTIVITIES BY NICKEL

Enzyme	Activation	Inhibition	References
oxaloacetic decarboxylase	Yes	Yes	35
ribonuclease (bovine pancreas)	Yes	Yes	36
deoxyribonuclease I (pancreas)	yes	-	36
carboxypeptidase	yes (for the apoenzyme)	-	37,38
arginase	yes	-	39,40
enolase	yes	-	41,42
phosphoglucomutase	yes	-	43,44,45
amino acid decarboxylase(s) (from E.coli and C. welchii)	yes	-	46
acetyl CoA synthetase	yes	-	47
pyridoxal phosphokinase	yes	-	48
thiaminokinase	yes	-	49
pyruvic acid oxidase	yes	-	50
salivary amylase (human)	yes	-	51
citritase	yes	-	52
ribulose diphosphate carboxylase	yes	-	53
dialkylfluorophosphate fluorohydrolase	-	yes	54,55
aspartase	-	yes	54,55
alkaline phosphatase(s)	yes	yes	56,57,58
5'-nucleotidase (from bull seminal plasma)	-	yes	58
adenosine triphosphatase	-	yes	59,60

proteins more strongly than does calcium.[64,65] Nickel essentially causes a prolonged action potential and uncoupling between membrane activation and muscle contraction. Only the prolonged action potential occurs in the presence of calcium, and this effect has a threshold nickel concentration of 0.00001 moles.

8.1.6.1. Excitable Membranes--Mechanistically, nickel chloride is thought to prolong the nodal action potential by delaying and reducing inactivation of sodium permeability and by delaying increase of potassium permeability. These effects are explained by the assumption that divalent nickel and divalent calcium mpete for the same membrane binding sites. Studies on this phenomenon have been performed using the giant barnacle muscle, the vagus nerve of the cat, large nonmyelinated axons of the lobster, and stretch receptors from crayfish.[67,68,69] It is interesting to note that the action potential of the giant squid axon is not affected by nickel.[70]

Divalent nickel has also been shown to increase the threshold for neural action-potential production. This increase in threshold by divalent nickel antagonizes the effects of tetrodotoxin and procain.

8.1.6.2 Contractile Tissue--Divalent nickel increases the surface action potential of skeletel muscle which leads to a potentiation of the twitch in both duration and amplitude and a lowering of the tetanus fusion frequency.[73,74] The observed increased duration of the active state is believed to be related to these effects.

Divalent nickel also affects cardiac muscle by lengthening the plateau phase of the ventricular action potential and reducing the contractile forces of both atrium and ventricle.[75,76,77]

With smooth muscle, application of millimolar quantities of nickel results in a long lasting tonic response with inhibition of the phasic response.[78]

8.1.6.3 Neuromuscular Transmission--Nickel has several effects at the neuromuscular junction but none of them results in blocked transmission. Prolongation of the axonal action potential by divalent nickel increases the ion of the presynaptic potential which delays and prolongs the release of transmitter.[79] Divalent nickel also decreases the number of acetylcholine "quanta" released by a single action potential probably by competing with divalent calcium for the active site that controls quantal content and miniature endplate potential frequency.

8.1.6.4 Central Nervous System--Few effects of nickel on the central nervous system have been reported. Intravenous injection of high concentrations of nickel chloride caused breakdown in the blood-brain barrier in rats. Epileptic seizures and death have been produced by implantation of metallic nickel in the cerebral cortex.[82]

8.1.7 Essentiality of Nickel

Criteria for essentiality as a micronutrient include: demonstration of the element in the fetus or newborn, presence of a homeostatic mechanism regulating the metal's concentration, demonstration of a metabolic pool of the element that is specifically altered by hormonal fluctuations or pathologic states, presence of an enzyme in which the element is an integral part, and demonstration of a deficiency state that can be prevented or reversed by the element.

Nickel is situated in the periodic table among a number of essential elements. A possible biochemical role for the metal is suggested by the

fact that it readily undergoes transitions among several coordination structures which may have different biological activities.

8.1.7.1 Presence of Nickel in the Fetus and Newborn--Schroeder and coworkers[95] have shown that nickel is present in human fetal tissues. Their conclusion that nickel can cross the human placenta was confirmed by McNeely et al.[83] with the finding that the mean concentration of nickel in cord serum from 12 newborn human infants (0.30 ± 0.12 μg/100 ml; range, 0.13 to 0.49 μg/100ml It should be noted that the presence of nickel in the fetus or newborn does not necessarily indicate essentiality but may simply reflect maternal contamination.

8.1.7.2 Homeostasis of Nickel--Mertz and associates[84] demonstrated in 1970 that the human kidney possesses an active excretory mechanism for nickel. Also, Nielsen and Sauberlich[85] demonstrated concentration of radiolabeled nickel in liver, spleen and aorta by chicks on a nickel deficient diet as compared to controls on the same diet supplemented with nickel. Thus, mechanisms apparently exist to explain the fact that serum nickel is normally maintained within narrow and characteristic concentration ranges.[3]

8.1.7.3 Metabolic Pools of Nickel--Metabolic pools of nickel do not appear to be altered by endocrine factors or hormonal substances. For example, there are no differences in serum nickel concentrations between males and females of any species studied, and maternal serum levels do not change upon giving birth.[83,86] However, changes in metabolic pools of nickel do occur in certain disease states. Serum nickel concentrations are significantly increased following myocardial infarctions and after stroke and burns.[83,87,88] They are decreased in hepatic cirrosis and chronic uremia.[89] Hepatic nickel levels are also increased in hepatic cirrosis.[89]

8.1.7.4 A Nickel-Containing Metalloprotein--As previously mentioned, human and rabbit serum has been demonstrated to contain a nickel metalloprotein that appears free of other metals.[3,4,86] This alpha-macroglobulin possesses protein esterase activity, as is characteristic of this group of globulins, and, therefore, conforms to the essentiality criterion as a metalloenzyme.

8.1.7.5 Nickel Deficiency in Experimental Animals--Nielsen and coworkers[90,91] have shown that nickel deprived chicks (40 to 80 ppb in diet) have swollen hock joints, reduced length: width rations of the tibias, yellow-orange discoloration with scaly dermatitis of the legs and fat depleted livers. Others have not observed such a syndrome and subsequently Nielsen and Ollerich were not able to repeat their original work.[91,92] However, Sunderman et al[93] did observe decreases in mean serum and hepatic nickel levels in chicks on a 44 ppb nickel diet. Sunderman et al. also reported perimitochondrial dilatation of rough endoplasmic reticulum in nickel deprived chicks which according to Piccardo and Schwarz[94] may be the earliest ultrastructural lesion in hepatocyte degeneration. This finding was confirmed by Nielsen and Ollerich[92] and thus indicates the probable dietary essentiality of nickel.

8.2 HUMAN MECHANISMS OF RESPONSE

8.2.1 Uptake

Though the usual oral intake of nickel by American adults is estimated to be 300 to 600 μg/day, most of this remains unabsorbed within the gastrointestinal tract. Schroeder and associates[95] suggested that there is a mechanism which limits absorption of nickel in mammals, despite the relatively large amount of nickel present in food. If such a mechanism exists, it adds credence to the possibility that nickel may be an essential trace element in human metabolism.

Nickel may be inhaled into the respiratory tract both from the atmosphere and from tobacco smoke. An adult resident of New York City could have inhaled as much as 2.36 μg of nickel a day (1966), and a resident of East Chicago, Illinois, could have inhaled a maximum of 13.8 μg of nickel per day (1964).[96] Sunderman made similar estimates for nickel inhalation from smoking: a maximun of 14.8 μg of nickel per day for a two-package a day smoker.[97]

Percutaneous absorption and parenteral administration are negligible means of nickel uptake but are clinically significant because of the development of hypersensitivity.

8.2.2 Distribution and Excretion

There are approximately 10 μg of nickel in a normal man, but wide variations exist. Tipton et. al.[98] studied autopsy tissues from 173 subjects, apparently healthy Americans who had died suddenly and had no visible

disease condition at the time of death. There was a significantly higher nickel concentration among males. Nickel was observed in only about one-third of all samples analyzed (29 tissues per subject), although it was observed in every tissue. The greatest frequency and the highest concentration occurred in skin. The lung, omentum, and intestinal caecum had the highest median values for nickel content among the tissues examined. As to frequency in occurrence of nickel among the tissue samples, the following percentages describe the distribution: lung, 65 percent; aorta, 49 percent; trachea, 49 percent; heart, 42 percent; kidney 38 percent; larynx, 31 percent; liver, 25 percent; and 87 percent of intestine and skin samples.[99]

McNeely and associates[100] have shown that measurements of nickel in serum and urine can serve as biological indices of environmental exposure to nickel. This study compared serum and urine nickel levels from healthy hospital employees in Sudbury, Ontario and in Hartford, Connecticut. For the Sudbury subjects, the mean serum nickel concentration was 4.6 ± 1.4 µg/liter (n=25) and their average urinary nickel excretion was 7.9 ± 3.7 µg/day (n=19). For the Hartford subjects, the mean serum nickel concentration was 2.6 ± 1.0 µg/liter (n=26), and their average urinary nickel excretion was 2.5 ± 1.4 µg/day (n=20).

The major route of elimination of nickel from the human body is that of fecal excretion.[101] In a study of ten healthy hospital employees in Hartford, Connecticut, the fecal excretion of nickel averaged 258 µg/day (SD, 1126). This was approximately 100 times greater than the mean daily excretion of nickel in urine.

Nickel is also excreted from the body in sweat. The mean concentration of nickel in arm sweat from 33 healthy men exposed to dry heat of a sauna bath was 52 ± 36 µg/liter.[102]

Measurement by atomic absorption spectrometry of the nickel content of human hair specimens indicated a mean concentration of 0.1 $\pm$ 0.08 µg/g (n=20). There was no significant difference observed in mean nickel concentration between men and women; however, there was a significant diminution in nickel concentration with advancing age.[103] Elimination of nickel in desquamated hair is one of the physiologic routes for the excretion of nickel from the body.

8.2.3 Metabolism

Studies have shown that nickel is maintained within a characteristic range of concentrations in the blood serum of man: mean, 2.6 µg/ liter; range, 1.1-4.6 µg/liter; standard deviation, $\pm$ 0.8; and n=47.[104] Pathological alterations of serum nickel concentrations have been found to occur in various common diseases of man--with an elevated serum nickel occurring following myocardial infarction, stroke, and severe burns; and a lowering of serum nickel occurring in patients with hepatic cirrhosis, or chronic uremia.[105]

The occurrence of nickeloplasmin, a nickel-containing matalloprotein in serum, suggests that nickel, like other metals in the first transition of the periodic table, may play an essential physiologic role.[104]

The biologic effects of nickel depend upon the nickel binding sites within the human cell. Nickel binding to biologically important sources are generally like the effects of other metal ions, particularly ions of the

first transition series, to which nickel belongs.[106] Nickel and other metal ions exert profound effects on genetic material. It has been demonstrated that divalent nickel binds to both the phosphates and heterocyclic bases of DNA and RNA.[107]

The biological synthesis and degradation of nucleic acids involve the nucleotides, which bind primarily through the phosphate groups, but also by base binding. This binding occurs with adenosine triphosphate (ATP), an important cellular constituent involved in energy transfer and many enzymatic reactions.[106]

8.3 PLANTS

Plants exhibit a wide variation in their response to nickel concentrations in the soil. Plant response is associated with their tolerance to metals. The factors which determine the response are not well known. Few gymnosperms grow in soils with high concentrations of nickel. The majority of the flora found on serpentine soils are perennial herbs.[108] It has been noted that the chromosome numbers of these plants differ from those of plants growing on non-serpentine soils.

Tolerance mechanisms in plants may be "external" or "internal". External mechanisms prevent the entrance of metal ions. The circumstances which prevent entry are not strictly plant controlled, but still are important in determining plant response. Antonovics et al.[108] have outlined both the "external" and "internal"mechanisms (Table 8.3). Basically, these mechanisms are the same for the majority of heavy metals.

Some of the plants growing in soils with high concentrations of nickel have developed a mechanism which prevents the metal from reaching the sites of active metabolism by chelation in the cell wall. Alyssum bertoloni, which accumulates nickel and grows on serpentine soils, concentrates the nickel in the epidemis and sclerenchymatous areas (non-living cells which provide the plant with support).[108] Nickel is also accumulated in the leaves of Hybanthus floribundus. It has been suggested that this accumulation of nickel is an adaptation by the plant to the xeric conditions under which it grows.[109]

8.3. POSSIBLE MECHANISMS OF METAL TOLERANCE IN PLANTS[108]

A. *External*	B. *Internal*
• Form of metal is not directly soluble in water and/or if dissolved then rapidly diluted by surrounding water.	• Differential uptake of ions.
• Actual amount of freely diffusable metal ions is small compared to total amount present.	• Removal of metal ions from metabolism by deposition in vacuole.
• Lack of permeability to heavy metals under specific conditions.	• Removal of metal ions from metabolism by pumping from cell.
• Metal ion antagonisms.	• Removal of metal ions from metabolism by rendering into an innocuous form.
	• Excretory mechanisms—removal of "metal storage organ".
	• Greater requirement of enzyme systems for metal ions.
	• Alternative metabolic pathway by-passing inhibited site.
	• Increased concentration of metabolite that antagonizes inhibitor.
	• Increased concentration of enzyme that is inhibited.
	• Decreased requirement for products of inhibited system.
	• Formation of altered enzyme with decreased affinity for inhibitor or increased relative affinity for substrate compared to the competitive inhibitor.
	• Decreased permeability of cell or subcellular units to metal ions.
	• Alteration in protoplasm so that enzymes may function even when toxic metals replace physiological metals.

Tolerant plants have been found to be metabolically different from normal plants at low metal levels.[108]

Plants which cannot tolerate high concentrations of nickel, do not grow on nickeliferous soils.

Iron and sulfur oxidizing bacteria are capable of using metal sulfide minerals as energy sources.[108-112] For example, Thiobacillus ferroxidans converts millerite (NiS) to divalent nickel, sulfhydryl, and sulfate ions through an oxidation process. This results in the solublization of the nickel sulfide ore and the production of sulfuric acid.[110,111] Because of the production of sulfuric acid, the medium surrounding this process becomes highly acidic--pH 1 to 2. These reactions are typical of mine drainage areas.

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9. UNDESIRABLE EFFECTS

9.1 HUMAN

9.1.1 Hypersensitivity

Nickel dermatitis--the "nickel itch"--is a common malady among nickel miners, smelters, refiners, and nickel-plating workers. Currently, however, nickel dermatitis is being reported frequently by non-industrial populations who contact the metal in the course of their everyday activities.[1] Women have a high rate of nickel hypersensitivity,[2] either from greater susceptibility or greater exposure.

The symptoms of the skin eruption begin as an itching or burning papular erythema in the web of the fingers and spread to the fingers, wrists, and forearms. The clinical pattern of nickel dermatitis progresses from areas of direct contact with the metal, to selective symmetrical areas involved when the skin eruption spreads to other areas of the body which may have had no nickel contact.[3]

In order to elicit epidermal sensitivity, it is necessary for the nickel to be in contact with the skin, to penetrate the epidermis, and to combine with a body protein. The leaching of nickel from objects is enhanced through the action of human sweat. The diffusion of divalent nickel occurs at sweat duct and hair follicle openings, and it has a special affinity for keratin, the protein of hair.

A study by Spruit[4] indicated that divalent nickel reaches and is bound to the dermis. Sometimes nickel dermatitis persists for months following removal of all apparent nickel contact, which may indicate fixation of nickel in the skin.

The studies to determine the extent of nickel hypersensitivity have been on patients having eczema rather than on the general population. Among persons seeking medical attention for a skin eruption, about 11percent reacted positively to nickel on skin testing. However, the prime question of true incidence in the general population has not been answered, nor has the capacity of nickel to act as a skin sensitizer been ascertained.[5]

9.1.2 Nickel Carbonyl Toxicity

Nickel carbonyl [$Ni(CO)_4$] is a colorless, volatile liquid organonickel compound which is particularly dangerous if inhaled. The acute inhalation toxicity of $Ni(CO)_4$ is approximately 100 times greater than that of carbon monoxide.[6]

The clinical pattern of nickel carbonyl intoxication begins with symptoms such as frontal headache, vertigo, nausea, vomiting, and sometimes sternal or epigastric pain. Often a latent period follows of from 12 to 36 hours during which these symptoms subside and the patient feels better. After this, the more serious symptoms occur: constrictive chest pain, cough, breathing difficulty, cyanosis, gastrointestinal symptoms, and weakness. The temperature usually does not exceed 38.3°C (101°F); ıite blood cell count is less than 12,000 per mm^3; the pulse may be elevated; and the patient may lapse into a terminal delirium. If the patient survives, convalescence requires several months, during which the characteristic symptom is muscular weakness.[7]

The diagnostic method employed for nickel carbonyl intoxication is to measure the urinary concentration of nickel during the first three days after exposure using the following classifications: mild exposure, 10 µg/100 ml; moderately severe, 10-50 µg/100 ml; and severe exposure, 50 µg/100 ml.[8]

The pathology of nickel carbonyl poisoning has been explored in autopsy studies of fatal cases. Death was usually attributed to respiratory failure, but cerebral edema and punctate cerebral hemorrhages were often present also. A mild to moderate parenchymal degeneration was observed in liver, kidneys, adrenal glands, and spleen.[9]

After inhalation, nickel carbonyl can pass across the alveolar membrane in either direction without metabolic alteration. In animal studies, $Ni(CO)_4$ that is inhaled or injected does not immediately decompose; and by either route of administration, the pulmonary parenchyma has been found to be the target tissue for the compound. The lung is an excretory organ for nickel carbonyl. The remainder of the $Ni(CO)_4$ present in the body slowly undergoes intracellular dissociation within red cells and other tissues to liberate elemental nickel (Ni^0) and carbon monoxide. The Ni^0 becomes oxidized to divalent nickel (Ni^{2+}) and is released into the serum, from which it is gradually cleared by the kidney and excreted. It has been suggested that the nickel reacts with adenosinetriphosphate (ATP) to form a stable binary complex, and that the acute toxicity of nickel carbonyl may derive, in part, from inhibition of ATP utilization.[10]

Nickel carbonyl is not considered an environmental hazard for the general public. However, the presence of the compound in cigarette smoke may pose a problem of some chronic toxic effects among smokers.

9.1.3 Carcinogensis

There have been epidemiological studies of cancer among nickel workers in Wales Norway, Germany, France, Russia, Japan, Canada, and the United States. At least 327 cases of lung cancer and 115 cases of nasal cancer have occurred among workmen exposed to the inhalation of nickel compounds. It seems unlikely that any one nickel compound can be implicated as the sole carcinogenic factor, but rather several nickel compounds are carcinogenic for man following chronic exposures by inhalation.[10]

There seemed to be a greater risk of cancer for the workers who were involved in nickel processing than workers whose duties were removed from the process. Among Welsh nickel workers, it was found that most of the cancers occurred among workers employed prior to 1924 when a number of changes were made in the operation. One of these changes was the elimination of arsenic as an impurity in one of the process components.[11]

The latent period between time of employment in the nickel industry and diagnosis of cancer varies in length from less than five years to more than 40 years. Among the Welsh nickel workers, the average latent period for lung cancer was four years longer than for nasal cancer. Doll[12,13] reported that susceptibility to induction of cancer of the nasal cavities increased with age at first exposure, but that susceptibility to induction of pulmonary cancer was not similarly correlated.

There is currently little understanding of the exact mechanisms whereby nickel compounds exert their carcinogenic effect. There are several hypotheses regarding chemical initiation of carcinogenesis,[10] however, and these hypotheses are summarized in Table 9.1. All of these possible carcinogenic effects are postulated on the basis that nickel is able to freely pass through the cell membrane, and 70-90 percent of the metal is then concentrated in

Table 9.1. CURRENT HYPOTHESES REGARDING CHEMICAL INDUCTION OF CARCINOGENESIS[10]

I. Genetic Mechanisms

A. Direct modification of existing DNA ("somatic mutation"), in which replication of chemically altered DNA causes inheritable modifications, deletions, or rearrangements of the DNA nucleotide sequence, causing permanent changes in growth regulation

B. Alterations of DNA polymerase, which temporarily decrease the fidelity of DNA replication, causing mutations of the DNA genome

C. Chemical modification of RNA, which is later transcribed into DNA that becomes integrated in the host genome; this may involve viral RNA-primed DNA polymerase ("reverse transcriptase")

II. Epigenetic Mechanisms

A. Chemical modification of RNA or proteins (e.g., histones and nuclear acidic proteins) that regulate DNA template activity, causing expression of normally repressed portions of the DNA genome

B. Chemical modification of RNA or proteins, causing depression of tumor viruses or oncogenes

C. Carcinogen-induced changes in immunologic or hormonal mechanisms, leading to preferential proliferation of previously existing preneoplastic or neoplastic cells

the cell nucleus. The most common histopathologic types of respiratory cancer in nickel workers have been epidermoid, anaplastic, and pleomorphic carcinomas.[10]

The carcinogenic effect of nickel seems to be enhanced by certain physical conditions or the simultaneous occurrence of some other substances. The effect of nickel dust in the heated air of furnace rooms resulted in more lung cancer cases than were found among workers in other locations.[14] The question of synergistic effect of nickel and benzo[a]pyrene has been raised because of animal study results on carcinogenesis.[15] Cralley[16] has advanced a theory of metal interaction in asbestos carcinogenesis in which he proposes that the asbestos fiber simply serves as a transport mechanism for the introduction of nickel, chromium, and manganese into the tissues and that the other metals enhance the carcinogenesis of nickel. A possible interrelationship of nickel with certain parasites and viruses in the carcinogenic process has also been suggested.[17,18]

Though the hazard of nickel carcinogenesis seems relatively controlled among nickel workers under the present industrial safety standards, the hazard may still exist to some extent among cigarette smokers. Long term exposure to small quantities of nickel carbonyl in cigarette smoke, along with other toxic components present in the smoke, may contribute to the high rates of lung cancer among smokers.

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9.2 ANIMAL

9.2.1 Laboratory Animals

Nickel salts are relatively non-toxic by the oral route but quite toxic when given intravenously. Less information is available regarding toxicity by inhalation, except for nickel carbonyl.

The toxicity of inorganic nickel salts is summarized in Table 9.2. The toxicity of nickel complexes and organonickel compounds will be considered separately.

9.2.1.1. Inorganic Nickel by the Oral Route--The oral toxicity of nickel sulfate for rabbits and dogs was established in the early 1800's by the studies of Gmelin.[20] Large oral doses of nickel salts resulted in gastrointestinal irritation with vomiting and diarrhea. Subcutaneous or

Table 9.2. TOXICITY OF INORGANIC NICKEL COMPOUNDS IN ANIMALS[19]

Compound	Formula	Mol. Wt.	Route of Administration[a]	Animal	Toxicity Data[b]	
Nickel	Ni	58.71	ims	rat	TDLO:	110 mg/kg
			ims	mouse	TDLO:	800 mg/kg
			ivn	dog	TDLO:	10 mg/kg
			orl	guinea pig	LDLO:	5 mg/kg
Nickel acetate	$Ni(C_2H_3O_2)_2$	202.84	ims	rat	TDLO:	420 mg/kg
Nickel carbonyl	$Ni(CO)_4$	170.75	inl	rat	LC50:	240 mg/m^3
			ivn	rat	LD50:	22 mg/kg
Nickel chloride	$NiCl_2$	129.61	ivn	dog	LDLO:	10 mg/kg
Nickel fluoborate	---	---	orl	rat	LDLO:	500 mg/kg
Nickel fluoride	NiF_2	96.71	ivn	mouse	LD50:	130 mg/kg
Nickel nitrate	$Ni(NO_3)_2$	210.80	orl	rat	LD50:	1,650 mg/kg
Nickel oxide	NiO	74.71	ims	rat	TDLO:	180 mg/kg
			ims	mouse	TDLO:	400 mg/kg
			ivn	dog	TDLO:	7 mg/kg
Nickel perchlorate	---	---	ipr	mouse	TDLO:	100 mg/kg
Nickel sulfamate	---	---	ipr	mouse	LDLO:	250 mg/kg
Nickel sulfate hexahydrate	$NiSO_4 \cdot 6H_2O$	262.89	scu	dog	LDLO:	500 mg/kg
Nickel subsulfide	Ni_3S_2	240.25	ims	rat	TDLO:	90 mg/kg
			ims	mouse	TDLO:	200 mg/kg

[a] ihl = inhalation; ims = intramuscular; ipr = intraperitoneal; ivn = intravenous; orl = oral; scu = subcutaneous.

[b] LC50 = lethal concentration (50% killed)
LD50 = lethal dose (50% killed)
LDLO = lowest published lethal dose
TDLO = lowest published toxic dose

intravenous administration is also known to produce gastroenteritis. In dogs, central nervous system effects including tremor, spasmodic movements and paralysis have been reported. A lethal oral dose of nickel salt for a dog contains approximately 500 mg/kg of nickel. The metal itself is tolerated at 1 to 3 g/kg by dogs.

Young rats tolerated dietary levels of 250, 500 or 1000 µg/g nickel as nickel carbonate, nickel soaps or raney nickel for eight weeks without effect on growth rate. Absorption and retention was greatest with the carbonate. Highest tissue concentrations were 140-360µg/g in bone; other tissues contained 10-50 µg/g.[21] A level of 250µg/g as nickel catalyst was without effect in a 16 month feeding.[22] For the first eight months, nickel tissue concentration increased; it then fell despite continued intake. Once nickel was withdrawn from the diet, it could not be detected after 20 days in feces or after 40 days in urine.[22]

Nickel acetate was judged to be inert at the 5 µg/g level in the diet of mice in terms of effects on growth, survival, and tumor incidence.[23,24]

No deleterious effects on growth, behavior, hemoglobin concentrations, red cell, or white cell counts were observed in monkeys (Macaca sinicus) fed nickel at 250, 500, or 1000 µg/g for 24 weeks.[21] Compounds included nickel catalyst, nickel soap and nickel carbonate. Analyses of nickel content of tissues or pathological findings were not reported.

Toxicity by the oral route was observed in male Holstein calves given nickel carbonate in their diet.[25] Animals fed nickel at 62.5 µg/g showed normal growth and weight gain. At 250 µg/g food intake and growth were slightly reduced; and at 1000 µg/g the reduction was marked. At the highest

concentration, the animals appeared smaller, but were not emaciated. When nickel was removed from diet of the animals fed 1000 µg/g, their weight gain was equal to that of the others. Of the organs examined, only the kidneys showed abnormalities. This was true in all groups, but pyelonephritis (inflammation of kidney and surroundings) was observed only at 1000 µg/g.

With chicks fed diets containing nickel sulfate or acetate, growth was significantly reduced between 300 and 700µg/g with further reduction at 900 to 1,300 µg/g.[26] Nitrogen balance was negative above 500µg/g. Paired feeding at 1,100 µg/g showed that growth was not affected, but the nitrogen balance remained negative in the animals receiving nickel.

Rabbits given nickel chloride, 500 µg/day for 5 months, exhibited depressed liver glycogen, elevated muscle glycogen, and prolonged hyperglycemia following galactose loading.[27]

Parenterally administered nickel is excreted mainly in the urine. Immediately following injection of nickel-63 in the rat the distribution of radiolabelled nickel depends directly on blood volume.[28] After 48 hours, however, all radioactivity disappears from whole blood and plasma. After 72 hours, the label is present only in the kidneys and by this time 61 percent has been excreted in the urine and 5.9 percent in the feces.

In studies on the kinetics of nickel-63 metabolism in rats and rabbits, Onkelinx et al.[39] determined that the radiolabelled metal was rapidly cleared from plasma or serum during the first 2 days following a single intravenous injection. Seventy-eight percent was excreted in the urine during the first day in rabbits. Three days were required for the urinary excretion of 78% of the administered dose in rats. Disappearance of the nickel-63 from the serum was at a much lower rate from day 3 to day 7. Measurements of nickel-63 distribution and excretion suggested that in both species nickel-63 is diluted within two compartments and eliminated by first order kinetics. This two compartment model was verified by its ability to predict nickel-63 concentrations in serum or plasma with continuous infusion or repeated daily injections.

Parenteral injection of nickelous chloride has been reported by Berenshteyen and Shifrina[30] to increase or decrease blood glucose depending upon dose. Clary and Vigniati[31] have observed immediate development of hyperglycemia following intraperitoneal injection of nickel chloride in rats at 10 to 80 mg/Kg. The hyperglycemia could be prevented by simultaneous administration of insulin.

9.2.1.3. Inhalation of Inorganic Nickel--Bingham et al.[32] have shown that exposure of rats to nickel oxide and nickel chloride by inhalation at a concentration of approximately 100 $\mu g/m^3$ for 12 hours daily and six days per week resulted in the following effects: After two weeks, inhalation of nickel oxide produced a marked increase in the number of alveolar macrophages in the lungs as compared to controls. Nickelous chloride did not produce such an effect but resulted in pathological respiratory changes after four to six weeks exposure. The bronchial epithelium was hyperplastic

with evidence of marked mucous secretion, and peribronchial infiltration was also seen. With longer exposure four to six weeks, to nickel oxide, the cellular infiltration seen earlier subsided, leaving thickened alveolar walls distributed throughout the lungs and occassionally in the bronchi. Macrophages were variable in size with a shift to smaller cell diameters. The experiments of Bingham et al.[32] were performed at approximately one tenth of the current Threshold Limit Value* for nickel which is 1,000 $\mu g/m^3$. A threshold Limit Value (TLV) represents an airborne concentration of a substance to which nearly all workers may be repeatedly exposed occupationally, day after day, without adverse effect. Although the changes observed may not be of pathologic significance or irreversible, they occur at such low levels as to suggest the need for additional investigation if the current TLV is to be considered valid.

Sanders et al.[33] using Syrian golden hamsters demonstrated that more nickel oxide particles were found free in alveolar lumens when pulmonary clearance was impaired by exposure to cigarette smoke. This effect might be expected to potentiate adverse responses to nickel oxide although none were described.

In another study with Syrian golden hamsters Wehner and Craig[34] demonstrated, in agreement with the ICRP Committee II Task Force on Lung Dynamics,[35] that nickel oxide displays moderate lung retention. Almost 20 percent of the inhaled nickel oxide remained after initial clearance and, of this, 45 percent was still present after 45 days. Nickel oxide concentrations ranged from 10,000 to 190,000/g/m^3. The compound was not acutely toxic at any level employed. However, prolonged lung retention increases the concern over the possibility of inducing chronic lung changes.

9.2.1.4 Toxicity of Nickel Complexes and Organic Nickel Compounds--Table 9.3 and 9.4 summarize toxicity studies that have been reported for nickel complexes and organic nickel compounds in experimental animals. In the studies by Nofre et al.,[37] Joesten and Hill,[38] and Haro et al.[39] the acute toxic effects of several nickel complexes were compared to related nickel salts. Depending upon the nature of the complex, toxicity was enhanced or reduced, usually in a predictable manner. For example, as shown in Table 9.3, the LD_{50} for nickel with disodium EDTA and for nickelocene was greater than that for nickel sulfate, nickel acetate, or nickel chloride. On the other hand, the LD_{50} for the complex of nickel perchlorate with the insecticide, octamethylpyrophosphoramide, was about one-seventh of that for nickel perchlorate.

By far, the greatest amount of toxicological information on pi-complexes of nickel is on nickel carbonyl. Table 9.4 summarizes toxicity studies of this compound in experimental animals. The first inhalation studies on this compound[45,46] demonstrated that it is approximately 100 times as toxic as carbon monoxide. Symptoms of exposure in experimental animals include difficult and rapid breathing, cyanosis, fever, apathy, aversion to food, vomiting, diarrhea, and occasionally hind limb paralysis. Generalized convulsions are frequently a terminal effect. The pathologic lesions that have been observed to develop in experimental animals following exposure to nickel carbonyl are summarized in Table 9.5. These studies indicate that the pulmonary parenchyma is the target tissue for nickel carbonyl regardless of the route of exposure. The time course of the pulmonary response following exposure to nickel carbonyl is

Toxicity Studies of Nickel Complexes in Experimental Animals[a]

Compound	Route of administration	Animal	LD_{50}	Investigator
Nickel chloride hexahydrate	Intraperitoneal	Mouse	48 mg/kg	Franz [36]
Nickel-disodium-EDTA[b]	Intraperitoneal	Mouse	600 mg/kg	Nofre *et al.* [37]
Nickel sulfate heptahydrate	Intraperitoneal	Mouse	38 mg/kg	
Nickel perchlorate-3OMPA[c]	Intraperitoneal	Mouse	15 mg/kg	Joesten and Hill [38]
Nickel perchlorate hexahydrate	Intraperitoneal	Mouse	100 mg/kg	
Nickelocene[d]	Intraperitoneal	Mouse	86 mg/kg	Haro *et al.* [39]
Nickel acetate	Intraperitoneal	Mouse	32 mg/kg	
Nickelocene	Intraperitoneal	Rat	50 mg/kg	
Nickel acetate	Intraperitoneal	Rat	23 mg/kg	
Nickelocene	Oral	Mouse	600 mg/kg	
Nickel acetate	Oral	Mouse	420 mg/kg	
Nickelocene	Oral	Rat	500 mg/kg	
Nickel acetate	Oral	Rat	350 mg/kg	
Ni-DBDTC[e]	Oral	Mouse	(MTD = 0.1 mg[f])	Innes *et al.* [40]

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[a]The data permit comparisons of the relative toxicities of nickel complexes and nickel salts.

[b]EDTA = ethylenediaminetetraacetate.

[c]OMPA = octamethylpyrophosphoramide.

[d]Nickel dicyclopentadiene.

[e]DBDTC = dibutyldithiocarbamate.

[f]MTD (maximal tolerated dose) = maximal oral dose resulting in zero mortality after 19 daily doses.

Table 9.4

TOXICITY STUDIES OF NICKEL CARBONYL IN EXPERIMENTAL ANIMALS

Route of administration	Animal	Lethal dose	Investigator
Subcutaneous	Rabbit	LD_{100} = 25 mg/kg	McKendrick and Snodgrass [41]
Intravenous	Rabbit	LD_{100} = 40 mg/kg	Hanriot and Richet [42]
	Dog	LD_{100} = 33 mg/kg	
Intravenous	Dog	LD_{100} = 33 mg/kg	Langlois [43]
Subcutaneous	Dog	LD_{100} = 50 mg/kg	Vahlen [44]
Inhalation	Rabbit	LD_{80} = 1.4 mg/liter for 50 min	Armit [45]
	Cat	LD_{80} = 3.0 mg/liter for 75 min	
	Dog	LD_{80} = 2.7 mg/liter for 75 min	
Inhalation	Mouse	LD_{80} = 0.17 mg/liter for 5 min	Garland [46]
Inhalation	Rat	LD_{80} = 0.9 mg/liter for 30 min	Barnes and Denz [47]
Inhalation	Mouse	LD_{50} = 0.067 mg/liter for 30 min	Kincaid *et al.* [48]
	Rat	LD_{50} = 0.24 mg/liter for 30 min	
	Cat	LD_{50} = 0.19 mg/liter for 30 min	
Inhalation	Mouse	LD_{100} = 0.2 mg/liter for 120 min	Sanotskii [49]
	Mouse	LD_{0} = 0.01 mg/liter for 120 min	
Inhalation	Rat	LD_{100} = 0.3 mg/liter for 20 min	Ghiringhelli [50]
	Rat	LD_{50} = 0.1 mg/l for 20 min	
Inhalation	Mouse	LD_{80} = 0.048 mg/liter for 30 min	West and Sunderman [51]
	Rat	LD_{65} = 0.50 mg/liter for 30 min	
Inhalation	Dog	LD_{90} = 2.5 mg/liter for 30 min	Sunderman *et al.* [52]
Inhalation	Rat	LD_{30} = 0.51 mg/liter for 30 min	Sunderman [53]
Intravenous	Rat	LD_{50} = 65 mg/kg	Hackett and Sunderman [54]
Subcutaneous	Rat	LD_{50} = 61 mg/kg	
Intraperitoneal	Rat	LD_{50} = 38 mg/kg	
Inhalation	Rat	LD_{50} = 0.58 mg/liter for 15 min	
Inhalation	Mouse	LD_{100} = 0.1 mg/liter for 120 min	Sanina [55]
		LD_{0} = 0.01 mg/liter for 120 min	

PATHOLOGICAL LESIONS FOLLOWING ACUTE EXPOSURE OF EXPERIMENTAL ANIMALS TO NICKEL CARBONYL

Route of administration	Animal	Dose	Observation period after exposure	Observations	Investigators
Inhalation	Rabbit	1.4 mg/liter for 50 min	1-5 days	Lungs: intra-alveolar hemorrhage, edema, and exudate and alveolar cell degeneration; adrenals: hemorrhages; brain: perivascular leukocytosis; and neuronal degeneration	Armit[45]
Inhalation	Rat	0.9 mg/liter for 30 min	2 hr-1 year	Lungs: at 2-12 hr, capillary congestion and interstitial edema; at 1-3 days, massive intra-alveolar edema; at 4-10 days, pulmonary consolidation and interstitial fibrosis	Barnes and Denz[47]
Inhalation	Rat	0.24 mg/liter for 30 min	0.2 hr-6 days	Lungs: at 1 hr, pulmonary congestion and edema; at 12 hr-6 days, interstitial pneumonitis with focal atelectasis and necrosis, and peribronchial congestion; liver, spleen, kidneys, and pancreas: parenchymal cellular degeneration with focal necrosis	Kincaid *et al.*[48]
Inhalation	Rat	1.0 mg/liter for 30 min	1-6 days		Sunderman *et al.*[52]
	Dog		1-7 days	Lungs: at 1-2 days, intra-alveolar edema and swelling of alveolar lining cells; at 3-5 days, inflammation, atelectasis, and interstitial fibroblastic proliferation; kidneys and adrenals: hyperemia and hemorrhage	

Table 9.5 continued

Route of administration	Animal	Dose	Observation period after exposure	Observations	Investigators
Intravenous	Rat	65 mg/kg	0.1 hr-21 days	Lungs: at 1-4 hr, perivascular edema; at 2-5 days, severe pneumonitis with intra-alveolar edema, hemorrhage, subpleural consolidation, hypertrophy and hyperplasia of alveolar lining cells, and focal adenomatous proliferation; at 8 days, interstitial fibroblastic proliferation; liver, kidneys, and adrenals: congestion, vacuolization, and edema	Hackett and Sunderman 54
Intravenous	Rat	65 mg/kg	0.5 hr-8 days	Lungs: ultrastructural alterations, including edema of endothelial cells at 6 hr and massive hypertrophy of membranous and granular pneumocytes at 2-6 days	Hackett and Sunderman 56
Intravenous	Rat	65 mg/kg	0.5 hr-6 days	Liver: ultrastructural alterations of hepatocytes including nucleolar distortions at 2-24 hr, dilatation of rough endoplasmic reticulum at 1-4 days, and cytoplasmic inclusion bodies at 4-6 days	Hackett and Sunderman 57

as follows:

- 1 hour - edema develops in the alveolar septal interstitium
- 1 day - polymorphonucleur leukocytes accumulate in the tissues around the bronchioles and alveolar septa and to a lesser extent in the alveolar spaces; abnormal multiplication of the bronchiolar epithelium and alveolar lining cells are observed
- 2 to 5 days - severe intra-alveolar edema with focal hemorrhage and changes in the alveolar epithelial cells
- 3 to 5 days - death usually occurs
- 6 to 10 days - in surviving animals alveolar epithelial cell alterations regress toward normal; however there are still some sites of abnormal cell multiplication within the alveola and in connective tissue
- 14 to 21 days - the functional elements of the lung are essentially normal except for interstitial fibrosis

Pathological findings in other organs after acute exposure of animals to nickel carbonyl are generally less severe. Focal hemorrhage, congestion, edema, mild inflammation, and vacuolization have been reported in brain, liver, kidneys, adrenals, spleen, and pancreas. Dilatation of rough endoplasmic reticulum is consistently observed in the hepatic parenchyma (functional parts of the liver). Nucleolar alterations also develop within hepatocytes between two to 24 hours after exposure to nickel carbonyl.

Table 9,5.

Radiotracer[58,59] and gas chromatographic studies[60] have demonstrated that nickel carbonyl can pass across the alveolar membrane in either direction without metabolic alteration. Nickel carbonyl that is inhaled or injected does not immediately decompose. In the rat approximately 36 percent of an injected dose of nickel carbonyl is excreted within 4 hours in the expired breath. Thus, the lung is a major excretory organ for nickel carbonyl. The remainder of the nickel carbonyl slowly decomposes within red cells and other tissues to liberate elemental nickel (Ni^0) and carbon monoxide. The carbon monoxide is bound to hemoglobin and is transported to the lungs for exhalation; within six hours following the injection of nickel carbonyl, approximately 49 percent of the nickel carbonyl moiety is expired as carbon monoxide and 1 percent as carbon dioxide. In the rat carbon monoxide saturation of hemoglobin peaks during the second hour, and thereafter decreases exponentially with a half-time of approximately 90 minutes, paralleling the exhalation rate of carbon monoxide. The nickel (Ni^0) that is released from nickel carbonyl is oxidized intracellularly to Ni^{2+} and is released for binding to blood serum components as previously described. Nickel is rapidly cleared from the serum and excreted by the kidneys. In the rat, an average of 23 percent of nickel, injected as nickel carbonyl, is excreted in the urine within 12 hours, and an average of 27 percent, within 24 hours. Only approximately 0.2 percent of injected nickel is excreted in the bile within 6 hours. By the end of 4 days, an average of 38 percent of injected nickel can be recovered in breath, 31 percent in urine, and 2 percent in feces. Within homogenates of lung and liver, small portions of the intracellular nickel

remain bound to DNA, RNA, and proteins. These apparent associations of nickel with nucleic acids and proteins may occur secondarily during the homogenization and extraction procedures.

It has been suggested by S. and coworkers[54,56,59] that lung lesions may result from damage produced during transit of nickel carbonyl across the alveolar epithelium rather than from the toxicity of the small amount of nickel that remains in the lungs after 24 hours. On this basis the optimal therapy for acute nickel carbonyl poisoning would theoretically be to minimize the pulmonary exhalation of nickel carbonyl and to mobilize nickel carbonyl and carbon monoxide by extracorporeal gas exchange. To date, this approach to therapy of nickel carbonyl poisoning has not been tested either in experimental animals or in man. There has, however, been considerable success in the therapeutic use of chelating drugs. Dimercaprol (BAL), thioctic acid, penicillamine, and sodium diethyldithiocarbamate (dithiocarb) have all been reported to be beneficial in acute nickel carbonyl poisoning in experimental animals. Sodium diethyldithiocarbamate is by far the most effective therapeutic agent on the basis of animal experiments.

Studies on the biochemical mechanisms of nickel carbonyl toxicity are summarized in Table 9.6.

Sunderman[68] suggested that the acute toxicity of nickel carbonyl may result, in part, from inhibition of ATP utilization. This suggestion was prompted by the following studies: Sanotskii[49] determined that the

STUDIES OF BIOCHEMICAL MECHANISMS OF NICKEL CARBONYL TOXICITY IN EXPERIMENTAL ANIMALS

Route of administration	Animal	Observations	
Inhalation	Mouse	Diminution of body oxygen consumption	Sanotskii 49
Inhalation and Intravenous	Rat	Inhibition of phenothiazine induction of benzopyrene hydroxylase in lungs and liver	Sunderman 61
Intravenous	Rat	Inhibition of cortisone induction of hepatic tryptophan pyrrolase	Sunderman 62
Intravenous	Rat	Inhibition of phenobarbital induction of hepatic cytochrome	Sunderman 63
Intravenous	Rat	Inhibition of RNA polymerase in hepatic nuclei	Sunderman and Esfahani 64
Intravenous	Rat	Inhibition of orotic acid incorporation into hepatic RNA	Beach and Sunderman 65
Intravenous	Rat	Inhibition of RNA synthesis by hepatic chromatin-RNA polymerase complex	Beach and Sunderman 66
Intravenous	Rat	Inhibition of phenobarbital induction of aminopyrine demethylase in lungs and liver	Sunderman and Leibman 67
Intravenous	Rat	Slight inhibition of leucine incorporation into hepatic microsomal proteins	Sunderman 68
Intravenous	Rat	Increased hepatic ATP concentration	Sunderman 69
Intravenous	Rat	Inhibition of RNA synthesis in liver, but not in lungs	Witschi

whole body consumption of oxygen in mice was immediately diminished following exposure to nickel carbonyl and remained diminished for 3 days. Sunderman[68] found that nickel carbonyl resulted in increased hepatic ATP concentrations in rats that were killed 30 minutes or 24 hours after injection. That divalent-nickel inhibition of hepatic ATPase activity may be involved is suggested by *in vitro* studies showing inhibition of ATPase activity in rat liver microsomes;[70] Divalent nickel in millimolar concentrations also inhibits ATPase activity of cilia of *Tetrahymena pyriformis*,[71] and ATPase activity of sheep alveolar macrophage cells *in vitro*[72] and brain capillaries *in vivo*[73,74]. Nickel has also been reported to reversibly inactivate ATP:creatine phosphotransferase *in vitro* at a concentration of 0.0005 molar. As previously mentioned, Sigel et al.[75] have shown that nickel reacts *in vitro* with ATP to form a stable binary complex. Such a stable nickel-ATP complex might reversibly inhibit ATP utilization by saturating the binding sites for ATP on ATPase and creatine phosphotransferase. This could result in acute toxicity as observed with nickel carbonyl.[68]

9.2.1.5. *Nickel Sensitization in Experimental Animals and Lymphocyte Cultures*--Several investigators have reported experimental sensitization to nickel using guinea pigs.[76,77,78] Several others have been unable to confirm these findings.[47,79] Sodium lauryl sulfate has been used with nickel sulfate solutions to sensitize experimental animals by repeated topical application.[76] However, this treatment may produce local irritation rather than allergic reactions.[79] No technique is available for consistent induction of delayed hypersensitivity in animals.

Several studies suggest that lymphocyte transformation in vitro may be a sensitive method for the detection of delayed human hypersensitivity.[80,81,82] Some investigators have questioned the specificity of the test;[82,83,84] however, more recent reports are favorable.

9.2.1.6 Nickel Carcinogenesis in Experimental Animals--Experimental systems that have been used to study nickel carcinogenesis in animals are listed in Table 9.7. Localized malignant sarcomas[86,87] are observed with parenteral administration of metallic nickel dust or pellets to rats, guinea pigs, and rabbits.[88,90] Nickel subsulfide (Ni_3S_2) injected intramuscularly into rats is a very potent inducer of rhabdomyosarcomas (malignant muscle tumors). Epidermoid carcinomas and adenocarcinomas are observed in the sinuses of cats after implantation of nickel sulfide disks. Pulmonary carcinomas in rats have been reported after inhalation of nickel dust,[91] or nickel carbonyl.[92] Carcinomas and sarcomas have been reported in diverse organs--including liver and kidney--of rats that received multiple intravenous injection of nickel carbonyl.[93] Carcinogenic synergism between some nickel compounds (NiO and Ni_3S_2) and polycyclic aromatic hydrocarbons (methylcholanthrene and benzo[a]pyrene).[94,95] Thus, nickel carcinogenesis has been demonstrated in several species of animals after administration by inhalation or other parenteral routes. However, there is no experimental evidence that nickel compounds are carcinogenic when administered orally or percutaneously.

As pointed out in the Report by the National Academy of Sciences,[5] the carcinogenicities of the nickel compounds in rats appear to be inversely correlated with their solubilities in aqueous media. In

Table 9.7. EXPERIMENTAL MODELS OF NICKEL CARCINOGENESIS[85]

Substances	Animals	Route of administration	Tumors
Nickel dust	Mice	Inhalation	Unspecified
Nickel dust	Rats and rabbits	Intravenous and intrapleural	Sarcomas
Nickel dust	Guinea pigs	Inhalation	Anaplastic and adenocarcinomas
Nickel carbonyl	Rats	Inhalation	Squamous cell carcinomas anaplastic carcinomas, and adenocarcinomas
Nickel pellets	Rats	Subcutaneous	Sarcomas
Ni_3S_2 and NiO dust	Rats and mice	Intramuscular	Sarcomas
NiO and methyl cholanthrene	Rats	Intratracheal	Squamous cell carcinomas
Nickel dust	Rats	Intramuscular	Sarcomas
Nickelocene	Rats	Intramuscular	Sarcomas
Ni_3S_2 disks	Cats	Sinus implants	Squamous cell carcinomas, adenocarcinomas & sarcomas
Ni_3S_2 and benzo[a]pyrene	Rats	Intramuscular	Sarcomas
Nickelocene	Hamster	Intramuscular	Sarcomas

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Table 9.7 (continued). EXPERIMENTAL MODELS OF NICKEL CARCINOGENESIS[85]

Substances	Animals	Route of administration	Tumors
Nickel carbonyl	Rats	Intravenous	Carcinomas and sarcomas
Nickel dust	Rats	Intrathoracic and intraperitoneal	Mesotheliomas
Ni_3S_2 and benzo[a]pyrene	Rats	Intratracheal	Squamous cell carcinomas
Ni_3S_2	Rats	Subcutaneous	Fibrosarcomas
Nickelocene	Fetal rats	Transplacental	Malignant neurinoma

general, the strong carcinogens, nickel subsulfide and nickel oxide are practically insoluble in aqueous media, while the noncarcinogens, nickel sulfate, nickel chloride, and nickel ammonium sulfate are very soluble. Exceptions to this rule include nickel sulfide which has low solubility and was not carcinogenic in one study, and nickel acetate which is relatively soluble and only moderately carcinogenic in three studies.

The possibility that induction of sarcomas in rats might constitute a nonspecific reaction to intramuscular injection of insoluble metallic dust was investigated by Sunderman et al.[96] using nickel subsulfide. Intramuscular injection of equimolar quantities of nickel subsulfide, manganese, chromium, copper, and aluminum dusts in Fisher rats resulted in development of sarcomas at the injection site in 23 of 24 rats that received nickel subsulfide. No such neoplasms were observed in similar groups of rats that received manganese, chromium, copper, and aluminum.

Particular attention has been focused on nickel carbonyl because of its extreme toxicity and its widespread use. Neoplasms have been induced in rats after administration of nickel carbonyl by inhalation and by parenteral injection. These pulmonary carcinomas closely resemble the lung cancers that develop in nickel workers. However, from an experimental point of view, the latent period for induction of lung neoplasms is long, 24 to 27 months, and the incidence of lung neoplasms is low--4 to 21 percent in 2 year survivors.[85]

Investigations of the induction of sarcomas in rats by intramuscular injections of nickel subsulfide, Ni_3S_2, are summarized in Table 9.8. In investigations on the carcinogenicity of various metallic constituents

Table 9.8. INDUCTION OF SARCOMAS IN RATS BY INTRAMUSCULAR INJECTIONS OF Ni_2S_2[96]

Form and dosage of Ni_2S_2	Strain of rat	Observations
Dust, 40 mg	Wistar	Sarcoma incidence, 89% (80% rhabdomyosarcomas, 20% fibrosarcomas; lung metastases, 76%
Dust, 20 mg Disks, 500 mg Chips, 500 mg	Fischer	No effect of physical form of Ni_3S_2 implant on sarcoma incidence (71-95%) or lung metastases (69-100%)
Dust, 20 mg	Fischer	Precancerous changes in muscle cells: nucleolar hypertrophy; mitoses; evolution of myoblasts
Dust, 10 mg	Fischer	Tumor susceptibility not sex-dependent; greatest at age of 2 months promoted by methandrostenolens
Disks, 250 mg	Fischer	Tumorigenesis prevented by excision of Ni_3S_2 disks within 6 days after implantation
Dust, 10 mg Disks, 250 mg	Fischer	Higher sarcoma incidence after intramuscular injection (80%) than after subcutaneous (44%) or intraperitoneal (24%) injection, inhibited muscle tumorigenesis
Dust, 20 mg	3 strains	Fischer and hooded rats more susceptible to Ni_3S_2 sarcomas than Bethesda black rats.
Dust, 10 mg	Fischer	Tumor-specific antibodies in serum from rats with Ni_3S_2 sarcomas
Dust, 20 mg	Sprague-Dawley	Sarcoma incidence, 37%; description of ultrastructure of rhabdomyosarcomas
Dust, 10 mg	Fischer	Arginase activity much higher in Ni_3S_2 rhabdomyosarcomas than in adult or embryonic muscle

Table 9.8 (continued). INDUCTION OF SARCOMAS IN RATS BY INTRAMUSCULAR INJECTION OF Ni_3S_2[96]

Form and dosage of Ni_3S_2	Strain of rat	Observations
Dust, 3.3 and 10 mg	Fischer	At 3.3 mg, mean survival time longer (42 wk) than at 10 mg (36 wk); sarcoma incidence not affected (97% and 85%)
Dust, 20 mg	Fischer	Sarcoma incidence, 100% (81% rhabdomyosarcomas, 19% fibrosarcomas); lung metastases, 57%; survival time, 33 $\pm$ 5 wk
Dust, 2.5 mg	Fischer	Sarcoma incidence, 96%; induction of sarcomas by Ni_3S_2 antagonized by simultaneous injection of manganese dust;
Dust, 20 mg	Fischer	Scanning electron microscopy demonstrated chromosomal abnormalities in a nickel sulfide-induced sarcoma

of refinery dust (Ni_3S_2, NiO, $NiSo_4 \cdot 6H_2O$, CoS, CoO, CuS, Cu_2S, CuO, FeS, FeO, and Fe_2O_3), Gilman[97] identified nickel subsulfide as the most carcinogenic component.

Table 9.9 summarizes several studies of the induction of sarcomas in rats by intramuscular or subcutaneous implantation of metallic nickel as pellets, dust, or sponge. Friedmann and Bird[98] have reported that rhabdomyosarcomas (malignant muscle tumors) induced by metallic nickel are indistinguishable from those induced by Ni_3S_2.

Heath et al. and Webb et al.[87,99] have investigated the subcellular distribution and binding of nickel in rhabdomyosarcomas induced by Ni dust. They found that 70-90 percent of the nickel content of rhabdomyosarcoma cells is intranuclear, bound to DNA and RNA.[87] Webb and associates have shown that at least 50 percent of the nickel within rhabdomyosarcoma cell nuclei is in the nucleolar fraction.[99] The intranucleolar localization of nickel may have implications in the induction of rhabdomyosarcomas. It should be noted that Kasprzak and Marchow[100] recently published a comprehensive review of the literature on experimental carcinogenesis with nickel sulfide.

9.2.1.7 Possible Mechanisms of Nickel Carcinogenesis--The mechanisms whereby nickel enters target cells is undoubtedly important in the etiology of nickel carcinogenesis. It appears likely that at least two transmembrane mechanisms are operative; one involving penetration of the intact compound and the other involving transport of a soluble complex species. Because of its lipid solubility, nickel carbonyl is able to pass across cell membranes without metabolic alteration.[59,60,101] This ability is presumed to be responsible for the extreme toxicity of the

Table 9.9

INDUCTION OF SARCOMAS IN RATS BY INTRAMUSCULAR OR SUBCUTANEOUS INJECTION OF METALLIC NICKEL[85]

Form and dosage of nickel	Strain of rats	Observations
4 pellets (2 x 2 mm) subcutaneously	Wistar	Fibrosarcoma incidence, 50%
dust (28 mg) intramuscularly	Hooded	Rhabdomyosarcoma incidence, 100% lymph node metastases, 30%
dust (28 mg) intramuscularly	Hooded	Nickel bound to DNA and RNA in rhabdomyosarcoma nuclei
sponge (20 mg) intramuscularly	Sprague-Dawley	Rhabdomyosarcoma incidence, 24%
powder (5 mg) intramuscularly 6 times at 4-wk intervals	Fischer	Sarcoma incidence, 76%; latent period 6-12 months
dust (28mg) intramuscularly	Hooded	Intranuclear nickel in rhabdomyosarcoma cells is 53% in nucleolar fraction
dust (5 mg) intramuscularly 5 times at 4-wk intervals	Fischer	Sarcoma incidence, 50-75%

compound. Nickel carbonyl also decomposes extracellularly to liberate Ni, which can be taken up and oxidized to Ni^{2+} intracellularly.[60,101] It appears that nickelocene is also able to penetrate cellular membranes without decomposition and then exert its toxic effects.[102] Following intramuscular injection of insoluble inorganic carcinogens, such as nickel dust and nickel sulfide, these compounds are presumed to be deposited extracellularly and to dissolve slowly in the extracellular fluid. The study of Singh and Gilman[103] suggests that a diffusible intermediate complex is involved in the intracellular transport of nickel subsulfide. In studies with nickel dust, Heath et al.[104] suggested that metal-serum protein complexes, adsorbed at the surface of the myoblast, may enter the cells by endocytosis and that later hydrolysis of the carrier proteins by lysosomal proteinases might lead to intracellular release and redistribution of the electrophilic metal ion. In 1972, Webb et al.[105,106] suggested an alternative hypothesis that complexes of nickel with small molecules play key roles as intermediates in the intracellular transport of nickel. They found that nickel dust incubated with rat muscle homogenates slowly dissolves and becomes complexed almost entirely (90 percent) with ultrafiltrable molecules.[107] The ultrafiltrable nickel complexes obtained <u>in vitro</u> were similar to those formed when nickel implants slowly dissolved in muscle <u>in vivo</u>.[107] Weinzierl and Webb[108] speculated that myoblasts involved in repair of muscle injury may take up the diffusible nickel complexes and undergo neoplastic transformation. The uptake of diffusible nickel-63 complexes was subsequently demonstrated using mouse dermal fibroblasts in tissue culture.[109]

Once entrance to the cell is gained, the intracellular biochemical effects of the Ni^{2+} ions become an important aspect of nickel carcinogenesis. The biochemical alterations that develop in rats after administration of nickel carbonyl have been investigated by Sunderman et al.[62,66] Nickel carbonyl was found to inhibit the induction of several enzymes in lung and liver.[62,63,67,110] Nickel carbonyl did not affect substrate (tryptophan) induction of hepatic tryptophan pyrrolase, but did impair hormonal (cortisone) induction of tryptophan pyrrolase. This suggested that nickel carbonyl may produce a metabolic block at the level of messenger RNA.[62] Nickel carbonyl also inhibited phenothiazine induction of benzopyrene hydroxylase[110] and phenobarbital induction of cytochrome P_{450} and aminopyrine demethylase in liver. It was subsequently determined that 24 hours after injection of an LD_{50} of nickel carbonyl, there was 60 percent inhibition of DNA-dependent RNA-polymerase activity in hepatic nuclei[64] and 75 percent inhibition of RNA synthesis, as measured by incorporation of carbon-14 labelled orotic acid into RNA.[65] Under the same conditions, nickel carbonyl produced only 8 percent reduction of hepatic protein synthesis, as measured by incorporation of carbon-14 labelled leucine into microsomal proteins.[111] Using a chromatin-RNA polymerase complex that was prepared from hepatic nuclei from rats exposed to nickel carbonyl, Beach and Sunderman[66] demonstrated that inhibition of RNA synthesis persists after disruption of the nuclei. Inhibition resulting from impaired transport of RNA precursors across the nuclear membrane was thus excluded. Witschin[69] independently confirmed the inhibitory effect of nickel carbonyl on hepatic RNA synthesis.

The intracellular distribution of nickel in nickel-induced rhabdomyosarcomas has been studied by Webb et al.[105] who found that a major portion (70-90 percent) of the nickel is within the nucleus. Subfractionization indicated that an average of 53 percent (range, 41-63 percent) of nuclear nickel was contained in the nucleolar fraction, the remainder distributed equally between the nuclear sap and the chromatin fractions.[105] Similar observations were made by Webb and Weinzierl[106] in mouse dermal fibroblasts grown in vitro in the presence of nickel-63 complexes. These observations may relate to the findings of Beach and Sunderman[66] that nickel is bound to an RNA polymerase-chromatin complex which can be isolated from hepatocyte nuclei of rats treated with nickel carbonyl.

Treagan and Furst[112] have demonstrated that addition of nickel chloride to tissue cultures of mouse L-929 cells inhibits their capacity to synthesize interferon and antiviral protein following inoculation with Newcastle disease virus. This finding may have significance with regard to viral-induced neoplastic transformation. Basrur and Gilman[113] and Weierenga and Basrur[114] have shown that nickel sulfide inhibits mitotic activity and induces abnormal mitotic figures in embryonic muscle cells. Their findings suggest that nickel may alter gene replication and the control of cell division. Although there has been considerable speculation,[115-118] the exact mechanisms whereby nickel compounds exert their carcinogenic actions are incompletely understood.

9.2.1.8 Nickel Devices and Prostheses

It has generally been assumed that nickel in stainless steels is biologically inert. However, Ferguson and co-workers[119] have reported

that intramuscular implantation of cylinders of stainless steel (Incoloy--stainless steel #316--and stainless steel #A-286) in rabbits resulted in increased nickel concentrations in parenchymal tissues. There is a paucity of evidence concerning the possible carcinogenicity of implanted nickel alloys in experimental animals. Mitchell et al.[90] found that pellets of nickel-gallium dental filling material (60 percent nickel and 40 percent gallium) implanted subdermally in Wistar rats produced local sarcomas in nine of 10 rats. Local sarcomas developed in five of 10 rats that received implants of pure nickel. No sarcomas developed in any of 10 other experimental groups of 10 rats each, which received implants of other dental materials.

9.2.1.9 Interrelations of Nickel with Polycyclic Aromatic Hydrocarbons

Evidence of carcinogenic synergism between nickel compounds and polycyclic aromatic hydrocarbons has been derived from carcinogenesis studies in animals[94,95] and biochemical studies of the effects of nickel compounds on the metabolism of benzo[a]pyrene.[61,120,121] In a study by Toda,[94] five of 30 rats that received intratracheal injections of nickel oxide in combiantion with 20-methylcholanthrene developed pulmonary neoplasms (squamous cell carcinomas).

Maenza et al.[95] reported that the latent period between administration of carcinogen and development of sarcomas was significantly shorter, by 30 percent, in rats that received intramuscular injections of nickel sulfide and benzo[a]pyrene than in rats that received only one of the two. Reduction of the latent period was not achieved by increasing the dosage of nickel sulfide or benzo[a]pyrene administered singly. Sunderman[61]

demonstrated that exposure of rats to nickel carbonyl by inhalation or intravenous injection inhibited the induction of benzopyrene hydroxylase activity in lung and liver. Sunderman[61] and Dixon et al.[120] suggested that nickel might promote carcinogenesis by inhibiting benzopyrene hydroxylation, thus prolonging tissue retention of benzo[a]pyrene. Subsequently, Sunderman and Roszel[121] demonstrated that exposure to nickel carbonyl inhibited the mobilization of benzo[a]pyrene from lung and liver for 48 hours. Furthermore, Kasprzak et al.[122] observed that the incidence of premalignant pathological reactions in the lungs of rats that received an intratracheal injection of nickel subsulfide and benzo[a]pyrene was significantly greater than in the lungs of rats that received only one of the two compounds.

9.2.1.10 Possible Interrelations of Nickel with Parasites

Kasprzak et al.[123] have studied the effect of Trichinella spiralis infection on the induction of sarcomas in rats after intramuscular injection of nickel sulfide. Administration of T. spiralis larvae in rats five days before the injection of nickel sulfide significantly increased the incidence of rhabdomyosarcomas.

9.2.1.11 Nickel in the Reproductive Process

The results of Phatak and Patwardhan[124] suggest that litter size was reduced in rats fed nickel at 1000 μg/g in the diet. Hoey[125] studied the acute and chronic effects of nickel sulfate given subcutaneously at 0.04 millimole/kg on testicular development. Shrinkage of central tubules, hyperemia of intertubular capillaries, and disintegration of spermatazoa were observed 18 hours after a single dose. Multiple doses extended the acute effects but all changes proved to be nearly

completely reversible. Inhibition of spermatogenesis has also been reported after oral administration of daily doses of nickel sulfate at 25 mg/kg.[126] After 120 days of dosing, the male rats were apparently infertile, since no pregnancies resulted when the males were caged with females in estrus.

Soluble nickel fats given in drinking water also produced adverse effects on reproduction in rats.[127] Nickel administered at 5 mg/liter continuously over three generations resulted in a reduction in the average litter size with each succeeding generation and increased mortality of offspring as compared to controls. The number of runts was increased in each succeeding generation and fewer males than normal were born by the third generation.

9.3 VEGETATION

Nickel has not been demonstrated to be essential for proper growth and development of plants, therefore, the problems associated with plant growth are due to an overabundance and not a lack of nickel.

Dwarfing or growth repression are the first symptoms of nickel toxicity. In time, a chlorosis develops similar to the symptoms associated with iron deficiency. In cereals, the chlorosis appears as white or light yellow and green striping. In dicotyledonous plants, a mottling of the leaf occurs.[128] If toxicity is severe, chlorosis is followed by death of the plants.

The concentrations of nickel in soil reported as being toxic to plants range from 0.5 μg/g for buckwheat and 2 μg/g for beans, barley, and oats.[128] The concentration of nickel in the soil is not as important as its availability to the plant. The available or exchangeable nickel content in toxic soils was found to range from 3 μg/g upward.[128] The high nickel (4000 μg/g maximum) and chromium content of serpentine soils of southern Rhodesia causes the soil to be highly infertile. The nickel content of indigenous grasses is closely correlated with the amount of exchangeable nickel in the soil. Oats grown on a soil with 70 μg/g of exchangeable nickel developed transverse white banding due to chlorosis while lucerne exhibited intense yellow chlorosis within two days of emergence and died within forty.[129] The pH of the soil plays an important part in the availability of nickel to plants. The nickel-calcium ration has been shown to be important in plant assimilation of nickel. Higher levels of calcium tend to reduce the uptake of nickel.[130]

It has been shown however, that the application of lime does not eliminate nickel uptake or the occurrence of nickel toxicity symptoms in oats where available nickel is present in very high concentraitons. Calcium carbonate was added to soil with 70 μg/g exchangeable nickel increasing the pH from 5.9 to 8.2. This reduced the nickel content of dried oat leaves and stems from 233 to 84 μg/g, but did not eliminate the toxic effects.[129]

Experimentally, nickel (II) ions have inhibited degradative changes associated with senescence and injury in plants. The breakdown of chlorophyll, protein, and RNA was inhibited by the treatment of detached rice (oryza sativa) leaves with nickel (II).[131] If degradative processes in plants are changed, littler breakdown and humus formation from plant material could be significantly reduced.

9.4 MICROORGANISMS

The accumulation of heavy metals in litter and humus could influence the rate of decomposition as most bacteria are sensitive to them.[132] Nickel has been shown to be quite toxic to microorganisms in general.[133,134] Nickel (II) inhibits fermentation in yeast cells[131] and also is effective in the control of fungal infection of grain commonly known as rusts (Puccinia spp.).[135,136] In addition, nickel (II) causes a narcotic effect in ciliated protozoans resulting from the reduced availability of ATP.[131]

The inhibition of microbial activity in litter as well as in soil through the addition of sewage sludge or other substances containing high concentrations of nickel and other metals could influence litter degradation and plant uptake of minerals as well as biogeochemical cycling. This problem has not been sufficiently illucidated.

9.5 MATERIALS

Nickel and nickel compounds and cations have no damaging effects on materials.

9.5.1 Laboratory

No documented materials effects studies have been reported.

9.5.2 Field

No documented materials effects studies have been reported.

9.6 WEATHER, VISIBILITY, AND CLIMATE

No information could be found on the effect of nickel on weather, visibility, and climate. Apparently, the relatively small amounts of this element that occur in the atmosphere have been of no particular concern to meteorologists. Nickel is released into the atmosphere from both natural and man-made sources. It is in dust particles picked up from the surface of the earth by the wind, and it is a minor constituent of the meteor dust that is continuously raining down on the earth. Wood contains nickel so forest fires are thought to be a significant source. It is conceivable that nickel associated with particulates could affect the formation of precipitation or perform a catalytic function in chemical transformations of other air pollutants, however, its effects are expected to be far outweighed either by more active elements or by elements present in much larger amounts. Therefore, natural sources of airborne nickel do not appear to have any undesirable effect on weather, visibility, and climate.

Man-made sources can produce significant concentrations of nickel in the atmosphere. The burning of coal is responsible for much of the nickel in the atmosphere in urban areas. Other sources are the smoke from burning wood and leaves, cement dust, and the dusts and mists from manufacturing.

9.7 LAND RESOURCES

The toxicity of nickel in soil to plants is well known. Insufficient information is available to indicate that nickel in soils results in other undesirable effects. However, trace elements applied to soils might find their way into surface and subsurface water, and thereby impair water quality.[138]

Any factor that affects the availability of the toxic elements in the soil also effects the plant accumulation. Although our knowledge of pH effects on metal accumulation is insufficient, cadmium, manganese, and zinc are easily translocated to plant tops in acid soils, whereas copper, lead, mercury, and nickel are translocated in appreciable quantities only during severe injury to the plants.

The presence of competing ions also affects the accumulation of toxic metals in plants. Phosphate availability is an important competing ion and excessive phosphate is known to injure some plants. In contrast, however, it appears to decrease the stunting injury from toxic levels of copper, nickel, and zinc. Information is insufficient on the effects of the excess phosphate added with sludge and effluent on the toxicity and accumulation of nickel and other toxic metals. Total management of the soils and the application of the sludges containing the nickel and other heavy metals is important to control the toxic effects of the added metals. Chaney[132,133] suggested recommended sludges and the amounts that could be added to soils.

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10. CONTROL TECHNOLOGY AND REMEDIAL ACTIONS

10.1 STATIONARY SOURCES

10.1.1 Air

Control of nickel emissions from stationary sources is largely dependent upon the degree of particulate control attainable. The gaseous nickelcarbonylemitted in some processes is highly toxic but easily controlled by thermal decomposition above 60°C. Therefore, the emission of nickel to the atmosphere can be controlled with adequate particulate control devices. The ore processing emissions can be controlled with present technology such as fabric filters. The clean-up of metallurgical fumes is a much tougher problem because the preponderance of material is less than 5 μm in diameter with up to 80 percent less than 1 μm.[1] Electrostatic precipitators have been applied with good overall mass efficiency but data has confirmed theoretical predictions that a drop is noted in collection of 0.5 μm to 1.0 μm particles (Figure 1) which exist in such large numbers in metallurgical processes. Baghouses have been successfully applied to such processes but extensive cooling is required before the gases can be handled. Though scrubbers are generally considered to lose significant collection capability below 1 μm, a recently developed high energy scrubber has been extremely successful in controlling metal fume from blast furnaces (Figure 2) and electric furnace steel production. This unit needs large amounts of waste heat to be economically feasible, but most metallurgical processes have such supplies of untrapped energy.

Some methods have been explored to remove metals from the oil during refining and this offers the major hope of reducing nickel

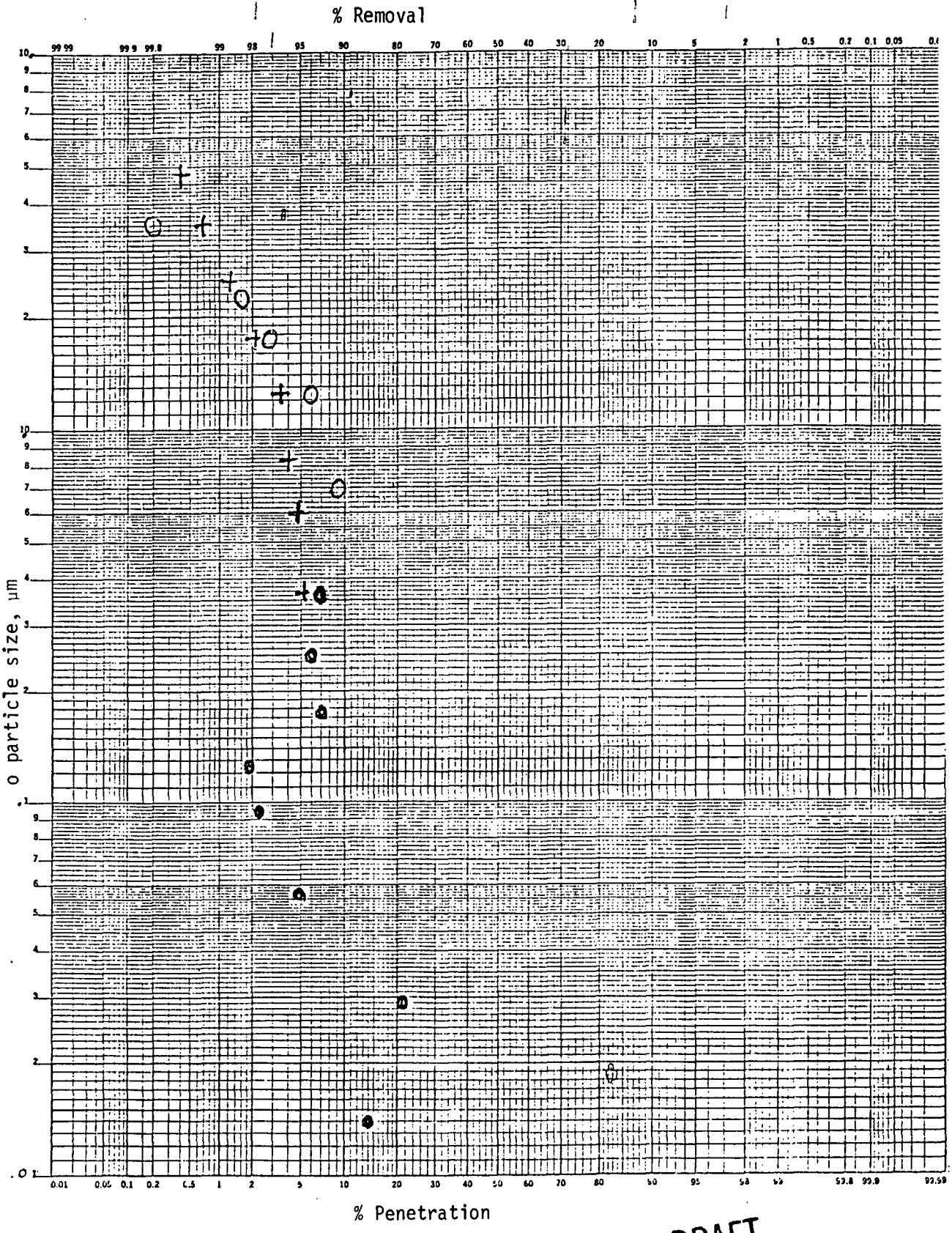

Figure 1. Efficiency of Electrostatic Precipitator on a Coal Fired Power Boiler

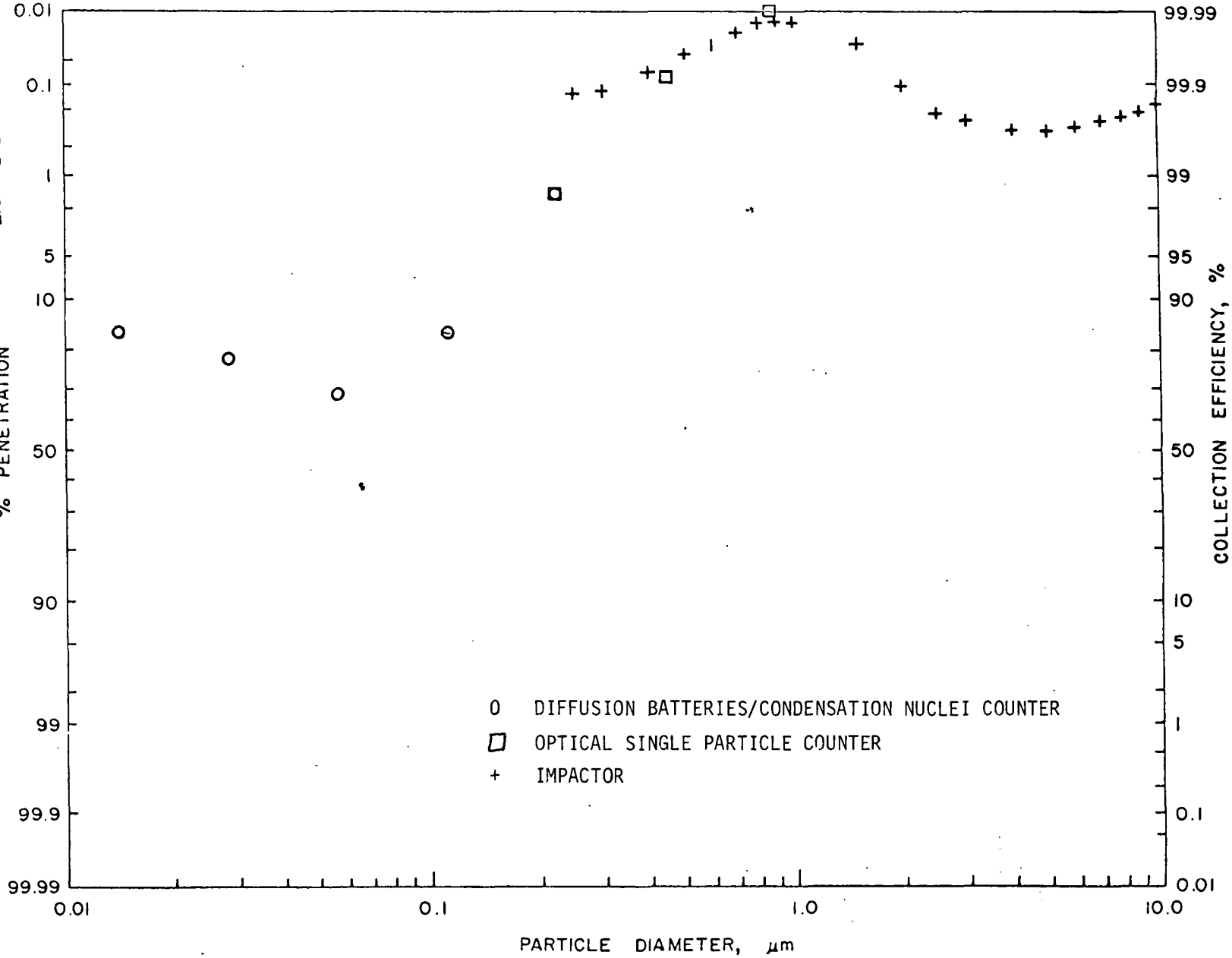

Figure 2. Fractional Efficiency of the Lone Star Steel Steam-Hydro Scrubber.

emissions from residential combustion.

Reductions of nickel emissions are dependent upon the control of the particulate emission at the specific source. Mining, metallurgical, and product sources can probably be highly controlled with proper installation of control devices. Control of combustion sources is less optimistic due to the size of the nickel containing particulate and the anticipated degree of control needed to meet emission standards based on total particulate.

10.1.2 Solid Waste

Land disposal has been, historically, the predominant method of removing solid waste from view, but it is not necessarily the best disposal method from an environmental standpoint. A landfill does represent a potential stationary source of nickel contamination, especially if industrial liquid and sludge wastes are incorporated into the site.

Detailed planning and the application of sound engineering, geological, hydrological, meterological, chemical, and biological techniques to all stages of planning, design, construction, operation and final site utilization have helped reduce the number and magnitude of many of the environmental impacts of land disposal procedures. Control technology involves all of the aforementioned; specifically, however, proper site selection, liners, tertiary treatment of liquids, and encapsulation procedures represent modern procedures to prevent contamination.

Recently, some states have initiated regulations that landfills must have some kind of impermeable membrane at the bottom of the fill. In addition, a few require that some system of leachate collection be installed for treatment. The liners include several feet of clayey soils, organic polymer material, or several lifts of asphalt several inches thick. This is an added economic burden the landfill operator must assume, but it is small when considering the potential ground water intrusion from leachate contaminated with toxic materials.

Presently, the EPA is investigating the process of encapsulating hazardous materials prior to placement in landfills. This is still in the experimental laboratory phase but preliminary results hold forth hope that this may be a viable process. Another control procedure for protecting against toxic materials transport in a landfill is tertiary treatment followed by sludge concentration and isolation. This allows for the handling of smaller volumes of material so that sound isolation procedures may be utilized, perhaps encapsulation in the future.

The prime factor involved in all solid waste control technology still remains proper site selection. Without this even the best operated landfills may eventually fail due to circumstances beyond the control of the operator. Some considerations are: local springs fed from underground supplies, fissures in the limestone area, depth of ground water supply, and local terrain.

When considering landfilling solid waste, it is advisable to consider it a potential stationary source of many pollutants, and institute proper preventative measures.

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