criteria for a recommended standard....

OCCUPATIONAL EXPOSURE
TO
INORGANIC NICKEL

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Public Health Service

Center for Disease Control

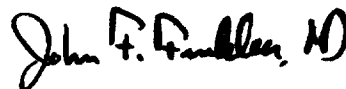National Institute for Occupational Safety and Health

May 1977

PREFACE

The Occupational Safety and Health Act of 1970 emphasizes the need for standards to protect the health and safety of workers exposed to an ever-increasing number of potential hazards at their workplace. The National Institute for Occupational Safety and Health has projected a formal system of research, with priorities determined on the basis of specified indices, to provide relevant data from which valid criteria for effective standards can be derived. Recommended standards for occupational exposure, which are the result of this work, are based on the health effects of exposure. The Secretary of Labor will weigh these recommendations along with other considerations such as feasibility and means of implementation in developing regulatory standards.

It is intended to present successive reports as research and epidemiologic studies are completed and as sampling and analytical methods are developed. Criteria and standards will be reviewed periodically to ensure continuing protection of the worker.

I am pleased to acknowledge the contributions to this report on inorganic nickel by members of the NIOSH staff and the valuable constructive comments by the Review Consultants on Inorganic Nickel, by the ad hoc committee of the American Occupational Medicine Association, and by

Robert B. O'Connor, M.D., NIOSH consultant in occupational medicine. The NIOSH recommendations for standards are not necessarily a consensus of all the consultants and the professional society that reviewed this criteria document on inorganic nickel. A list of Review Consultants appears on page vi.

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The Division of Criteria Documentation and Standards Development, National Institute for Occupational Safety and Health, had primary responsibility for development of the criteria and the recommended standard for inorganic nickel. The division review staff for this document consisted of Keith H. Jacobson, Ph.D. (Chairman), Frank L. Mitchell, D.O., and Richard A. Rhoden, Ph.D., with Harry M. Donaldson (Division of Surveillance, Hazard Evaluations, and Field Studies) and Eula Bingham, Ph.D. Stanford Research Institute (SRI) developed the basic information for consideration by NIOSH staff and consultants under contract No. CDC-99-74-31. Imogene F. Sevin, Ph.D., served as criteria manager.

The views expressed and conclusions reached in this document, together with the recommendations for a standard, are those of NIOSH, after review of the evidence and consideration of the comments of reviewers; these views and conclusions are not necessarily those of the consultants, other federal agencies, and professional societies, or of the contractor.

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·CRITERIA DOCUMENT:
RECOMMENDATIONS FOR AN OCCUPATIONAL
EXPOSURE STANDARD FOR INORGANIC NICKEL

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I. RECOMMENDATIONS FOR AN INORGANIC NICKEL STANDARD

The National Institute for Occupational Safety and Health (NIOSH) recommends that employee exposure to inorganic nickel in the workplace be contolled by adherence to the following sections. The standard is designed to protect the health and provide for the safety of employees for up to a 10-hour work shift, 40-hour workweek, over a working lifetime. Compliance with all sections of the standard should, at the minimum, substantially reduce the risk of nickel-induced cancer and dermatitis and prevent other adverse effects of exposure to nickel in the workplace. The employer should regard the recommended workplace environmental limit as the upper boundary for exposure and make every effort to keep the exposure as low as possible. The criteria and standard will be subject to review and revision as necessary.

Even though the available evidence indicates an association between human exposure to inorganic nickel and the development of cancer, the mixed exposures, both to different nickel compounds and to other elements, frequently occurring in the workplace have prevented complete differentiation of the effects of individual compounds. Should sufficient information become available to indicate that the standard offers greater or lesser protection from some nickel compounds than is needed, it will be considered for revision.

"Nickel" is defined in this standard as elemental nickel and all nickel compounds except organonickel compounds with a covalent carbon-nickel bond, such as nickel carbonyl. "Occupational exposure to nickel" is defined as working with compounds, solutions, or metals containing nickel

that can become airborne or can spill or splash on the skin or in the eyes. Occupational exposure to nickel does not include the handling of solid products, such as stainless-steel tools, provided no particle-generating operations, such as grinding or cutting, occur. The recommended method of sampling and analysis does not differentiate between individual nickel particles; thus, the standard applies to all particulate nickel. Where no occupational exposure to nickel occurs, but nickel is present in the workplace, adherence is required only to Section 8(a).

Section 1 - Environmental (Workplace Air)

(a) Concentration

Occupational exposure to nickel shall be controlled so that no employee is exposed to nickel at a concentration greater than 15 micrograms, measured as nickel, per cubic meter of air (15 μg Ni/cu m), determined as a time-weighted average (TWA) concentration for up to a 10-hour work shift, 40-hour workweek.

(b) Sampling and Analytical Methods

The TWA concentration limit represents the lowest reliably detectable concentration of nickel measurable by the recommended sampling and analytical methods selected. Procedures for the collection and analysis of environmental samples shall be as provided in Appendices I and II, or by any methods at least equivalent in accuracy, precision, and sensitivity to the methods specified.

Section 2 - Medical

Medical surveillance shall be provided, as outlined below, to all employees occupationally exposed to nickel.

(a)   Preplacement or initial medical examinations for workers shall include:

(1)   Comprehensive medical and work histories with special emphasis on skin conditions or allergies, illnesses or sensitizations of the upper and lower respiratory systems, and smoking history.

(2)   A complete physical examination giving particular attention to examination of the upper respiratory tract membranes for evidence of irritation, bleeding, ulcerations, or perforations, and examination of the skin for evidence of dermatitis or irritation.

(3)   Specific clinical tests, such as a 14" x 17" postero-anterior chest X-ray film and pulmonary function tests including the forced vital capacity (FVC) and forced expiratory volume during the first second (FEV 1). In addition, more specific tests, such as sputum cytology, should be considered by the responsible physician after having evaluated their availability and applicability to the situation. Measurements of concentrations of nickel and protein in urine and administration of a questionnaire to assess symptoms of chronic respiratory disease are also suggested.

(4)   A judgment of the employee's ability to use positive or negative pressure respirators.

(b)   Initial medical examinations shall be made available to all workers within 6 months after promulgation of a standard based on these recommendations.

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(c)   Periodic   examinations   shall   be   made   available   at   least annually. These examinations shall include:

(1)   Interim medical and work histories.

(2)   Physical   examination   as outlined in paragraphs (a)(2) and (a)(3) of this section.

(d)   Employees   or   prospective   employees with medical conditions, eg, dermatitis, which may be directly or indirectly aggravated by exposure to nickel shall be further counseled on the increased risk of impairment of their health from working with this substance.

(e)   Appropriate   medical   services   shall be made available to any employee with adverse health effects from nickel in the workplace.

(f)   In the event of wound contamination by nickel, the wound shall be promptly and thoroughly washed.

(g)   Pertinent   medical   records   shall   be   maintained   for   all employees exposed to nickel in the workplace.   Such records shall be retained for at least 40 years after the last occupational exposure to nickel. These records shall be made available to the designated medical representatives of the Secretary of Health, Education, and Welfare, of the Secretary of Labor, of the employer, and of the employee or former employee.

Section 3 - Labeling and Posting

A label shall be placed on each shipping and storage container of nickel in liquid, powder, or crystalline form, and all areas where there is occupational exposure to nickel shall be posted.

All labels and warning signs shall be printed both in English and in

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the predominant language of non-English-reading workers. Illiterate workers and workers reading languages other than those used on labels and posted signs shall receive information regarding hazardous areas and shall be informed of the instructions printed on labels and signs.

(a)   Labeling

Each container of nickel in liquid, powder, or crystalline form shall carry in a readily visible location a label stating:

NAME OF COMPOUND

(Trademark, Common Name, or Chemical Name)

DANGER! CONTAINS NICKEL
INHALATION IS HAZARDOUS AND MAY CAUSE NASAL OR LUNG CANCER
SKIN CONTACT MAY CAUSE IRRITATION OR RASH

Keep container closed.
Avoid breathing dust, fume, or mist.
Use only with adequate ventilation.
Do not get in eyes, in open wounds, or on skin or clothing.

First Aid: In case of skin or eye contact or contact with an open wound, flush promptly with running water.

(b)   Posting

Warning placards shall be affixed in readily visible locations in or near areas where there is occupational exposure to nickel. The information shall be arranged as in the following example.

NICKEL

DANGER!
INHALATION CAN BE HARMFUL AND MAY CAUSE NASAL OR LUNG CANCER
SKIN CONTACT MAY CAUSE IRRITATION OR RASH

AUTHORIZED PERSONNEL ONLY

Do not get in eyes, in open wounds, or on skin or clothing.

First Aid: In case of skin or eye contact or contact with an
open wound, flush promptly with running water.

If respiratory protection is required in accordance with Section 4,
the following statement in large letters shall be added to the required
sign:

RESPIRATORY PROTECTION REQUIRED IN THIS AREA

Section 4 - Personal Protective Clothing and Equipment

 (a) Protective Clothing

  (1) The employer shall provide safety goggles or face
shields (8-inch minimum) with goggles and shall ensure that employees wear
the protective equipment during any operation in which nickel may enter the
eyes.

  (2) The employer shall provide appropriate protective
clothing, such as gloves, aprons, suits, hats, or face shields, for
employees, such as platers, who are likely to have appreciable skin contact
with nickel, and for those who are especially sensitive to nickel.

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(b)   Respiratory Protection

(1)   Engineering controls shall be used when needed to keep concentrations of airborne nickel at or below the recommended TWA concentration limit. Respiratory protective equipment may be used in the following circumstances:

(A)   During the time necessary to install or test the required engineering controls.

(B)   For operations such as nonroutine maintenance and repair activities in which brief exposure at concentrations in excess of the TWA concentration limit may occur.

(C)   During emergencies when concentrations of airborne nickel might exceed the TWA concentration limit.

(2)   When a respirator is permitted by paragraph (b)(1) of this section, it shall be selected and used in accordance with the following requirements:

(A)   The employer shall establish and enforce a respiratory protective program. The requirements for such a program are listed in 29 CFR 1910.134.

(B)   The employer shall provide respirators in accordance with Table I-1 and shall ensure that employees use the respirators in a proper manner when the concentration of airborne nickel exceeds the recommended TWA concentration limit. The respirators shall be those approved by NIOSH or the Mining Enforcement and Safety Administration. The standard for approval is specified in 30 CFR 11. The employer shall ensure that respirators are properly cleaned, maintained, and stored when not in use.

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TABLE I-1

RESPIRATOR SELECTION GUIDE

Concentration of Nickel	Respirator Type Approved under Provisions of 30 CFR 11
Greater than 15 µg/cu m or Emergency (entry into area of unknown concentration for emergency purposes)	(1) Self-contained breathing apparatus with full facepiece operated in pressure-demand or other positive pressure mode (2) Combination Type C supplied-air respirator with full facepiece operated in pressure-demand mode and auxiliary self-contained air supply

(C)   Escape equipment shall be located at clearly identified stations within the work area and shall be adequate to permit all employees to escape safely from the area.   Protective equipment suitable for emergency entry shall be located at clearly identified stations outside the work area.

Section 5 - Informing Employees of Hazards from Nickel

(a)   The employer shall ensure that each employee assigned to work in an area where there is occupational exposure to nickel is informed of the hazards and relevant symptoms of exposure to nickel, and of proper conditions and precautions for the handling and use of nickel.   Workers shall be advised that handling nickel may cause dermatitis and that exposure to airborne nickel may increase the risk of developing cancer of the respiratory organs.   Information shall be given to employees at the beginning of employment and at least twice a year thereafter.

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(b)   The employer shall institute a continuing education program, conducted by instructors qualified by experience or training, to ensure that all employees have current knowledge of job hazards, proper maintenance and cleanup methods, and proper respirator use. The instructional program shall include a description of the environmental and medical surveillance procedures and of the advantages to the employee of participating in these examinations. Instruction shall include the information specified in Appendix IV, which shall be kept on file and readily accessible to employees at all places of employment where there is occupational exposure to nickel. Workers engaged in maintenance and repair shall be included in these training programs.

(c)   Required information shall be recorded on the "Material Safety Data Sheet" shown in Appendix IV or on a similar form approved by the Occupational Safety and Health Administration, US Department of Labor.

Section 6 - Work Practices

(a)   Control of Airborne Nickel

Engineering controls, such as process enclosure or local exhaust ventilation, shall be used whenever feasible and necessary to keep concentrations of airborne nickel at or below the recommended TWA concentration limit. If used, ventilation systems shall be so designed and operated as to prevent accumulation or recirculation of airborne nickel in the workplace environment and to effectively remove nickel from the breathing zone of employees. Exhaust ventilation systems discharging to outside air must conform to applicable local, state,. and federal regulations and must not constitute hazards to employees or to the general

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population. Before maintenance work on control equipment begins, sources of airborne nickel shall be eliminated to the extent feasible.

Enclosures, exhaust hoods, and ductwork shall be kept in good repair so that design airflows are maintained. Airflow at each hood shall be measured at least semiannually and preferably monthly. Continuous airflow indicators are recommended, such as water or oil manometers properly mounted at the juncture of fume hood and duct throat (marked to indicate acceptable airflow). A log shall be kept showing design airflow and results of semiannual inspections.

(b)   Regulated Areas

Regulated areas shall be established and maintained where there is occupational exposure to nickel, and access to these areas shall be limited to authorized persons.

(c)   Cleanup of Spills

Dusts or solutions containing nickel shall be removed from work areas by vacuum cleaning or by other methods, including wet methods, which do not increase the concentration of airborne nickel. No dry sweeping, blowing by compressed air, or any other method of dust removal that increases the concentration of airborne nickel shall be allowed.

(d)   Emergency Procedures

Procedures for emergencies, including fires and the inadvertent formation of nickel carbonyl, shall be established to meet foreseeable events. Necessary emergency equipment shall be kept in readily accessible locations. Where appropriate, respirators shall be available for use during evacuation.

(e)   Disposal of Waste

Waste material shall be disposed of in a manner that is not hazardous to employees or to the general population. Nickel wastes shall be appropriately marked and any aerosol-generating operations shall be enclosed. In selecting the method of waste disposal, applicable local, state, and federal regulations should be consulted.

(f)   Storage

Containers of nickel in liquid, powder, or crystalline form shall be kept tightly closed when not in use. Containers shall be stored in a safe manner to minimize the possibility of accidental breakage or spills. Corrosion of nickel shall also be minimized during storage.

(g)   General Work Practices

(1)   Good housekeeping practices shall be observed to prevent contamination of areas and equipment with nickel dusts, liquids, or mists and to prevent buildup of such contamination.

(2)   Good personal hygiene practices should be encouraged. Employees who have skin or eye contact with nickel should promptly and thoroughly wash the affected part. Workers occupationally exposed to nickel shall be required to shower at the end of the workshift.

(h)   Work Clothing

(1)   Coveralls or similar full-body protective clothing and head, leg, and shoe coverings, fire retardant where necessary, shall be worn by each employee occupationally exposed to nickel.

(2)   Such clothing shall be changed daily at the end of the work shift or if accidentally contaminated with nickel.

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(3)   The employer shall provide for the laundering of this clothing and shall ensure that soiled work clothing is not taken home by the employee.   Precautions shall be taken to protect personnel who handle and launder soiled clothing. These workers shall be advised of the hazards of and means of preventing exposure to nickel.

Section 7 - Sanitation

(a)   Conveniently located washing facilities shall be provided for all employees occupationally exposed to nickel.   Locker-room facilities, including showers, located in nonexposure areas, shall be provided for employees required to change clothes before and after each work shift. The facilities shall provide for storage of street clothing and clean work clothing separately from soiled work clothing. Covered containers shall be provided for work clothing removed at the end of the work shift or after a contamination incident. The clothing shall be held in these containers until it is removed for decontamination or disposal.

(b)   Food preparation, dispensing (including vending machines), and eating shall be prohibited in areas where there is occupational exposure to nickel.

(c)   Smoking or carrying uncovered smoking or chewing materials, such as chewing tobacco and gum, shall be prohibited in work areas where there is occupational exposure to nickel.

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Section 8 - <u>Monitoring and Recordkeeping Requirements</u>

   (a)   Monitoring

   (1)   Within 6 months of the promulgation of a standard based on these recommendations, each employer who has a place of employment in which nickel is refined, handled, stored, or otherwise used shall determine by an industrial hygiene survey if occupational exposure to nickel may occur. Surveys shall be repeated at least once every year and within 30 days of any process change likely to result in occupational exposure to nickel. Records of these surveys, including the basis for any conclusion that there is no occupational exposure to nickel, shall be retained until the next survey has been completed.

   (2)   If occupational exposure to nickel is possible, a program of personal monitoring shall be instituted to measure or permit calculation of the exposure of all employees.

   (A)   In all personal monitoring, samples representative of the breathing zones of the employees shall be collected.

   (B)   For each TWA determination, a sufficient number of samples shall be taken to characterize the employees' exposures during each work shift. Variations in work and production schedules and in employees' locations and job functions shall be considered in choosing sampling times, locations, and frequencies.

   (C)   Each operation in each work area shall be sampled at least once every 3 months.

   (3)   If an employee is found to be exposed to nickel in excess of the recommended TWA concentration limit, the exposure of that employee shall be measured at least once a week, control measures shall be

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initiated, and the employee shall be notified of the extent of the exposure and of the control measures being implemented. Such monitoring shall continue until two consecutive determinations, 1 week apart, indicate that the employee's exposure no longer exceeds the recommended TWA concentration limit. Routine monitoring may then be resumed.

(b)   Recordkeeping

Environmental monitoring records shall be maintained for at least 40 years after the employee's last occupational exposure to nickel. These records shall include the dates and times of measurements, job function and location of employees within the worksite, methods of sampling and analysis used, types of respiratory protection in use at the time of sampling, TWA concentrations found, and identification of exposed employees. Each employee shall be able to obtain information on that employee's own environmental exposures. Daily rosters of authorized persons who enter regulated areas shall be retained for 40 years. Environmental monitoring records and entry rosters shall be made available to designated representatives of the Secretary of Labor and of the Secretary of Health, Education, and Welfare.

Pertinent medical records for each employee shall be retained for 40 years after the employee's last occuptional exposure to nickel. Records of environmental exposures applicable to an employee should be included in that employee's medical records. These medical records shall be made available to the designated medical representatives of the Secretary of Labor, of the Secretary of Health, Education, and Welfare, of the employer, and of the employee or former employee.

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II. INTRODUCTION

This report presents the criteria and the recommended standard based thereon which were prepared to meet the need for preventing impairment of health from occupational exposure to inorganic nickel. The criteria document fulfills the responsibility of the Secretary of Health, Education, and Welfare under Section 20(a)(3) of the Occupational Safety and Health Act of 1970 to "...develop criteria dealing with toxic materials and harmful physical agents and substances which will describe...exposure levels at which no employee will suffer impaired health or functional capacities or diminished life expectancy as a result of his work experience."

The National Institute for Occupational Safety and Health (NIOSH), after a review of data and consultation with others, formalized a system for the development of criteria upon which standards can be established to protect the health and to provide for the safety of employees exposed to hazardous chemical and physical agents. The criteria and recommended standard should enable management and labor to develop better engineering controls and more healthful work practices and should not be used as a final goal.

These criteria for a standard for inorganic nickel are part of a continuing series of criteria developed by NIOSH. The proposed standard applies to the processing, manufacture, and use of inorganic nickel as applicable under the Occupational Safety and Health Act of 1970.

The standard was not designed for the population-at-large, and any extrapolation beyond occupational exposures is not warranted. The standard

is intended to (1) protect against injury from inorganic nickel, (2) be measurable by techniques that are valid, reproducible, and available to industry and official agencies, and (3) be attainable with existing technology. However, it will only substantially reduce the risk of developing nickel-related cancers and minimize the risk of developing dermatitis.

Ingestion and inhalation of, and dermal exposure to, nickel are common, since nickel is present in air, soil, water, food, and household objects. Although nickel is commonly found in the air, it is present in higher concentrations where there is environmental pollution as a result of the burning of fossil fuels or the processing of nickel.

The recommended standard for inorganic nickel is based on the conclusion that these substances are carcinogenic. An excess number of deaths from lung cancer and nasal cancer has been observed in nickel refinery workers. After review of the relevant data, it was concluded that a substantial portion of those excess deaths was caused by exposure to airborne nickel compounds. It might be reasoned from the limited animal data that only nickel subsulfide is a carcinogen; or the interpretation might be made, based on some epidemiologic studies, that only one stage of nickel refining presents a risk of cancer. In addition, it might be concluded from limited data on human exposures and environmental concentrations that the safe threshold level of exposure to nickel compounds is greater than the recommended environmental limit. Should sufficient evidence be developed to demonstrate that any of these is a correct interpretation or that some nickel compounds are not carcinogenic,

the recommended standard for inorganic nickel will be considered for revision.

The available evidence indicates that workers can be adversely affected by skin contact with nickel, particularly when it is in solution. Because of the ubiquity of nickel in the nonoccupational environment, some individuals may develop a sensitivity to nickel regardless of precautions taken in the workplace. The standard cannot protect these individuals from developing recurrent dermatitis when occupationally exposed to inorganic nickel. However, it will greatly reduce the risk of unsensitized workers becoming sensitive to nickel in the course of their employment.

Even though there is considerable information about occupational health problems associated with inorganic nickel, several major areas require further research. Epidemiologic studies are needed to determine the risk of developing nickel-related cancers in occupations which have not been adequately studied, eg, welding, plating, and refining nickel oxide ore; inhalation experiments in suitable animal species are needed to supplement these studies. Both animal and human studies are needed to ascertain whether the limited information on reproductive effects has any relevance to human exposure. Animal studies are needed to characterize the acute and chronic toxicities of the many nickel compounds for which insufficient information is available.

The health effects of occupational exposure to nickel carbonyl are not discussed in this document, nor have the effects of simultaneous exposure to nickel and cadmium been reviewed herein. The effects of nickel carbonyl are discussed in "Special Occupational Hazards Review and Control Recommendations for Nickel Carbonyl" and the effects of cadmium are

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discussed in the "Criteria for a Recommended Standard—Occupational Exposure to Cadmium."

Two other reviews of nickel provide additional information on its toxicity. The International Agency for Research on Cancer (IARC) prepared monographs on nickel and nickel compounds in 1973 [1] and 1976 [2], in which evidence for the carcinogenicity of all nickel compounds was considered. The Committee on Medical and Biologic Effects of Environmental Pollutants of the National Academy of Sciences published in 1975 a comprehensive review (NAS-NRC report) [3] of nickel which also included nickel carbonyl.

III. BIOLOGIC EFFECTS OF EXPOSURE

Extent of Exposure

Nickel (Ni), atomic number 28, is the 24th element in order of abundance in the earth's crust [4]. According to Ademec and Kihlgren [4], nickel was first isolated by Cronstedt in 1751, and relatively pure metal was prepared by Richter, who described its properties in 1804. Most inorganic nickel compounds contain the nickel ion in the +2 oxidation state; the +3 and +4 states are also possible, but occur infrequently [5]. Nickel compounds have diverse chemical and physical properties. Selected compounds of industrial or chemical importance are listed in Table XV-1 [4-9].

Nickel in its natural forms is found mainly as either oxide (laterite) or sulfide ore [10]. Deposits of oxide ore have been formed from the weathering of nickel-containing rock, resulting in areas of increased nickel concentration, whereas sulfide ore deposits were created from the settling of nickel in molten rock. The nickel ores mined in the United States are oxide ores and do not contain sulfur.

In the United States, primary nickel is produced at one mine-smelter complex and at one refinery [11]. The only US nickel mine, in Oregon, produced 13,000 tons of nickel in 1975, which was smelted in the ferronickel form [12]. Since 1974, a refinery in Louisana capable of producing 40,000 tons of nickel per year has refined imported nickel matte. In 1975, 58,900 tons of nickel were recovered as a byproduct and from scrap [12]. All other primary nickel used in the United States is imported, predominantly from Canada, with smaller amounts from Australia, New

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Caledonia, and other countries.

US nickel consumption in 1975 was about 146,500 tons (US Bureau of Mines, written communication, December 1976), about 30% less than the record-high figure of 1974. The US Bureau of Mines [11] has projected a 1.8-3.4% increase in the annual consumption of nickel through the end of 20th century. The pattern of nickel consumption has changed little in recent years [12]. Nickel was consumed in 1975 in the following forms: unwrought nickel (68%), ferronickel (17.3%), nickel oxide (11.4%), nickel salts (1.2%), and other (2.1%); 43% of the nickel was used in ferro-alloys, 39% in other nickel-based alloys, 13% in electroplating, and the remainder as nickel chemicals or catalysts (US Bureau of Mines, written communication, December 1976).

Combined with other metals in alloys, nickel provides strength and corrosion resistance over a wide range of temperatures and is therefore vital to the iron, steel, and aerospace industries. Nickel is also used in a variety of chemical and catalytic operations. Commercial ammonia and hydrogen production require the use of nickel catalysts [13 (pp 495-497)]. The synthesis of natural gas from coal probably will also involve the use of large quantities of nickel catalysts.

NIOSH estimated that 250,000 persons in the United States are exposed to inorganic nickel in the workplace. Occupations involving potential exposure to inorganic nickel are listed in Table XV-2 [14].

Historical Reports

Da Costa [15], in 1883, reported on the therapeutic effects of nickel salts. Nickel sulfate was reported to be effective in relieving rheumatism,

as was nickel bromide in reducing the frequency of epileptic attacks. The author stated that 65-195 mg of nickel sulfate given orally were well tolerated, whereas 650 mg caused occasional giddiness and nausea in some individuals. Doses of nickel bromide (325-487.5 mg) were also tolerated in the stomach. In 1885, Leaman [16] described additional instances of the use of nickel bromide to relieve epileptic seizures.

As early as 1889, Blaschko [17] described dermatitis resulting from exposure to chemicals used in nickel plating. He noted that plating solutions containing ammonium nickel oxide were much less harmful than those containing nickel chloride and that eczema was more severe in those who had worked longest. Blaschko recommended the use of rubber gloves and protective creams as methods to reduce eczema.

Bulmer . and Mackenzie [18], in 1926, discussed the processes associated with the development of nickel dermatitis in workers at a Canadian nickel refinery, the factors involved in the disease, and the measures taken to prevent it. The development of skin rashes was most closely related to working in hot environments where finely divided nickel dust was present. Those workers exposed to the heat of the furnaces or to the heat and humidity of the electrolysis shop and those who shoveled nickel salts were affected most often. In 1923, 43 cases of nickel rash had caused a total lost time of 4,016 hours in an unspecified number of workers. A medical program consisting of oral administration of calcium chloride and topical application of calamine lotion was then begun. In 1924, there were 22 cases of rash causing a total lost time of 408 hours and, in 1925, there were 23 cases of rash causing only 72 lost hours.

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In 1931, DuBois [19] reported on an investigation of a Swiss factory where large metal discs were plated with nickel. In a 2-year period (1928-1929), 370 workers were employed in the nickel plating room but only about 20 had been able to continue work without interruption due to dermatitis. The plating solution contained 35% nickel sulfate, 18% magnesium sulfate, and 0.1-0.2% sulfuric acid. The plating tanks were kept at a temperature of 85 C; a thick cloud, reducing visibility in the room to less than 1 meter, was produced. Although the workers wore long-sleeved shirts, had scarves around their necks, and changed clothing or bathed at the end of the work shift, dermatitis was a continuing problem. Improved working conditions, the use of lanolin barrier creams, and a requirement for the immediate reporting of any rash were instituted, and the number of cases was reduced considerably. The results in this plant led DuBois to inspect plating plants where cold plating solutions were used. Although the total number of workers examined was not indicated, no cases of dermatitis were observed. DuBois concluded that this dermatitis was the result of exposure to nickel or its salts, perhaps accentuated by heat and humidity.

In a 1933 report on nickel dermatitis, Goldman [20] criticized the conclusions of DuBois [19] because, in the investigation reported by the latter author, patch-testing for sensitivity to nickel had not been performed. Goldman [20] found cases of dermatitis in two plating workers who had become sensitive to nickel within 1 week after beginning work. They had positive skin reactions when patch-tested for nickel sensitivity and negative reactions to cobalt and lime. Goldman [20] concluded that there was a specific skin disease characterized by sensitivity to nickel compounds.

In Great Britain, cases of lung cancer and nasal cancer in workers at a nickel works were listed in the Annual Reports of the Chief Inspector of Factories for 1932 [21] and 1949 [22]. In the earlier report, Bridge [21] noted that 10 cases of cancer of the nasal cavities and paranasal sinuses developed in workers at the nickel plant between 1921 and 1932. In the 1949 report, Barnett [22] indicated that 47 cases of cancer of the nose and 82 cases of cancer of the lungs had been reported. Workers who developed nasal cancer had been employed an average of 23 years, those with lung cancer an average of 25 years, before the onset of cancer. In a review of cases that occurred before 1946, Barnett found that none of the workers who developed nasal cancer and only two of those who developed lung cancer had started to work at the nickel works after 1924.

The nickel works mentioned in the above reports has been identified as the nickel refinery in Clydach, Wales [23]. Amor [24] suggested in 1938 that lung and nasal cancers in workers at the Clydach nickel refinery were associated with exposure to arsenic, present in process material at a concentration of about 2%. In 1949, the Ministry of Pensions of Great Britain designated lung and nasal cancers in workers employed in operations involving the "decomposition of a gaseous nickel compound" as compensable diseases, according to an NAS-NRC report on nickel [3]. Nickel carbonyl was not specifically mentioned, but it apparently was presumed to be the agent causing lung and nasal cancers in workers at the Clydach nickel refinery, because, at that time, no excess incidence of these cancers had been reported in workers at nickel refineries that did not use the carbonyl process.

Effects on Humans

The following effects have been reported in humans exposed to nickel: dermatitis [17-20,25-34]; cancer of the lungs [22,35-47], of the nasal sinus cavities [21,22,35-37,39,41,43-45,47,48], and of the larynx [41,43]; irritation [48-50] and perforation [49,50] of the nasal septum and loss of the sense of smell [48,49]; and asthma-like lung disease [51,52], pulmonary irritation [53], pneumoconiosis [54,55], and a decrease in lung function [55]. Information on the chemical compositions of nickel compounds to which workers were exposed and the concentrations and durations of exposure was not presented in most of the human studies reviewed. When process information useful for determining probable worker exposures is available, it is included in the appropriate section of Epidemiologic Studies. A glossary of terms used to describe the refining processes for nickel is included as Appendix V. Each word included in the glossary is followed by an asterisk (*) on its first appearance in the text.

(a)   Dermatitis

Two forms of nickel dermatitis have been described [3]. Early cases of dermatitis in nickel miners, smelters, refiners, and electroplaters were attributed to "nickel itch," a skin disease in which eruption began as an itching or burning papular erythema in the web of the fingers and spread to the fingers, the wrists, and the forearms. A second type of nickel dermatitis was described as a papular or papulovesicular dermatitis with a tendency for lichenification. The eruption was characteristic of atopic dermatitis, rather than eczematous contact dermatitis. Calnan [25] also described two patterns of nickel dermatitis; a primary eruption at the site of direct metal contact, and a secondary eruption or area of spread remote

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from the metal-contact site. It was noted in the NAS-NRC report [3] that by 1975 nickel dermatitis was seen infrequently as an occupational disease. In addition, it was stated that no studies had been done to determine the incidence of nickel dermatitis in the general population.

The incidence of nickel dermatitis in the work force has not been reported in the literature with the exception of a report from the USSR by Sushchenko and Rafikova [26], who noted dermatoses in workers at a nickel refinery. In the electrolytic process, sulfide ore was refined in solutions containing 74-85 g of nickel/liter. Environmental concentrations of nickel for the years 1966-1970 were reported to have ranged from 0.021 to 1.65 mg/cu m. From medical and attendance records it was determined that, for the years 1967, 1968, and 1969, there were 1.8-6.2 cases of dermatosis/100 workers and lost time ranged from 13.7 to 59.4 days/100 workers. In 1970, 651 workers were examined for dermatosis and 36 cases were found. The authors stated that the incidence of dermatosis increased in the spring and summer months, when the temperature and humidity in the shops were high, exposure to ultraviolet radiation was minimal, and hypovitaminosis occurred.

Chaumont and Himmelsbach [27], in 1961, published the results of examinations for dermatitis in workers from three plating shops. In the first shop, none of six women stationed at a nickel plating tank operated at 34-45 C developed skin lesions, probably because they all wore gloves. Another woman, who occasionally did plating work, developed erythema and blistering which disappeared when she was not exposed to the plating solution. There were 10 workers in the second shop, none of whom had skin lesions. However, between 1950 and 1955, seven workers had been affected

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and were transferred to other jobs. The third shop had five nickel plating tanks, one of which was operated at a temperature of 50-60 C. Eight workers in this shop were exposed to nickel salts. Two of them had only 15 days of exposure and showed negative reactions to nickel sulfate patch tests. The other six workers, who complained of severe itching and had been exposed 3.5-9 years, had positive reactions to patch tests with nickel sulfate; the extent of reaction varied from erythema alone to erythema with edema, papules, and blistering. The dermatitis vanished completely during the 18-day annual leave but returned within 1 day when work resumed. The authors thought that the elevated temperature of the plating solution in the third shop might have been responsible in part for the more severe problems there.

Tsyrkunov [28] examined 87 workers exposed dermally to nickel salts through electroplating and metal degreasing. Exposure occurred because the workers did not use gloves and aprons while lifting objects from the plating baths. Skin abrasions caused by the metal parts increased the risk of dermatosis. Of the 40 persons who developed dermatitis and eczema, only 14 did not have skin abrasions of some sort; 33 of them had positive skin reactions to 1% nickel chloride. Skin inflammations and rashes developed most frequently 2-5 months after the beginning of employment and were confined primarily to the forearms, hands, and fingers. The author concluded that skin damage induced by nickel salts was facilitated by the numerous skin lesions and by the degreasing agents used.

In 1961, Polipov and Mezentseva [29] reported their observations of 100 nickel workers who were exposed to nickel sulfate in the plating of strips and containers, to nickel sulfate and metallic nickel in the

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preparation of electrodes, and to nickel oxide hydrate in a battery shop. Of the 38 workers engaged in strip plating, 26 had dermatitis and eczema; 4 of the 12 who plated containers, 3 of the 25 electrode workers, and none of the 25 battery workers were similarly affected. The increased frequency of dermatoses in workers involved in the plating of strips was attributed in part to poor work habits such as frequent wetting of hands and arms which caused a loss of skin oil, and the handling of freshly plated strips without gloves. More importantly, the authors reported that the hands and forearms of these workers were constantly traumatized (abrasions, cuts) in the course of their work. All 50 workers in the plating shop were patch-tested; 28 of 38 strip platers and 4 of 12 container platers reacted positively to nickel sulfate. Eighteen of the 26 dermatosis-affected strip platers were transferred to other jobs at the plant, and 13 of them had no recurrences, but the other five had to be removed from all contact with nickel. Of the 8 who returned to the plating shop after recovery, 6 were reaffected within 1-2 weeks and were then transferred. The authors concluded that timely transfer of sensitive workers to other work areas was important in the prevention of nickel dermatosis, but that observance of proper work practices was also essential.

In 1974, Skripkin et al [30] reported on 225 patients with eczema or dermatitis, all of them workers in metal shops, chemical plants, or printing houses, including 56 nickel electroplaters. The authors observed increased sensitivity to the salts of nickel and chromium in 178 of the subjects (79%) but they did not differentiate between the two compounds. The authors described the skin disease as having developed from repeated contact with these salts. Coombs tests, used to measure antibody levels,

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indicated that 21 of the 67 workers with recurring dermatitis and eczema had increased antibody titers, which would have accounted for the persistence of the skin conditions even after the workers were transferred to different work.

Skog and Thyresson [31], in 1953, reported the results of 3 years of routine patch testing of Swedish patients suffering from eczema. Tests were performed on 1,774 women and 1,513 men to determine sensitivity to formalin, potassium dichomate, nickel sulfate, turpentine, and para-phenylendiamine. Nickel sensitivity was determined by a patch test with 5% nickel sulfate. Occupational histories were obtained from all the subjects. Overall, 120 (7.9%) of the men and 166 (9.4%) of the women showed positive reactions to nickel. When patients were classified by occupation, a statistically valid increase in sensitivity to nickel, compared to other allergens, was seen in men employed in the building trades (P<0.01), in men employed in shops and warehouses (P<0.02), and in women employed in offices (P<0.001). In their discussion of the results, the authors considered that the higher incidence of sensitivity to nickel in building trade and warehouse workers was due, in part, to the handling of nickel-plated tools, and that in shop employees to the handling of nickel-containing coins. The overall higher incidence in women was attributed to increased contact with nickel-plated "contrivances," both at work and in the home.

In 1967 and 1968, eleven dermatologists in six European countries jointly investigated 4,000 persons in whom contact dermatitis had been diagnosed [32]. Of these, 769 were considered to have occupational dermatitis described as "a pathological condition of the skin for which

occupational exposure could be considered to be a major causal or contributory factor." Nickel sulfate (5%) in petroleum jelly was one of 20 substances tested. Patches, placed in four vertical rows on the upper back, were occluded, and readings were taken 48, 72, and 96 hours after application. In the occupational dermatitis group, 53 of 769 patients (7%) had positive reactions to nickel sulfate; 216 of 3,231 nonoccupational patients (7%) also had positive reactions to nickel sulfate, indicating that the percentage of nickel sensitivity was the same in both groups.

Marcussen [33] reported on the occupations of 621 persons in Denmark who developed nickel dermatitis between 1936 and 1955. These cases were confirmed by a positive patch-test reactions to 5% nickel sulfate. Of the 621 verified cases of dermatitis, 24 cases (4%) were attributed to work in nickel plating shops, 59 cases (9.5%) were associated with other occupations, and 538 cases (86.5%) were reportedly of nonoccupational origin. Marcussen also stated that 14 of the persons with nonoccupational dermatitis later worked with nickel and developed dermatitis on their hands. The author concluded that the risk of sensitization was greater from the private use of nickel items than from workplace exposure. In addition, several dermatoses of the hands of workers in nickel industries were actually the result of sensitization prior to nickel exposure in the workplace.

Norgaard [34] used radioactive nickel sulfate to determine the amount of nickel absorbed by human skin over a 24-hour period. Ten μl of nickel sulfate in solutions of four strengths (5.0%, 2.5%, 1.25%, and 0.68%) was applied to the skin and allowed to evaporate. The radioactivity was then measured, and the areas were covered for 24 hours. After 24 hours, the

radioactivity was again measured to determine the amount of nickel absorbed into the skin. Absorption of all solutions was similar and ranged from 55% to 77%. Other trials were conducted in which the radioactivity was measured several times throughout the 24-hour period to determine how absorption was affected by time. It was found that most nickel was absorbed early in the 24-hour period. Nickel-sensitive individuals did not differ from others in the rate of nickel uptake.

(b)   Cancer

Cancer of the respiratory organs in nickel refinery workers has been studied extensively. Different terms have been used by authors to describe cancers in specific sites. In this review, "nasal cancer" denotes cancer of the nose, nasal cavities, nasal sinus cavities, and ethmoid sinuses. "Lung cancer" denotes cancer of the trachea, bronchus, and lung, or pulmonary cancer. "Cancer of the respiratory organs" is used for cancer in all organs of the respiratory tract combined, ie, nose, larynx, and lungs.

Cancer of the respiratory organs has been noted in workers exposed to nickel in Wales, Canada, Norway, the USSR, Japan, France, Germany, and the US. Increased risks of death from lung cancer and nasal cancer were first noted in workers at a nickel refinery in Clydach, Wales; the risks of death from lung and nasal cancer in these workers have been reported in four epidemiologic studies [35,37,39,40], in two of which were noted substantial decreases in these risks in workers first employed after 1925. In the most recent Clydach study, Doll et al [40] reported that the ratio of observed to expected deaths (O/E ratio of deaths) from lung cancer decreased from 7.0:1 in workers first employed before 1925 to 1.9:1 in workers first employed after 1925. The O/E ratio of deaths from nasal cancer was 329:1

in workers first employed before 1925, but only one worker first employed after 1925 has developed nasal cancer. The decrease in the risk of death from cancer of the respiratory organs in these workers appears to be closely associated with their use of gauze masks beginning about 1923 [41]. The 80 deaths from nasal cancer and the 176 deaths from lung cancer identified between 1920 and 1975 in Clydach nickel refinery workers are shown by year of death in Figures XV-1 (a and b).

In 1950, Loken [42] reported on three deaths from lung cancer in workers at a nickel refinery in Kristiansand, Norway. An epidemiologic study by Pederson et al [43] in 1973 showed that workers in that refinery had increased risks of developing cancers of the nose, larynx, and lungs. Workers in all four categories (roasting* and smelting*, electrolysis, other specified processes, and other work) had increased risks of developing cancer of the respiratory organs. The 22 cases of nasal cancer and 64 cases of lung cancer diagnosed up to 1975 in Kristiansand nickel refinery workers are shown by year of diagnosis in Figures XV-1 (c and d).

Two epidemiologic studies by Sutherland have shown that workers at a nickel refinery in Port Colborne, Ontario [44], and at a nickel sinter plant in Copper Cliff, Ontario [45], had an increased risk of death from cancer of the respiratory organs. A third study [46] has suggested that workers in four occupational groups at the Copper Cliff nickel smelter had a slightly increased but not statistically significant risk of death from cancer of the respiratory organs. The 36 cases of nasal cancer and 90 cases of lung cancer in Port Colborne nickel refinery workers identified by 1975, and the 6 cases of nasal cancer and 50 cases of lung cancer in Copper Cliff sinter plant workers identified by June 1976, are shown by year of

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diagnosis or death in Figures XV-1 (e-h). McEwan [56,57] also has reported an excess of lung cancer in former Copper Cliff sinter plant workers, in a study primarily concerned with the usefulness of sputum cytology screening programs.

Studies from the USSR have indicated that nickel refinery workers have developed erosions, perforations, and ulcers of the nasal cavities [49,50], and that they have had an increased risk of death from cancer [58,59]. Increases in the number of deaths from lung cancer have also been noted in studies of nickel workers in Japan [60] and of workers who refined nickel-arsenide ores in Germany [61].

In the US, deaths from cancer of the respiratory organs in nickel alloy plant workers in Huntington, West Virginia, have been reviewed in two epidemiologic studies [47,41]. Both of these studies are preliminary, and their results are inconclusive. The epidemiologic studies and associated reports mentioned above are discussed in detail in the section on Epidemiologic Studies.

A few case reports also have suggested an association between workplace exposure to airborne nickel and the development of cancer of the respiratory organs. In 1965, Tatarskaya [48] observed two cases of nasal cancer in workers engaged in the electrolytic refining of nickel. The first case was that of a 39-year-old woman employed for 18 years in the electrolysis shop of a nickel plant. During an initial examination, a large perforation of the nose and mild atrophic pharyngitis were found, although the woman's only symptom was a poor sense of smell. Eight years later, squamous-cell carcinoma of the right half of the nose, accessory

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sinuses, and eye socket was diagnosed. The second case was that of a 42-year-old man employed in an electrolysis shop of a nickel plant for 13 years. The worker's symptoms of swelling and flare of the antrum of the nose were originally diagnosed as a boil, but squamous-cell carcinoma was diagnosed after microscopic examination of the affected tissue. The tumor had apparently originated in the anterior corner of the maxillary sinus and had spread to the anterior and medial walls. Tatarskaya emphasized that, in both cases, the tumors were not detected until the later stages of development although the workers had received periodic medical examinations. The author suggested that workers engaged in the electrolytic refining of nickel have an X-ray of the accessory sinuses at least once a year, and that nasal polyps or any other anomalies detected should be promptly examined microscopically.

In 1966, Bourasset and Galland [62] reported a case of reticulosarcoma of the nose in a 59-year-old woman employed from 1922 to 1960 in a cutlery factory. The woman was a houseworker for 7 years before she was employed in the cutlery factory. She worked in various jobs at the factory from 1922 to 1955; from 1955 through 1960, her job entailed cleaning cutlery and electroplating it with nickel. The nickel sulfate and nickel chloride plating bath was maintained at 50 C and did not contain arsenic. Although she reportedly dipped her hands into the bath often, she did not wear gloves or use protective cream. Greenish-white vapors were given off by the bath, and the workspace was small and poorly ventilated. The woman also cleaned the sediments from the bottom of the nickel-plating bath every 3 months.

The authors [62] reported that the worker did not smoke, and, although no anomalies were found prior to 1955, rhinitis was noted after 1955. A tumor of the nasal fossa was diagnosed in 1960 after she reported symptoms of acute rhinitis. The tumor was identified microscopically as a primary reticulosarcoma with beginnings of angioendothelial differentiation. Since the worker was not exposed to other known irritants or carcinogens, and since both the location and the microscopic characteristics of this tumor were quite rare, Bourasset and Galland suggested that the development of the tumor was associated with exposure to nickel salts from electroplating baths.

In 1973, Sunderman [63] reported on a case of lung cancer in a 36-year-old man who had ground and polished nickel-plated material. The worker had smoked less than one pack of cigarettes a day since the age of 16 (FW Sunderman Jr, written communication, December 1976). The period between first employment and the diagnosis of lung cancer was 9 years. The tumor was identified by microscopic examination as an anaplastic large-cell adenocarcinoma in the left lung. Metastases to the mediastinal lymph nodes, intestine, and skin were also found. Atomic absorption spectrophotometry was used to determine the concentration of nickel in the lungs and heart of this worker and in four apparently healthy people not exposed to nickel in the workplace who had died suddenly from accidents or homicide. Sunderman [63] found that the concentration of nickel in the nickel worker's nontumorous lung was nearly 23 times greater than that in the lungs of the four control subjects. The concentrations of nickel in lung tissues were 197 μg/100 g dry weight in the nickel worker, 15 μg/100 g in a 44-year-old man, 12 μg/100 g in a 40-year-old woman, 3.3 μg/100 g in

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an 18-year-old man, and 4.3 μg/100 g in a 23-year-old woman. The concentration of nickel in the heart tissue of the nickel worker was also elevated compared to that in the heart tissues of the four control subjects.

In 1977, Sunderman [64] described the case of a 35-year-old man who had developed squamous-cell carcinoma of the nasal cavity. From 1965 to 1970 and from 1973 to 1975, this worker had been employed in a nickel-stripping operation, where nickel plating was removed from objects by dipping them into a solution of hydrochloric and nitric acid at 180 F. Although he was continuously exposed to acid fumes over the stripping tank, the worker reported that he never wore a respirator. He also noted that the most noxious part of his job was cleaning out nickel sludge from the nickel-stripping tank about once a week. During nickel-stripping operations, the worker was exposed to copper and silver, but not to chromium [64]. In 1970, the worker had severe symptoms of nasal irritation and was transferred to the pressroom, where he was exposed to airborne methylene chloride, carbon tetrachloride, and trichlorethane from 1970 to 1973. In 1975, he worked for 8 months in a metal-grinding room where stainless steel was fabricated. He had reportedly smoked 5-10 cigarettes a day since the age of 14. The worker developed an inflammation of the right nostril and sinusitis; 3 months later, squamous-cell carcinoma was diagnosed from a biopsy of a polyploid lesion in the nasal cavity. Nearly 1 year after the diagnosis, the concentration of nickel in the urine of the patient was measured and was found to be within normal limits. This was expected by the author, since the patient had not had any significant workplace exposure to nickel for several months. Sunderman concluded that

there was a "strong likelihood" that this case of nasal cancer identified in a worker engaged in nickel-stripping operations was caused by exposure to nickel.

(c)   Other Effects on the Respiratory Organs

In 1956, Tolot et al [51] described an asthmatic-type lung disease in a worker who had contact with nickel-plating baths. After 4.5 months of exposure in the plating room, the worker was hospitalized with acute lung disease. Environmental concentrations of nickel were not stated. Although the authors noted that acute symptoms responded to therapy, paroxysmal bronchial symptoms marked by coughing, expectoration, and labored breathing persisted for 2 months. The chronic symptoms improved after a 3-week hospitalization and drug therapy with theophyllin; the patient then returned to work. In 2 weeks, he was hospitalized again because of shortness of breath and a marked dry cough. X-ray examination showed that the bronchial tree was congested, and the cough reactions were considered by the authors to be very significant. They [51] concluded that the worker had developed signs of chronic bronchitis due to exposure to mists from a nickel plating bath. The authors did not discuss the possibility that the symptoms might have been associated with exposure to airborne substances other than nickel, such as sulfuric acid mist.

In 1973, McConnell et al [52] described a case of asthma associated with nickel sensitivity. Dermatitis, shortness of breath, chest tightness, wheezing, and a nonproductive cough developed in a 24-year-old male employee who had worked at a nickel metal plating plant for only 3 weeks. The symptoms were present during and for several hours after each work shift. The symptoms were relieved after 5 days of hospitalization;

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upon the patient's return to work, however, they recurred, and he was advised to change jobs. Inhalation of a mist containing 10 mg/ml of nickel sulfate (total volume delivered unspecified) under controlled conditions established the role of nickel salts in the development of the asthmatic symptoms. After a 15-minute exposure to nickel sulfate, progressive shortness of breath occurred, and five hours later, pulmonary function was reduced by 50%. Under the same conditions, a control subject did not develop any significant functional changes. A patch test with nickel sulfate was positive. The symptoms described in this patient were attributed to hypersensitivity to nickel.

Arvidsson and Bogg [53], in 1959, observed a case of nickel dermatitis that also involved lung lesions and marked eosinophilia. A 48-year-old woman was hospitalized with severe dermatitis and fever. In the course of the disease, eosinophilia (31-32% eosinophils) and transitory pulmonary lesions and edema were noted. The dermatitis was not of occupational origin, since it was attributed by the authors to contact with nickel-containing earrings, but this report again suggests the possibility of pulmonary involvement in instances of nickel sensitivity.

In 1969, Zislin et al [54] studied the respiratory functions of 13 persons in the USSR with what they described as nickel pneumoconiosis. The persons averaged 42.9 years of age and were exposed to nickel dust for 12.9-21.7 years. Although no quantitative data were given, the authors noted that residual lung capacity and what was described as oxygen retention in the blood were lowered. The respiratory rate was also increased. Chest X-rays revealed diffuse fibrosis in the lungs (pneumosclerosis), and the authors concluded that pulmonary emphysema, at a

stage undetectable by X-ray, was present in these persons.

Jones and Warner [55], in 1972, described the effects of oxides of iron, nickel, and chromium on workers employed in a steel mill. The deseaming and cutting of stainless steel produced a fume containing oxides of iron, nickel, and chromium in a ratio of 6:1:1. Fumes from nonstainless steels were almost pure (96.9%) iron oxide. Total airborne dust concentrations ranged from 1.3 to 294.1 mg/cu m. Radiographic examinations indicated that 7 of the 19 workers had pneumoconiosis. Initial pulmonary function tests of the affected men were all normal, but in followup examinations of four men, reductions in expiratory volume and vital capacity were noted in two workers. The authors concluded that, since none of the affected workers had been exposed to iron oxide alone, their diseases could not be described as pure siderosis, and suggested that three of the men showed mixed-dust pneumoconioses. The presence of impairments in pulmonary function, which are suggestive of fibrotic lung changes, was indicative of exposure to oxides other than those of iron, which reportedly did not produce fibrotic changes.

In 1972, Sushchenko and Rafikova [26] studied workers engaged in nickel sulfide ore hydrometallurgy. Electrolytic solutions in the shop contained 75-85 g of nickel/liter of solution. Trace amounts (0.005-0.9 g/liter) of copper, cobalt, and iron were also present. The concentrations of nickel in aerosols in the shop environment ranged from 0.035 to 1.65 mg/cu m in the years 1966-1970. In 1970, 37 of 151 workers reported nasopharyngeal illness. Nasal membrane erosion was seen in 14 of these affected workers.

(d)   Other Effects

In 1948, Friberg described renal effects found in workers exposed to nickel and cadmium dusts during the manufacture of alkaline storage batteries [65]. Evidence of kidney damage was found in most of the 19 workers employed for more than eight years, although proteinuria or other pathologic changes were not observed in 19 others employed for less than three years. A more extensive study of these workers was reported by Friberg in 1950 [66]. On the basis of information obtained from animal experiments and from other battery producers, Friberg [66] concluded that kidney damage in these workers was caused by exposure to cadmium. No other information concerning the possibility that exposure to inorganic nickel may also damage human kidney function was found. Information is needed to determine if nickel could primarily affect glomerular function, or if it could affect tubular function, as does cadmium. Without supporting data, the effects of workplace exposure to nickel on kidney function cannot be adequately assessed on the basis of Friberg's reports [65,66]. His findings are reviewed in detail in "Criteria for a Recommended Standard--Occupational Exposure to Cadmium."

In 1965, Nechiporenko reported on eye damage in nickel electrolysis workers in the USSR [67] who were exposed to aerosols of nickel sulfate and to sulfuric acid mist and chlorine gas when mixing hot solutions and monitoring open electrolysis tanks. Sensations of having a foreign body beneath the lid and sharp pains in the eyes were reported. Excessive tear flow was also found, but further studies apparently indicated that the function of the tear ducts was not impaired. Many workers had diseases of both the nose and the eyes. In these workers, hypertrophic rhinitis and

conjunctivitis, frequently with hemorrhage, were found in the anterior segments of the eyes. After engineering controls were introduced to lower worker exposure to aerosols and vapors, eye damage decreased from 6.2 to 2.6 cases/100 workers.

The extent of eye damage in workers exposed to aerosols from nickel electrolysis tanks cannot be adequately assessed on the basis of this study [67], since the extent of exposure to aerosols, the procedures and criteria used to determine the extent of eye damage, and the number of workers studied were not reported. In addition, the eye damage may have resulted from an allergic conjunctivitis rather than from exposure to nickel. The study does suggest, however, that damage to the nose and eyes may occur in workers exposed to aerosols from nickel electrolysis tanks, even though the role of nickel sulfate in producing these effects is not clear.

Epidemiologic Studies

Comparisons of mortality in the discussions of epidemiologic data that follow are expressed as ratios of observed (O) to expected (E) deaths. Probabilities have been calculated from the cumulative Poisson distribution when E was less than 5 and from the chi-square test when E was 5 or more. These ratios are considered significant at $P < 0.05$.

(a) Wales

The nickel refinery at Clydach, Wales, where nickel is purified by the Mond (carbonyl) process, began operations in 1902 [36]. The refining process at Clydach was originally divided into six stages: crushing and grinding of nickel-copper matte*; calcining* of the crushed matte at 800 C [41] to produce mixed oxides of copper and nickel; extraction of copper by

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(a)   Wales

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leaching with sulfuric acid; reduction* of nickel oxide to impure nickel powder; revolatilization of impure nickel powder in the presence of carbon monoxide to form nickel carbonyl; and decomposition of nickel carbonyl gas in the presence of heat to form pure nickel and carbon monoxide [36].

The refinery receives nickel-copper matte from a nickel smelter in Canada. Thus, the composition of the matte has changed as the smelting processes used in Canada have improved. Before 1933, the matte contained 40-45% nickel, 35-40% copper, and 17% sulfur [23]. In 1933, the matte was changed to 74% nickel, 2.3% copper, and 23% sulfur, and in 1936, the sulfur content of the matte was reduced to 6.5% [23]. In 1945, nickel oxide was substituted as the feed material at Clydach [36], eliminating potential worker exposure to nickel sulfides*. Between 1945 and 1961, the nickel oxide from Canada, formed by sintering* impure nickel matte, was ground and calcined at Clydach to remove impurities before entering the carbonyl refining process [23]. Grinding and calcining were discontinued at Clydach in 1961, since the nickel oxide formed in fluid bed roasters in Canada was pure enough to be refined directly by the carbonyl process [23].

The first epidemiologic study of deaths of workers at the Clydach nickel refinery was conducted by Hill in 1939. Hill's findings, reviewed and updated by Morgan in an unpublished report [35], were submitted to NIOSH by International Nickel (U.S.), Inc. (Inco). From company insurance and employment records, Hill determined the total number of deaths and the number of deaths from lung cancer and nasal cancer in refinery workers and pensioners between June 1929 and January 1938. The expected number of deaths for the group was estimated from age- and cause-specific death rates for men in England and Wales, which were available for 1931-1935.

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Hill found that the O/E ratios of deaths were 16:1 for lung cancer (16 observed, 1 expected, P<0.05) and about 22:1 for nasal cancer (11 observed, 0-1 expected, P<0.05) [35]. Since the numbers of observed and expected deaths for all other causes were nearly the same (67 observed, 72 expected), Hill concluded that the increase in the number of deaths in these nickel refinery workers (105 observed, 84 expected) was due almost entirely to the increase in deaths from nasal and lung cancers.

For futher analysis, pensioners were excluded and workers were divided by occupation into process and nonprocess workers [35]. Process workers included calciner, reverberatory, and cupola* furnace workers; repairmen, electricians, and superintendents; special order, traffic, and yard workers; and those involved in the extraction of copper, the concentration of nickel sulfate, or the leaching of nickel matte. The occupations of nonprocess workers were not described. The study included about 438 process workers and 389 nonprocess workers. Since the process-worker group was slightly larger and older, a few more deaths would normally be expected in this group. The number of deaths in process workers from causes other than lung or nasal cancer was nearly equal to the number in nonprocess workers (35 in process workers, 34 in nonprocess workers). In contrast, 15 deaths from lung cancer and 11 deaths from nasal cancer occurred in process workers, but only one death from lung cancer and no deaths from nasal cancer occurred in nonprocess workers. Based on these findings, Hill concluded that workers at the Clydach nickel refinery had a very high incidence of deaths from nasal and lung cancer between 1929 and 1938, and that nearly all of these deaths occurred in process workers.

Hill indicated that the number of deaths recorded for the nickel refinery workers was probably underestimated, since deaths of former workers not eligible for pensions were not listed in the company records [35]. In addition, he found inconsistencies in the recording of deaths by the company. The summary report [35] apparently quoting Hill, stated that "certain names on the list of cases of lung cancer appear on the list [of deaths] as due to other causes and some do not appear on the list of deaths at all." Since all of the deaths may not have been identified, Hill stressed that emphasis should be placed on the O/E ratio of deaths in the worker-pensioner group, rather than on the actual number of recorded deaths.

In the update of Hill's findings, Morgan reviewed data on deaths in workers and pensioners at the Clydach nickel refinery between 1938 and 1946 [35]. He found that the O/E ratios of deaths were 13.3:1 for lung cancer (40 observed, 3 expected, P<0.05) and about 40.0:1 for nasal cancer (20 observed, 0-1 expected, P<0.05). Morgan's findings indicated that the death rate from lung and nasal cancer had remained elevated in workers who died through 1946.

In a 1958 report, Morgan [36] compared changes in the number of deaths from lung cancer and nasal cancer in workers and pensioners at the Clydach nickel refinery with changes in the processes used to refine nickel. In addition, Morgan determined the departments or processes in which most of the workers who died from lung or nasal cancer had been employed and attempted to identify the cancer-causing agents to which these workers may have been exposed. Morgan [36] also summarized Hill's [35]

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unpublished epidemiologic study [35] on the risks of death from lung and nasal cancer in workers at this refinery.

From company employment and insurance records, Morgan [36] identified 131 deaths from lung cancer and 61 deaths from nasal cancer in 9,340 workers and pensioners who were first employed at the nickel refinery between 1900 and 1957. Morgan [36] observed that most of these deaths occurred in workers first employed at the refinery before 1925. This finding is not reviewed in detail here, since the variations in the risk of death from lung and nasal cancer according to the year of first employment in workers at the Clydach nickel refinery were also assessed in epidemiologic studies by Doll et al in 1970 [39] and in 1976 [40].

From occupational histories of workers who had died, Morgan [36] identified 507 who had been employed for 15-25 years in only one department. He then determined the percentage of workers who died from lung or nasal cancer for each department. As shown in Table III-1, deaths from both lung cancer and nasal cancer were most frequent in calciner furnace workers and copper sulfate workers, followed by other furnace workers, crushing and grinding department workers (concentrators), and workers transporting matte to the nickel sheds where nickel carbonyl was formed as an intermediate in the Mond (carbonyl) process for refining nickel. The author also reported that deaths from nasal cancer occurred most frequently in workers who cleaned the underground flues of the calciner furnaces.

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TABLE III-1

LUNG AND NASAL CANCERS IN WORKERS EMPLOYED
AT A NICKEL REFINERY IN CLYDACH, WALES*

Process or Department	Average Annual Population		Lung Cancer Cases		Nasal Cancer Cases	
	No.	%	No.	%	No.	%
Gas production	–	–	1	2	–	–
Calcination	58	12	14	25	14	42
Copper sulfate	87	17	20	35	8	25
Nickel sulfate	57	11	4	7	3	9
Furnace	36	7	2	3	5	15
Crushing and grinding	26	5	2	3	1	3
Nickel sheds	163	32	5	9	1	3
Fitters	80	16	9	16	1	3
Total	507	100	57	100	33	100

*Employed in one department 15-25 years between 1900 and 1957

Adapted from Morgan [36]

Morgan [36] observed that the decline in the numbers of deaths from lung cancer and nasal cancer paralleled improvements in both work practices and refinery processes. Changes that contributed to a decrease in worker exposure to dust and fume included: improvements in calciner furnaces, the use of arsenic-free sulfuric acid beginning in 1922, and the issuance of nose and mouth respirator pads also beginning about 1922 [36]. Calciner furnaces that released less dust than those used previously were installed

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in 1910 and improved in 1924. Until 1936, however, calciner flues were cleaned manually. By 1936, the calciner furnaces, each with its own grinding mill, had been replaced by a central grinding plant with an air-swept ball mill and 12 rotary-hearth calciners equipped with dust collectors and electrostatic precipitators [36]. The calciner sheds were considered by Inco to be the dirtiest part of the refinery [41]. Dust was generated by crushing and grinding nickel-copper matte, by handling finely divided residues returned from the Mond process, and by operating calciner furnaces with insufficient draft and dust collecting equipment [41].

Estimates of the concentrations of airborne nickel and total airborne dust at the Clydach nickel refinery were provided in 1976 by Inco [41]. The concentration of total airborne dust was measured in two calciner sheds in 1932 by determining the difference in tare and final weights of a plug of wool in a tube, through which 100 liters of air were drawn at a height of about 5 feet in each shed. In one shed, 14 and 8 mg/cu m of airborne dust were measured; in another, in which older calcining equipment was used, dust concentrations of 42, 13, and 12 mg/cu m were found. No information on the collection efficiency of this sampler is available, but it was probably quite low. Concentrations of sulfur dioxide were measured by absorption in an oxidizing solution, followed by acidimetric analysis. In a calciner shed with newer equipment, an average of 1.5 ppm sulfur dioxide (range 0.2-3.8) was found in 4 samples; in an older shed, 12 samples contained an average of 25.4 ppm sulfur dioxide (range 3.8-54). Apparently the use of newer equipment reduced sulfur dioxide concentrations but did not greatly affect total dust levels. Moreover, in 1932, the plant was operating at reduced capacity because of economic events [41] and the

concentrations of airborne dust probably would have been much greater under full operating conditions. The concentration of total airborne dust was measured at the refinery in millions of particles per cubic foot (mppcf) in 1945 and in 1949 [41]. In 1945, four locations in the central grinding plant were sampled, and ranges of 1.8-13.7, 2.6-19.1, 1.4-7.5, and 1.9-16.8 mppcf were reported for particles less than 10 μm in diameter. In 1949, eight samples in the grinding plant averaged 5 mppcf (SD=3.7, range 1.7-8.1), four samples in the calciner buildings averaged 10.5 mppcf (SD=2.2, range 9.5-11.8), and 17 samples in the carbonyl sheds averaged 6 mppcf (SD=5.2, range 3.1-10.6). Based on analyses of the process material, it was estimated that the dusts may have contained about 70% nickel [41].

Inco provided the data they used to convert the dust-counting data from the grinding plant, calciner buildings, and carbonyl sheds to concentrations expressed as mg/cu m [41]. Based primarily on particle sizing of the dusts from a currently operating fluid-bed roaster and density data from a 1915-1917 study in a nickel plant in New Jersey that is no longer operating, conversion factors of 5 for grinding dusts, 3 for calciner dusts, and 1 for carbonyl process dusts were assigned. Applying these factors, the grinding plant total dust concentration ranged from 7 to 95.5 mg/cu m in 1945 and averaged 25 mg/cu m in 1949. Calciner dusts averaged 31.5 mg/cu m and carbonyl process dusts averaged 6 mg/cu m in 1949. The data were probably broad estimates, since information from which the validity of these conversion factors may be determined is not available.

Inco has recently tested the efficiency of the gauze masks that were issued to workers about 1923 [41]. Dust generated in the modern fluid-bed

roasting processes was used to test the efficiency of double gauze masks (workers wore two masks at a time), which was reported as ranging from 85-95%. Concentrations of dust from fluid bed roasting that were swept through the mask ranged from 1.43 to 8.39 mg/cu m, and the average particle size of this dust was about 6 μm. Inco also reported that the double gauze masks were 70-90% efficient in filtering fine dust from both the new and old carbonyl plants at Clydach, although the size distribution of the dust was not given. Data on the dust generated in the years of greatest cancer hazard are not available, but it seems reasonable to assume that the dust exposure of workers was greatly reduced by the introduction of gauze masks in 1923.

Based on estimates of environmental concentrations of airborne nickel and estimates of the efficiency of the gauze masks, it appears that workers who did not wear gauze masks, ie, workers first employed before 1923, were exposed to concentrations of airborne nickel refinery dust about ten times greater than those to which workers near new calciner furnaces who wore double-gauze masks, ie, workers first employed after 1936, were exposed. Inco has recently concluded that the use of double gauze respirator masks was the most significant factor in reducing worker exposure to dust and fumes at the Clydach nickel refinery [41].

Morgan [36] attempted to identify the agents associated with the development of lung or nasal cancer in workers by comparing the pattern of deaths from lung cancer and nasal cancer with possible exposure to radiation, nickel carbonyl, and arsenic. He indicated that there was no evidence of radioactivity in nickel matte at any stage in the refining process, although supporting data were not reported. In addition, Morgan

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[36] concluded that deaths from lung and nasal cancer in the Clydach nickel refinery workers were not associated with exposure to nickel carbonyl, for three reasons: first, these deaths were not limited to workers in the nickel sheds where nickel carbonyl was formed; second, workers in the nickel sheds were also exposed to dust from nickel matte; and third, the number of deaths from lung and nasal cancer declined substantially with the year of first employment, particularly in the years after 1924, although the carbonyl refining process was not changed during the study period. Morgan also concluded that these deaths in nickel refinery workers were probably associated with exposure to dusty operations, to drying and powdering copper sulfate, to arsenic present in the sulfuric acid used for copper extraction, or to a combination of these factors. Morgan reported that the arsenic content of the sulfuric acid used for copper extraction was highest between 1917 and 1919 and then declined rapidly, so that sulfuric acid was nearly arsenic-free by 1926. Since the decline of the arsenic content in the sulfuric acid paralleled the decline in the number of deaths in workers from lung and nasal cancer by year of first employment at the refinery, Morgan concluded that arsenic was probably the carcinogenic agent associated with the development of lung and nasal cancer in Clydach nickel refinery workers.

As previously stated, Morgan's report [36] indicates that many of the deaths of workers from lung cancer and nasal cancer could not be linked to nickel carbonyl exposure. However, Morgan's study is insufficient either to substantiate or to refute the suggestion that exposure to nickel carbonyl is associated with the development of cancer of the respiratory organs. Morgan's [36] theory that deaths from lung or nasal cancer were

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probably associated with exposure to arsenic in heated calcined dusts is not well supported by his study, because the use of arsenic-free sulfuric acid coincided with the introduction of double gauze masks which reduced worker exposure to airborne nickel as well as to airborne arsenic. Thus, agents associated with the development of lung and nasal cancer in workers at the Clydach nickel refinery have not been conclusively identified in Morgan's study. It appears, however, that improvements in equipment and engineering controls and the use of double-gauze masks by workers contributed to decreased exposures to cancer-causing agents and to subsequent decreases in the risk of death from lung and nasal cancer in workers at this plant.

In 1937, a plant was built at Clydach to produce nickel sulfate, and, in 1939, a department, which currently (1976) produces nickel chloride and nickel carbonate, was opened to produce other nickel salts [41]. Each plant employed about 80 people. No cases of nasal cancer and 2 cases of lung cancer were identified in nickel sulfate plant workers who had not been employed in any other areas of the refinery before 1925. Likewise, no cases of nasal cancer and two cases of lung cancer were identified in chemical salt department workers first employed after 1925. Although the methods used to identify nasal and lung cancer cases and the risk of developing these cancers were not reported, the number of cases of lung cancer found in these workers does not appear to be excessive.

In a 1958 epidemiologic study, Doll [37] estimated the risks of death from lung cancer and from nasal cancer in Clydach nickel refinery workers. He reviewed death certificates for all men who died between 1938 and 1956 in health districts where nickel refinery workers lived; death certificates

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were obtained from two health districts between 1938 and 1956 and from two additional health districts between 1948 and 1956. Information from death certificates was used to classify each death according to the occupation of the worker at the time of death or when last employed. Deaths were then classified by cause within each occupational group. Information on residents dying outside the district was included in the local health records, and Doll concluded that nearly all of the deaths in workers employed at the nickel refinery at the time of death and a large proportion of the deaths of workers last employed at the refinery were identified.

The ratio of deaths from lung cancer to deaths from all causes except lung and nasal cancer was determined for men other than those who were last employed in aluminum, copper, spelter (zinc), or patent fuel works, in nickel or oil refineries, in steel industries, or in coal mines. These ratios were determined for each 10-year age group and were used to estimate the expected number of deaths from lung cancer in nickel refinery workers based on the number of deaths from all causes other than cancers of the nose and lung in these workers.

Although Doll [37] indicated that nasal cancer is quite rare in the general population, 16 deaths from nasal cancer were identified in men who were not listed as nickel refinery workers on their death certificates. Doll contacted the relatives of most of these men and found that at least seven of them had worked in the nickel refinery at some time. Since the death rate from nasal cancer in the four health districts was elevated by the inclusion of former nickel refinery workers, Doll estimated the expected number of deaths from nasal cancer in Clydach nickel refinery workers from national rather than from local mortality statistics. The

expected number of deaths from nasal cancer between 1938 and 1956 in
workers last employed at the nickel refinery was derived from the age-
specific death rates from nasal cancer in England and Wales, first
available in 1950. Doll indicated that the estimate was unlikely to be
greatly in error since the crude death rate for nasal cancer in England and
Wales had remained nearly constant from 1938 to 1956.

In nickel refinery workers, the O/E ratio of deaths from lung cancer
was 13.8:1 between 1938 and 1947 in two health districts (36 observed, 2.6
expected, P<0.05) [37]. Between 1948 and 1956, the ratio decreased to
6.7:1 in the same two health districts (39 observed, 5.86 expected, P<0.05)
and it was 4.9:1 in all four health districts (48 observed, 9.88 expected,
P<0.05) for the same period. The O/E ratio of deaths from nasal cancer was
242:1 in two health districts between 1938 and 1947 (16 observed, 0.066
expected, P<0.05) and decreased to 159:1 in all four health districts
between 1948 and 1956 (13 observed, 0.082 expected, P<0.05). Doll
indicated, however, that the apparent decline in the risk of death from
lung cancer in nickel workers could not be regarded as evidence of an
actual decrease, since the death rate from lung cancer had increased
substantially in England and Wales between 1938 and 1956. In fact, the
data indicated that the actual number of excess deaths from lung cancer in
Clydach nickel refinery workers was about the same in 1938-47 and 1948-56.

To evaluate the influence of occupation within the refinery on the
risk of death from lung or nasal cancer, the O/E ratios of deaths from
these causes were compared in process workers and nonprocess workers [37].
Doll's findings, shown in Table III-2, suggest that although process
workers were more likely to die from lung or nasal cancer than nonprocess

workers, the number of deaths from these causes was significantly greater in both groups of nickel workers than in the general population.

TABLE III-2

DEATHS FROM CANCERS OF THE NOSE AND LUNG IN PROCESS
AND NONPROCESS WORKERS AT A NICKEL REFINERY IN CLYDACH, WALES*

Work Category	Nasal Cancer			Lung Cancer		
	O	E	O/E**	O	E	O/E
Process workers	19	0.064	297	28	3.93	7.1
Nonprocess workers	10	0.084	119	20	5.95	3.4
Total	29	0.148	196	48	9.88	4.9

*Nasal cancer deaths recorded in two health districts from 1938 to 1947 and four health districts from 1948 to 1956; lung cancer deaths recorded in four health districts from 1948 to 1956
**O = observed deaths; E = expected deaths; O/E = ratio of observed to expected deaths; underscored values are statistically significant at the 0.05 level (P<0.05).

Adapted from Doll [37]

Since the procedures and criteria used to identify process and nonprocess workers were not reported, the study suggests, but does not clearly indicate, that both process and nonprocess workers at the Clydach nickel refinery had increased risks of death from lung and nasal cancer.

In 1958, Williams [38] reported the results of a microscopic examination of the lungs of five men who had been employed at the Clydach nickel refinery. The occupational histories and the date at death (where

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applicable) were given for each worker. In addition, the concentrations of nickel and arsenic in the lungs of 2 of the 5 workers were measured, and these values were compared with the average concentrations of nickel found in the lungs of 25 coal miners and 25 nonminers who had no known workplace exposure to nickel, and with the average concentrations of arsenic found in the lungs of 10 coal miners and 10 nonminers. Four of the 5 men with workplace exposure to nickel had worked in areas where they could have been exposed to nickel carbonyl, and 3 of the 4 had recently experienced "one mild, transitory attack of acute nickel carbonyl poisoning." One man who had an attack had been employed for 17 years and had worked only in the nickel sheds where nickel carbonyl was formed. The other 3 had worked in the wet-treatment plant, in the copper sheds, as gas producers, or as general laborers, but they had never been employed as furnace workers. The fifth person had not worked in the nickel sheds, but had been a furnace worker for 33 years.

Williams [38] found that the concentrations of nickel in the lungs from the two nickel workers were 90 and 120 ppm of dry tissue and that the average concentration of nickel in the lungs of 25 coal miners and 25 nonminers was below the limit of detectability of 5 ppm for nickel. In contrast, the average concentrations of arsenic in the lungs of the two nickel workers, the 10 coal miners, and 10 nonminers were all below the limit of detectability of 0.2 ppm for arsenic. Williams indicated that lung cancers were found in 4 of the 5 workers. Diffuse interstitial fibrosis was seen in the lungs of all five nickel workers. Squamous-cell metaplasia was found in the lungs of two workers who also had squamous-cell carcinoma, and alveolar-cell metaplasia was found in the lung of one

worker. The author concluded that bronchial squamous-cell metaplasia should not necessarily be considered a premalignant condition and that there were no pathologic changes observed that could be specifically associated with exposure to nickel.

In a book published in 1956, Goldblatt and Goldblatt [68] concluded that it was unlikely that exposure to arsenic was associated with the development of lung cancer and nasal cancer in nickel workers. The authors indicated that extensive exposure to arsenic dusts caused perforations of the nasal septum but was not associated with the development of cancers of the nose and ethmoid sinuses. Goldblatt and Goldblatt also indicated that there was no reported evidence of an increase in lung and nasal cancer in workers in other industries using sulfuric acid, although sulfuric acid containing oxides of arsenic had been used for many years in industries where exposure to dusts and fumes was prevalent. The authors did not indicate, however, if adequate epidemiologic studies of workers using arsenic-containing sulfuric acid had been conducted.

In a 1966 review of cancers of the respiratory system, Hueper [69] concluded that nickel, not arsenic, was the principal agent associated with lung cancer and nasal cancer in workers at the Clydach nickel refinery. Citing studies available at that time, he emphasized that not all nickel workers were exposed to arsenic, but that all were exposed to vapors (probably carbonyl), dusts, and fumes of nickel. Hueper also indicated that, according to available records, symptoms of arsenic poisoning and arsenic-related cancers at nonrespiratory sites were not evident in nickel workers.

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In 1970, Doll et al [39] reported an additional epidemiologic study designed to assess the risk of death from lung cancer and nasal cancer in Clydach nickel refinery workers. From company paysheets, workers employed at the refinery for at least 5 years between 1934 and 1949 were identified and included in the study; all but 27 (3.2%) of the 845 workers in the study were traced from their year of first employment until death or until January 1, 1967. Death certificates were obtained for all workers who died and the cause of death was classified according to the seventh revision of the World Health Organization (WHO) classification [70].

The workers were divided into six groups according to year of first employment and the number of years at risk from 1939 to 1966 was determined for each group. The expected number of deaths was estimated from the number of years at risk and the corresponding annual age-specific death rate for England and Wales. The observed and expected numbers of deaths were determined for nasal cancer, lung cancer, other cancers, all other causes, and all causes. Since age-specific death rates for nasal cancer were not available before 1950, the age-specific death rate for nasal cancer for 1950-1954 was used to estimate the expected number of nasal cancer deaths in nickel refinery workers between 1939 and 1950.

Doll et al [39] found that 482 (57%) of the 845 workers in the study had died before the beginning of 1967, 39 of them from nasal cancer and 113 from lung cancer. The number of workers, the number of years at risk, the numbers of observed and expected deaths, and the O/E ratios of deaths from several causes by year of first employment are shown in Table III-3. In workers first employed before 1925 the O/E ratio of deaths from nasal cancer averaged 364:1. In contrast, no deaths from nasal cancer were

identified in the 282 workers first employed between 1925 and 1944. The

O/E ratio of deaths from lung cancer averaged 7.5:1 in workers first

employed before 1925, decreased to 1.8:1 in workers first employed between

1925 and 1929, and to 1.1:1 in workers first employed between 1930 and

1944. The O/E ratio of deaths from causes other than cancer was 1.2:1 and

did not vary appreciably with year of first employment at the nickel

refinery. Doll et al indicated, however, that this ratio was probably not

excessive since the death rate in the part of Wales where the nickel

refinery was located was usually greater than that for all of England and

Wales.

TABLE III-3

DEATHS IN WORKERS AT A NICKEL REFINERY IN CLYDACH, WALES, AS OF JANUARY 1, 1967*

Year of First Employment	Number of Workers	Years at Risk	Cause of Death																
			Nasal Cancer			Lung Cancer			Other Cancers			Other Causes			All Causes		
			O	E	O/E	O	E	O/E	O	E	O/E	O	E	O/E	O	E	O/E
Before 1910	96	955.5	8	0.026	308	20	2.11	9.5	9	8.43	1.1	49	50.86	0.96	86	61.43	1.4
1910-1914	130	1,060.5	20	0.023	870	29	2.75	10.5	10	7.18	1.4	48	40.98	1.2	107	50.94	2.1
1915-1919	87	915.0	6	0.015	400	13	2.29	5.7	9	4.32	2.1	31	23.33	1.3	59	29.94	2.0
1920-1924	250	2,923.0	5	0.043	116	43	6.79	6.3	21	11.57	1.8	86	62.01	1.4	155	80.41	1.9
1925-1929	77	1,136.0	0	0.014	–	4	2.27	1.8	3	3.67	0.8	20	20.06	1.0	27	26.01	1.0
1930-1944	205	2,945.0	0	0.022	–	4	3.79	1.1	6	5.49	1.1	38	28.43	1.3	48	37.73	1.3
Before 1925	563	5,854.0	39	0.107	364	105	13.94	7.5	49	31.5	1.6	214	177.18	1.2	407	222.72	1.8
1925-1944	282	4,081.0	0	0.036	–	8	6.06	1.3	9	9.16	0.98	58	48.49	1.2	75	63.74	1.2
Total	845	9,935.0	39	0.143	273	113	20.00	5.7	58	40.66	1.4	272	225.67	1.2	482	286.46	1.7

*845 workers employed for at least 5 years, first employed on or before April 1944 and traced until January 1, 1967

Adapted from Doll et al [39]

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Doll et al [39] also determined that the risk of death from nasal cancer but not from lung cancer increased with the age at which the worker was first employed at the nickel refinery. In addition, the authors reported that the risk of death from lung cancer but not nasal cancer decreased as the length of time since 1925 increased. Doll et al reasoned that the risk of death from lung cancer appeared to decrease with time, since nickel refinery workers who smoked cigarettes may have died from lung cancer at an earlier age than cigarette smokers in the general population. Since smoking histories were not available for these workers, the hypothesis cannot be confirmed from this study.

The study by Doll et al [39] supports earlier findings [22,36] that suggested that the number of deaths from lung and nasal cancers had decreased substantially with the year of first employment at the Clydach nickel refinery, particularly for workers first employed after 1925. Doll et al did not attempt to identify the cancer-causing agents to which nickel refinery workers were exposed. In addition, the influence of occupation within the refinery on the increased risk of death from lung or nasal cancer was not determined, since it was considered impractical to obtain detailed occupational histories from all 845 men in the study. Since the decline in the risk of death from lung and nasal cancer had been both rapid and substantial, Doll et al concluded that the "results confirm the previous suggestion that the cancer hazard had been effectively eliminated by the beginning of 1925." As noted below, Doll et al [40] later revised their conclusions.

In 1976, Doll et al [40] updated the 1970 study [39] of deaths of workers at the Clydach nickel refinery. In the 1970 study, the authors

determined the number of deaths that occurred before January 1, 1967, in 845 workers employed for at least 5 years between 1934 and 1949. In the 1976 study [40], they determined the number of deaths that occurred before January 1, 1972, in 967 workers employed for at least 5 years between 1929 and 1949. The same methodology was used in both studies. Of the 967 workers in the 1976 study, all but 37 (3.8%) were traced until death or until the beginning of 1972. Doll et al reported that 689 of the workers in the study (71%) had died before the end of 1972, including 56 from nasal cancer and 145 from lung cancer. In addition, nasal cancer was listed as an associated cause of death on the death certificates of two workers; one worker was first employed at the refinery between 1920 and 1924 and the other between 1925 and 1929. The number of workers, the number of observed and expected deaths, and the O/E ratios of deaths from several causes by year of first employment at the refinery are shown in Table III-4.

Both studies by Doll and his coworkers [39,40] showed that the risks of death from nasal cancer and lung cancer have decreased substantially in Clydach nickel workers with year of first employment at the refinery. As shown in Tables III-3 and III-4, the number of deaths from nasal cancer increased from 39 in the 1970 study [39] to 56 in the 1976 study [40], but the O/E ratios of deaths from nasal cancer, 273:1 in the 1970 study and 252:1 in the 1976 study, were nearly the same. The number of deaths from lung cancer increased from 113 in the earlier study to 145 in the update. The O/E ratio of deaths from lung cancer for workers first employed before 1925 decreased slightly, from 7.5:1 in the 1970 study to 7.0:1 in the 1976 study. For workers first employed between 1925 and 1944, however, the O/E ratio of deaths from lung cancer was greater in the 1976 study. For

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TABLE III-4

DEATHS IN WORKERS AT A NICKEL REFINERY IN CLYDACH, WALES, AS OF JANUARY 1, 1972*

Year of First Employment	Number of Workers	Cause of Death														
		Nasal Cancer			Lung Cancer			Other Cancers			Other Causes			All Causes		
		O**	E	O/E	O	E	O/E	O	E	O/E	O	E	O/E	O	E	O/E
Before 1910	119	14	0.036	389	24	2.389	10.0	10	14.637	0.68	69	84.95	0.81	117	102.01	1.2
1910-1914	150	24	0.037	649	34	3.267	10.4	10	13.549	0.74	69	75.95	0.91	137	92.84	1.5
1915-1919	105	11	0.023	440	20	3.070	6.5	10	8.064	1.24	48	44.28	1.08	89	55.44	1.6
1920-1924	285	7(1)	0.071	99	50	9.642	5.2	27	20.902	1.29	125	115.63	1.08	209	146.25	1.4
1925-1929	103	0(1)	0.026	-	9	3.613	2.5	7	7.247	0.97	44	41.02	1.07	60	51.91	1.2
1930-1944	205	0	0.034	-	8	5.463	1.5	11	8.786	1.23	58	46.14	1.26	77	60.42	1.3
Before 1925	659	56(1)	0.170	329	128	18.367	7.0	57	57.152	1.00	311	320.85	0.97	552	396.54	1.4
1925-1944	308	0(1)	0.060	-	17	9.078	1.9	18	16.033	1.12	102	87.16	1.17	137	112.33	1.2
Total	967	56(2)	0.230	252	145	27.445	5.3	75	73.183	1.02	413	408.01	1.01	689	508.87	1.4

*967 workers employed for at least 5 years between 1929 and 1949 and traced until January 1, 1972
**Nasal cancer was given as "associated cause" of death in 2 additional cases, 1 for 1920-24 and 1 for 1925-29.

Adapted from Doll et al [40]

workers first employed between 1925 and 1929, the O/E ratio of deaths from lung cancer was 1.8:1 in the 1970 study and 2.5:1 in the 1976 study; the ratio was statistically significant in the 1976 study. In workers first employed between 1930 and 1944, the O/E ratio of deaths from lung cancer was 1.5:1 in the 1976 study compared to 1.1:1 in the 1970 study; this increase was not statistically significant. The O/E ratio of deaths from lung cancer for workers first employed between 1925 and 1944 was 1.3:1 in the 1970 study and 1.9:1 in the 1976 study; the ratio was statistically significant in the 1976 study.

By increasing the number of workers included in the study and by increasing the followup period by 6 years, Doll et al [40] found that the risk of death from lung cancer in workers first employed after 1925,

although greatly decreased, was still greater than that of the general population of England and Wales. Nasal cancer was not listed as the cause of death of any for the 308 workers first employed at the refinery between 1925 and 1944, although, for one worker, nasal cancer was listed as a contributing cause of death, with heart failure considered the primary cause.

Doll et al [40] concluded that the 1976 study "provides strong evidence that some element of risk persisted in this period," ie, that the risk of death from lung cancer was elevated in workers first employed at the Clydach nickel refinery after 1925.

(b)   Norway

In 1950, Loken [42] reported on three cases of lung cancer in workers employed at a nickel refinery in Kristiansand, Norway, where matte from nickel sulfide ore, originally from a Norwegian smelter and later from Canada, was processed [10]. The first case was that of a a 58-year-old man who had been employed at the refinery for 36 years and had worked in a roasting-kiln area. The second case was that of a 59-year-old man employed at the refinery for 22 years, first in shearing nickel metal and later as a shop foreman. Squamous-cell carcinomas of the lung without any associated pathologic lesions of significance were found on microscopic examinations of the lungs of both workers. The third case of lung cancer was reported in a 46-year-old man who had worked in the roasting-kiln area of the refinery for 10 years. The employee had left the nickel refinery after developing extensive nickel dermatitis and had worked at various jobs, usually in mechanical workshops, for 10 years prior to the diagnosis of lung cancer. Microscopic examination of his lungs revealed three

conditions: fibrous nodule and isolated asbestos bodies indicating pneumoconiosis, changes reportedly typical of Boeck's sarcoid, and squamous-cell carcinoma. Loken reported that the silica content in the lungs of this patient, 2.7 mg/g of dry tissue, was within normal limits, but the nickel content, 2.8 mg/g of dry tissue, was quite high, even though the patient had not been employed at the nickel refinery for 10 years. Since nickel was refined electrolytically at this plant, Loken's 1950 report was the first to suggest that respiratory cancer in nickel workers was not confined to workers employed in the Mond (carbonyl) process.

In 1973, Pedersen et al [43] conducted an epidemiologic study designed to assess the incidence of cancer of the respiratory organs in workers employed at the Kristiansand nickel refinery. They indicated that, particularly since 1950, major process changes have tended to reduce worker exposure to dusts and fumes, but these changes were not described. From company records, 1,916 male workers who were first employed at the refinery before 1961 and had been employed there for at least 3 years were identified. The date of birth, the dates on which employment began and terminated, and the length of employment in each department were listed in each worker's employment record. Workers employed in more than one department were classified by the department in which the longest time was spent, except that workers who had been employed for shorter periods in a process department were classified as process workers when their longest employment had been in departments that clearly entailed minimal exposure to nickel. The four work categories used by the authors were: roasting and smelting; electrolysis; other processes; and other. The "other" work group included office workers, general laborers, fitters, etc. The 1,916 workers

were traced in the Norwegian Cancer Registry and through national mortality statistics between 1953 and 1971. The observed number of deaths from all causes and the number of cases of cancer in the nose, larynx, lung, all respiratory organs, and all sites combined (except basal-cell carcinoma of the skin) were determined for each work category and by the year of first employment. The expected number of deaths from all causes and the expected number of cases of cancer in the sites mentioned above were determined for each worker in each year of observation between 1953 and 1971 using the appropriate age-, sex-, and time-specific incidence rates from the Norwegian Cancer Registry and from mortality rates for Norway. None of the workers were first employed between 1940 and 1945, since refinery operations were virtually discontinued during World War II. The year of and age at first employment at the refinery, the year of and age at diagnosis, and the interval between first exposure and diagnosis were determined for workers who developed cancers of the nose, larynx, and lungs.

Pedersen et al [43] reported that the incidence of cancer in the county where the nickel refinery was located was about 10% less for nearly all cancer sites than that in the rest of Norway. Because of the lower incidence of cancer in that county and the authors' belief that workers were healthier than the rest of the population, they determined only the O/E ratio of cases of cancer of the respiratory organs in each of the four work category groups. To facilitate comparison with other studies, the O/E ratios of deaths from all causes and the O/E ratios of cases of cancer in the sites mentioned above have been calculated from the available data [43] for workers in all work categories. The data, summarized in Table III-5,

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TABLE III-5

DEATH AND CASES OF RESPIRATORY CANCER IN WORKERS AT A NICKEL REFINERY
IN KRISTIANSAND, NORWAY*

Exposure Group	Number of Workers	Number of Deaths (all causes)			Cases of Cancer															
					Total			Nasal			Larynx			Lung			All Respiratory		
		O	E	O/E	O	E	O/E	O	E	O/E	O	E	O/E	O	E	O/E	O	E	O/E
Roasting and smelting	462	95	73.7	1.25	43	22.9	1.88	5	0.1	50.0	4	0.4	10.0	12	2.5	4.80	21	3.0	7.00
Electrolysis	609	139	108.5	1.28	59	32.7	1.80	6	0.2	30.0	0	0.5	-	26	3.6	7.22	32	4.3	7.44
Other processes	299	37	39.8	0.93	18	12.6	1.43	1	0.1	10.0	1	0.2	5.0	6	1.3	4.62	8	1.6	5.00
Other	546	74	79.7	0.93	22	24.5	0.90	2	0.1	20.0	0	0.3	-	4	2.7	1.48	6	3.1	1.94
Total	1916	345	303.7	1.14	142	92.7	1.53	14	0.3	28.0	5	1.4	3.6	48	10.1	4.75	67	12.0	5.58

*1,916 workers employed for at least 3 years, first employed before 1961 and traced from 1953 to 1971

Adapted from Pedersen et al [43]

show that an increased number of cases of cancer of the nose, of the larynx, of the lungs, of all respiratory organs, and of all sites combined were observed for all Kristiansand nickel refinery workers. The observed number of deaths or cases of cancer at all sites was not consistently greater than expected for all work categories, but the observed number of cancers of the nose, lungs, and all respiratory organs was greater than expected in each of the four work categories. Cases of cancer of the larynx were found only in workers in the roasting and smelting and other processes groups. Of the 67 cases of cancer of the respiratory organs, 30 occurred in 210 workers who were first employed before April 1940 and who were in either the roasting and smelting or the electrolysis groups. Sixteen cases of cancer of the respiratory organs were identified in the electrolysis group in 57 workers who had been employed at the refinery for

at least 15 years; the O/E ratios of cases in these workers were 250:1 for cancer of the nasal cavities (5 observed, 0.02 expected, P<0.05), 23.4:1 for cancer of the lungs (11 observed, 0.47 expected, P<0.05), and 4.2:1 for cancers in all sites combined (19 observed, 4.57 expected, P<0.05); and the O/E ratio of deaths from all causes was 2.1:1 (32 observed, 15.07 expected, P<0.05).

The O/E ratio of cases of cancer of the respiratory organs varied from 14.0:1 in workers first employed at the nickel refinery between 1910 and 1929 (16 observed, 1.14 expected, P<0.05) to 2.7:1 in those first employed between 1955 and 1960 (5 observed, 1.84 expected, P<0.05) [43]. The O/E ratio of cases of lung cancer varied from 10.4:1 in workers first employed before 1910 (10 observed, 0.96 expected, P<0.05) to 2.5:1 in those first employed between 1955 and 1960 (4 observed, 1.57 expected). In addition, 13 of the 14 cases of nasal cancer occurred in workers first employed before 1940, but four of the five cases of cancer of the larynx occurred in those first employed after 1945. Pedersen et al stressed, however, that the decline in the O/E ratio of cases of cancer of the respiratory organs with the year of first employment at the refinery could reflect the long latency period between exposure and development of cancer rather than an actual decrease in exposure to cancer-causing agents at the Kristiansand nickel refinery.

The data summarized in Table III-6 indicate that the interval between first employment at the nickel refinery and the diagnosis of lung cancer was shorter for those older workers first employed after 1945 [43]. In workers first employed before 1945 who developed lung cancer, the average age at first employment was about 30 years and the average interval between

first employment and the diagnosis of cancer was about 34 years. In workers first employed after 1945 who developed lung cancer, the average age at first employment was about 43 years and the average interval between first employment and the diagnosis of cancer was about 16 years. Pedersen et al were unable to find any evidence to suggest why the latent period was less for the 27 men first employed after 1945 who developed lung cancer. The occupational histories of 6 of these workers were reviewed, but there were no indications that any of them had been heavily exposed at the refinery, and two of the men had not been process workers. Three had worked on small farms before employment at the refinery; three were nonsmokers, and three were light smokers.

The study by Pedersen et al [43] showed that workers in all of the occupational groups at the Kristiansand nickel refinery, including nonprocess workers, had an increased risk of developing cancers of the respiratory organs, but that the risk was greatest in workers in the roasting and smelting group and in the electrolysis group. In addition, the risk of developing lung cancer was larger in the electrolysis group than it was in the roasting and smelting group, and even larger for electrolysis workers employed at the refinery for at least 15 years than it was in all electrolysis workers. Although exposure of electrolysis workers to nickel-containing dusts and fumes from roasting and smelting processes cannot be ruled out, this study suggests that exposure to agents in the electrorefining process may be associated with the development of cancer of the respiratory organs.

TABLE III-6

AGE AND EMPLOYMENT DATA OF WORKERS WHO DEVELOPED CANCER OF THE
RESPIRATORY ORGANS AT A NICKEL REFINERY IN KRISTIANSAND, NORWAY*

Year of Employment	No. of Cases	Age at Employment (years)		Duration of Employment (years)		Age at Diagnosis (years)		Latent Period (years)**	
		Mean	Range	Mean	Range	Mean	Range	Mean	Range
Lung cancer									
1910-1929	10	32	22-42	26.8	13-33	67.6	58-81	35.6	26-47
1930-1940	11	28.1	19-44	13.6	4-32	59.7	43-71	31.6	20-39
1945-1949	11	36.8	22-56	12.9	3-24	55.2	41-72	18.4	10-25
1950-1960	16	46.9	24-62	10.4	3-19	60.6	44-78	13.7	4-20
Nasal cancer									
1910-1929	6	28.2	23-39	30.0	23-42	65.0	52-79	36.8	26-49
1930-1949	8	40.6	28-54	18.3	7-33	68.4	55-79	27.8	18-36
Larynx cancer									
1936-1960	5	47.2	30-63	9	4-16	62.8	52-75	15.6	8-31

*Worker population same as in Table III-5
**Interval between start of employment and diagnosis of cancer

Adapted from Pedersen et al [43]

Information on the processes used to refine nickel, the dusts and
aerosols generated, and the concentrations of airborne nickel observed in
the last 5-6 years at various areas of the Kristiansand refinery was
provided by Wigstol (written communication, April 1977).

Until 1967, all nickel was refined in the following stages: crushing of the converter matte; roasting of the matte to form nickel-copper oxide; leaching with sulfuric acid to remove copper; drying, smelting, and casting of the residue to form nickel anodes; and electrorefining which included the removal of impurities such as iron, arsenic, copper, and cobalt. Since 1967, about 15% of the crushed matte has been refined by hydrochloric acid leaching to dissolve nickel and the resulting nickel chloride is solvent-extracted to remove impurities, crystallized, and oxidized. The nickel oxide formed is then reduced to metallic nickel. A new process, to be completed by 1980, includes the leaching of crushed matte with chlorine to selectively dissolve nickel, with the resulting solution used in electrolysis to produce pure metallic nickel. Part of this process has been operational since 1975; consequently, smelting has been eliminated.

Dusts in the roasting and smelting department have consisted of nickel sulfide or oxide with concentrations of airborne nickel averaging 0.5-0.8 mg/cu m (range 0.3-6.0) except in the casting area, where nickel levels were 0.1-0.2 mg/cu m. Nickel chloride and sulfate were predominant in the electrolytic tankhouse and purification areas. Concentrations of airborne nickel were at or below 0.1 mg/cu m in the tankhouse and 0.2-0.6 mg/cu m in the purification areas. In the production unit opened in 1967, nickel levels have averaged 0.1 mg/cu m (maximum 0.6). In the chlorine leaching plant, nickel concentrations generally have been below 0.01 mg/cu m (maximum 0.1). Information on the methods used to derive these results was not provided.

Recently, Pederson (written communication, November 1976) reported that three cases of kidney cancer in Kristiansand nickel refinery workers had been identified from the Cancer Registry of Norway. The first case, that of a 21-year-old woman who worked as a laboratory assistant at the refinery for five years, was diagnosed in 1961. In 1975, two cases of cancer of the kidney were identified in men who had worked "in various sections of the plant" for 20 and 23 years respectively, but who had terminated their employment 5 years earlier. The expected number of cases of kidney cancer in Kristiansand nickel refinery workers was not determined, but cancer of the kidney is rare in the general population of Norway. Between 1964 and 1966, the incidence rate of kidney cancer in Norway was 8.5/100,000/year for men and 5.3/100,000/year for women [71].

In 1976, Torjussen and Solberg [72] presented a preliminary study of microscopic changes in the nasal mucosa of workers at the Kristiansand nickel refinery. Biopsy samples of tissue from the mucosa of the middle turbinate from 92 nickel workers were compared with those from 37 people without any known exposure to nickel. The nickel workers were randomly chosen for inclusion in the study, but the procedures used to choose the control group were not reported. Information on age, duration of employment, and smoking habits was apparently obtained from these workers, but procedures used to match the group of nickel workers with the control group were not discussed. The samples were examined microscopically by a pathologist who did not know which ones were from the nickel workers or from the control group.

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Torjussen and Solberg [72] found inflammatory changes in all samples, but there were more changes, particularly leukocyte infiltration of the mucosa and keratinization and squamous metaplasia of the epithelium, in samples from nickel workers. Although the changes were not described, the authors reported that atypical epithelial changes were found in 17% of the samples from nickel workers, but none were found in samples from the control group. They noted that these changes were not related to age or smoking habits and were found only in workers employed at the refinery for more than 10 years.

This study [72] cannot be assessed adequately because the procedures used to select and match the nickel worker group and the control group and the criteria for the microscopic examination and classification of tissues were not discussed. The study does suggest, however, that microscopic examination of tissues may be useful for detecting malignant and premalignant lesions of the nose in workers exposed to airborne nickel.

Studies on concentrations of nickel in the plasma and urine of workers at the Kristiansand refinery are included in Chapter IV.

(c)   Canada

Deaths from cancer in workers at a nickel refinery in Port Colborne, Ontario [44], at a sinter plant in Copper Cliff, Ontario [45], and in four other occupational groups at the nickel smelter complex in Copper Cliff [46] have been studied by Sutherland. In addition, McEwan [56,57] has presented the findings of a sputum cytology screening program for workers formerly employed at the Copper Cliff sinter plant. Sutherland's 1959 epidemiologic study [44] of deaths from cancer in Port Colborne nickel refinery workers was updated by Inco in 1976 [41]. Inco has also provided

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information on the processes used to roast, smelt and refine nickel in Canada [23,41] that is useful in interpreting the results of these studies.

From 1921 to 1930, the Orford* process was used at the Port Colborne nickel refinery to separate nickel sulfides from copper sulfides [23]. The resulting nickel sulfides were leached with acid to remove the remaining copper, calcined to form nickel oxide, and then reduced by "fire-refining" to form nickel metal [18,23]. By the late 1920's, Dwight-Lloyd sintering machines were used to oxidize impure nickel sulfides and an electrolytic refinery was opened [23]. By 1938, electrorefining had almost completely replaced fire-refining. Sintering operations had ceased at Port Colborne by 1958, but calcining continued at a decreased rate until 1973 [23].

Additional information on the processes used at Port Colborne and a limited amount of environmental data were recently reported by Inco [41]. Between 1926 and 1958, impure nickel sulfides containing nickel subsulfide* were oxidized at Port Colborne in downdraft traveling-grate sintering machines at a temperature of about 1,650 C. The nickel subsulfide feed was mixed with about three times its weight in fine recirculated sinter and with about 2% of its weight in coke to form a feed with less than 6% sulfur. About 80% of the feed was recirculated until the product contained less than 0.5% sulfur. Large amounts of airborne dust were generated at the many locations where the nickel sinter was sized, transported, discharged, or recycled and blended with coke and fine nickel sinter. Recently, Inco reported that convection currents created by hot sintering machines and recirculating sinter were sufficient to suspend particles with diameters of less than 25 μm. Although some particles were captured by impingement, dust reportedly accumulated on horizontal surfaces at a rate

of about 1/8-1/4 inch/day until the angle of the dust pile became too steep and it became airborne again. The spread of dust through the sinter plant was not impeded, since the floors were made of open grating.

Between 1921 and 1973, refractory-lined, mechanically agitated calciner furnaces were used at Port Colborne to oxidize impure nickel subsulfide at temperatures of 600-1,200 C [41]. Inco indicated that calciner furnaces were probably less dusty than sinter furnaces since the oxidation temperature was lower and the area for gas-solid contact was smaller in calciner furnaces than in sinter furnaces. However, many workers were probably exposed to high concentrations of calciner furnace dust since manual labor was required to handle feed and product from calciner furnaces [41]. Although smaller amounts of the trace elements would normally be volatilized in the lower-temperature calciner furnaces than in the sinter furnaces, Inco indicated that large amounts of salt were added to the calciner furnace at the Port Colborne refinery and suggested that the so-called "chloridizing" atmosphere might have enhanced the volatilization of trace elements.

The processes used to refine nickel electrolytically at Port Colborne have not changed significantly since the refinery began operation, but only a limited amount of data on nickel exposures is available for electrolysis workers [41]. Recent measurements in two tankhouses at the Port Colborne electrolysis plant showed an average nickel concentration of 0.11 (range 0.022-0.254) mg/cu m for 14 high-volume samples. Concentrations of airborne nickel were determined by personal samples for three cementation* operators (mean 0.19, range 0.11-0.27 mg/cu m), one pressman (0.16 mg/cu m), one anode scrap washer (8.13 mg/cu m), and two tank cleaners

(<0.029 mg/cu m) [41]. In 1953, the Ontario Department of Health collected five high-volume samples in the Port Colborne sinter plant while it was being operated on a part-time basis. Concentrations of total airborne dust averaged 339.6 (range 61-1,075) mg/cu m. Chemical analyses of these dusts were not reported by Inco. One 1958 sample of process dust contained 52.1% nickel, 17.2% sulfur, 2.67% copper, 1.3% iron, 1.2% silicon dioxide, 0.05% lead, 0.32% arsenic, and varying amounts of other trace materials. No other exposure data for these workers are available.

In 1959, Sutherland [44] reported an epidemiologic study designed to assess the risk of death from several causes, including lung cancer and nasal cancer, in Port Colborne nickel refinery workers. This study was updated by Inco in 1976 [41]. In a review of company records, 2,355 men employed at the nickel refinery for at least 5 years between 1930 and 1957 were identified. Occupational histories were used to divide the workers into the eight exposure groups listed below:

(1) Furnace dust: Men who worked for least 5 years at converter, sinter, reducer, or anode furnaces.

(2) Other dust: Men who worked for at least 5 years in dusty operations other than furnace areas, including repairmen, machinists, laborers, and grinders.

(3) Mixed exposure/furnace dust: Men who worked for 3-5 years as furnace workers.

(4) Mixed exposure/other dust: Men who worked for 3-5 years in dusty occupations other than furnace work and for at least 2 years in other occupations at the refinery.

(5) Minimum dust exposure: Men who worked for less than 3 years as furnace workers or in other dusty occupations and for at least 2 years in another occupation at the refinery.

(6) Electrolysis: Men who worked for at least 5 years in the electrolysis department.

(7) Office: Men who worked for at least 5 years as office workers.

(8) Other: Men employed for at least 5 years in jobs such as yardmen or janitors but who did not work throughout the plant.

Information on deaths was compiled by reviewing company insurance records for workers and pensioners and by reviewing the registries of three nearby towns for deaths of former workers ineligible for pensions [44]. Incomplete information was supplemented by searching for death certificates from the Province of Ontario. The number of years at risk was determined for each 5-year period and 10-year age group within each exposure group. The expected number of deaths for each occupational group was determined by multiplying the number of years at risk in each 10-year age group and 5-year period by the corresponding age- and time-specific death rate for men in Ontario.

Sutherland [44] found that the 2,355 men accumulated a total of 42,637 years at risk, 32,342 while employed and 10,295 while on pension. During the study period, the average length of employment at the nickel refinery was 13.7 years, and the average number of years on pension was 4.4 years. The number of observed and expected deaths from lung cancer, nasal cancer, cancer in all sites combined (except Hodgkin's disease and leukemia), respiratory diseases, digestive diseases, and vascular lesions of the central nervous system (CNS) were determined for each exposure group. Since age-specific death rates for nasal cancer were not available in Ontario before 1950, the expected number of deaths for nasal cancer between 1930 and 1957 was based on the age-specific death rate for nasal cancer in Ontario from 1950 to 1957.

The O/E ratios of deaths in Port Colborne nickel refinery workers, summarized in Table III-7, indicate that the ratios were significantly higher than expected for nasal cancer, for lung cancer, and for cancer in all sites combined, but significantly lower than expected for vascular lesions of the CNS, for respiratory diseases, for digestive diseases, and for all causes of death. The number of observed and expected deaths and their ratios in each of the eight exposure groups, summarized in Table III-8, indicate that nearly all of the excess deaths from lung and nasal cancer occurred in the groups with exposure to furnace dust or to other dust in the refinery.

TABLE III-7

DEATHS IN WORKERS AT A NICKEL REFINERY IN PORT COLBORNE, ONTARIO,
1930-1957* AND 1930-1974**

Cause of Death	1930-1957			1930-1974		
	O	E	O/E	O	E	O/E
Malignant disease						
Nasal cancer	7	0.1886	37.12	24	0.47	51.06
Lung cancer	19	8.453	2.24	76	40.95	1.86
Larynx cancer	-	-	-	4	2.14	1.87
Stomach cancer	-	-	-	18	18.46	0.98
Pancreatic cancer	-	-	-	9	8.95	1.01
Gastrointestinal cancer	-	-	-	43	47.1	0.91
Bladder cancer	-	-	-	3	6.35	0.47
Hodgkin's disease and leukemia***	-	-	-	5	7.57	0.66
Nonmalignant disease						
Cerebrovascular disease	14	20.719	0.69	54	70.65	0.76
Cardiovascular disease	-	-	-	349	462.6	0.75
Respiratory disease	13	16.214	0.80	33	51.19	0.65
Digestive disease	9	16.072	0.56	23	37.89	0.61
Accidents and violence	-	-	-	55	69.36	0.79
Nasal and lung cancer	26	8.6416	3.01	100	41.42	2.41
Other cancer***	54	43.188	1.25	107	118.39	0.90
Other causes	165	256.746	0.64	563	694.54	0.90
All causes	245	308.35	0.79	770	854.35	0.90

*2,355 workers employed for at least 5 years and traced between 1930 and
1957; adapted from Sutherland [44]
**2,328 of the same workers, traced between 1930 and 1974; preliminary
results adapted from Inco [41]
***Includes Hodgkin's disease and leukemia for 1930-1974 but not for
1930-1957

TABLE III-8

DEATHS FROM CANCERS OF NOSE AND LUNG IN WORKERS
AT A NICKEL REFINERY IN PORT COLBORNE, ONTARIO*

Exposure Group	Number of Workers	Nasal Cancer			Lung Cancer		
		O	E	O/E	O	E	O/E
Furnace dust	292	1	0.0348	28.74	6	1.585	3.79
Other dust	296	0	0.0313	-	3	1.356	2.21
Mixed exposure/ furnace dust	257	4	0.0205	195.12	4	1.012	3.95
Mixed exposure/ other dust	476	1	0.0258	38.76	1	1.155	0.87
Minimum dust exposure	608	1	0.0332	30.12	4	1.519	2.63
Electrolysis	225	0	0.0210	-	1	0.949	1.05
Office	55	0	0.0067	-	0	0.261	-
Other	146	0	0.0153	-	0	0.617	-
Total	2355	7	0.1886	37.12	19	8.453	2.24

*Employed for at least 5 years and traced between 1930 and 1957

Adapted from Sutherland [44]

In addition, Sutherland [44] reported that the O/E ratios of deaths from all cancers combined were 1.7:1 for the furnace dust group (14 observed, 8.086 expected), 2.4:1 for the mixed exposure/furnace dust group (11 observed, 4.611 expected, P<0.05), and 1.9:1 for the electrolysis group (9 observed, 4.847 expected). The number of deaths from cancer in all nonrespiratory sites was not increased in the furnace dust and mixed exposure/furnace dust groups (10 observed, 10.045 expected). Sutherland identified a total of 25 deaths from cancer in Port Colborne nickel refinery workers classified in the furnace dust or mixed exposure/furnace dust groups; of these, ten were from cancer of the lungs, five from cancer of the nose, three from cancer of the stomach, two from cancer of the bowel, one each from cancer of the tonsil, nasopharynx, and prostate, one from a retroperitoneal sarcoma, and one from a glioma of the brain stem. The death from cancer of the nasopharynx may have been associated with exposure in the nickel refining process. The number of expected deaths from these causes were not reported, but these findings led Sutherland [44] to conclude that workers in the furnace dust and mixed exposure/furnace dust groups had increased risks of death from lung cancer and from nasal cancer, but not from nonrespiratory cancers.

Sutherland [44] also found that the O/E ratio of deaths from nonrespiratory cancers was 2.1:1 for workers in the electrolysis group (8 observed, 3.877 expected, P<0.05), although the risk of death from nasal cancer (none observed, 0.0211 expected) or lung cancer (1 observed, 0.949 expected) was not elevated. Nine deaths from cancer were identified in the electrolysis group: one from cancer of the lungs, one from cancer of the stomach, three from cancer of the bowel, three from cancer of the kidney,

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and one from a fibrosarcoma of the hip. Sutherland [44] therefore concluded that the increased risk of death from lung and nasal cancer in Port Colborne nickel refinery workers was limited to furnace workers.

The same study [44] indicated that 3 of the 225 workers originally classified in the electrolysis group died from cancer of the kidney. Since this type of cancer is relatively rare in the general population (between 1950 and 1969, the average death rate from cancer of the kidney in white men in the US, adjusted to the 1960 population, was 3.25/100,000 [73]), workers engaged in the electrolytic refining of nickel may also have an increased risk of developing cancer of the kidney.

Sutherland [44] found that the type of job held before 1930 had not been taken into account in classifying the Port Colborne nickel refinery workers into the eight exposure groups. The classification of workers into exposure groups was then revised for workers who died from lung cancer but not for the rest of the workers in the study. Since a revised number of expected deaths in each exposure group cannot be determined from Sutherland's data, the values reported for each exposure group in Table III-8 are inaccurate, but neither the degree of error nor its effects on the findings can be assessed. The manner in which workers were classified into exposure groups tended to favor the inclusion of workers who died from lung or nasal cancer in the mixed exposure/other dust or mixed exposure/furnace dust groups. For instance, a worker employed as a furnace worker for 4 years and as an electrolysis worker for 25 years would have been classified in the mixed exposure/furnace dust group. This was the first epidemiologic study to assess the risk of death from cancer of the respiratory organs in workers in different occupational or exposure groups

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in a nickel refinery. Because of methodologic problems, however, the study does not provide a complete basis for assessing the risk of death from nasal or lung cancer in various exposure groups.

In 1967, Mastromatteo [74] summarized the study by Sutherland [44] in a review of the effects on health associated with exposure to nickel in the workplace. On the basis of information available at that time, Mastromatteo concluded that "the epidemiological evidence from studies of workers engaged in nickel refining points to an association between the inhalation of freshly heated insoluble dust and/or fume and increased risk of respiratory-tract cancer."

Sutherland's 1959 epidemiologic study [44] was updated by Inco in 1976 [41]. Since 2,328 workers were included in the updated study, it appears that 27 of the 2,355 workers in the Sutherland study [44] were lost to followup (a loss of 1%, however, is probably unimportant). In the Sutherland study [44], deaths that occurred between 1930 and 1956 were identified. In the updated study [41], the period of follow-up was extended by 18 years to include deaths of workers that occurred between 1930 and 1974. The number of years at risk increased from 42,637 in the 1959 study to about 64,000 in the 1976 study.

The numbers of observed and expected deaths between 1930 and 1974 and the O/E ratios of deaths for Port Colborne nickel refinery workers from causes previously identified in the Sutherland study are also shown in Table III-7. The results of the updated study were considered by Inco to be preliminary [41]. The number of deaths from nasal cancer increased from 7 in the 1959 study to 24 in the 1976 study, and the O/E ratio of deaths from nasal cancer increased from 37.1:1 in the 1959 study to 51.1 in the

1976 study. The number of deaths from lung cancer increased from 19 in the 1959 study to 76 in the 1976 study; and the O/E ratio of deaths from lung cancer decreased slightly from 2.2:1 in the 1959 study to 1.9:1 in the 1976 study. The data in Table III-7 suggest that the slight decline in the risk of death from lung cancer is related to the increase in the number of expected deaths from lung cancer as the age of the workers increased.

Although deaths from cancer of the larynx were not reported in the 1959 study [44], four deaths from cancer of the larynx were identified in the updated study [41]; and the O/E ratio of deaths for cancer of the larynx was 1.9:1 in the updated study. The data presented in Table III-7 indicate that the number of observed and expected deaths from stomach cancer and from pancreatic cancer were nearly the same in the 1959 and 1976 studies. The O/E ratios of deaths from bladder cancer and from Hodgkin's disease and leukemia were lower than expected, but the numbers of both observed and expected deaths were small. In both the Sutherland study [44] and the updated study [41], the number of deaths from nonmalignant diseases was smaller than expected. Since those in the study were either actively working or on pensions, it is likely that fewer deaths from nonmalignant chronic diseases would occur in the workers than in the general population. Since the development of cancer has a long latency period, it was concluded in the Inco report [41] that a larger than expected number of cases of cancer of the respiratory organs will continue to occur in Port Colborne nickel refinery workers for some years.

Sutherland [44] reviewed in detail the occupational histories of workers at the Port Colborne nickel refinery who developed nasal cancer or lung cancer before November 1959. Seven of the 12 workers who had

developed nasal cancer and 19 of the 22 workers who had developed lung cancer were also included in Sutherland's 1959 epidemiologic study. The occupational histories of an additional 22 workers who had developed nasal cancer and 68 workers who had developed lung cancer were identified in a review of company records up to June 1976 and were recently reported by Inco [41]. The information in Tables XV-3 and XV-4 was derived from the latter report, and the cases originally reviewed by Sutherland [44] are marked with an asterisk. Sutherland's study suggested that the risk of death from lung and nasal cancer was greater in furnace workers than in other workers. In reviewing the occupational histories of the workers who developed nasal or lung cancer up to November 1959, Sutherland noted that 11 of the 12 workers with nasal cancer and 16 of the 22 workers with lung cancer had been employed as cupola furnace workers for at least 6 months or as sinter furnace workers for at least 3 years.

After reviewing these occupational histories, Sutherland [44] concluded that "mortality from respiratory cancer was most closely associated with cupola and sinter furnaces" and that "there was no clear evidence that employees about either the calciner or anode furnace carried an increased risk of sinus or lung cancer." He suggested that the risk of death from either nasal or lung cancer was increased in employees who worked 6 or more months near cupola furnaces, 3 or more years near sinter furnaces, or 5 or more years near calciner furnaces. His conclusion concerning calciner furnaces was based on data from Clydach and not on data from his own study.

Although he did not present the data, Sutherland [44] indicated that a spectrographic analysis of furnace fumes in 1953 showed no essential

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differences in the composition of fumes from calciner, sinter, and anode furnaces, and that arsenic was not detected in any of the samples. On the basis of his analysis of findings from the epidemiologic study, the occupational histories of workers who developed lung or nasal cancer, and the results of the spectrographic analysis of furnace fumes, Sutherland suggested that "perhaps the most important factor was that of 'dosage' or concentration of furnace dust in the air."

Inco reported that 55 of the 90 Port Colborne nickel refinery workers who developed lung cancer had been employed as calciner or sinter furnace workers for at least 1 year, and that 21 of the 35 remaining workers with lung cancer had been exposed to nickel from electrolysis operations [41]. The report indicated that these 21 cases of lung cancer were "not greater than the number of cases expected, based on Ontario mortality data," although the expected number of deaths or cases of lung cancer was not reported. Of the 36 workers who developed nasal cancer, 9 were exposed to nickel in electrolysis operations and only 4 of these 9 had worked on furnaces for as much as 1 year. Three of the nine workers had apparently not worked in furnace operations or in any other dusty job. It was suggested by Inco that the apparent increase in cases of nasal cancer in workers engaged in electrolysis operations might have been associated with unrecognized dust exposures due to job mobility, physical contamination of the tankhouse by dust from calcining operations, and certain dusty jobs associated with electrolytic purification and the handling of anode slimes* [41].

The data in Table XV-3 indicate that the length of employment at the nickel refinery for the 36 workers who developed nasal cancer averaged 25.5

years (SD=9.1, range 6.9-41.9), and that the number of years between first employment and the diagnosis of, or death from, nasal cancer averaged 32.8 years (SD=8.4, range 6.9-41.9) [41]. The data in Table XV-4 indicate that the length of employment at the nickel refinery for the 90 workers who developed lung cancer averaged 22.5 years (SD=8.3, range 5.4-37.7), and that the length of time between first employment and the diagnosis of, or death from, lung cancer averaged 33.0 years (SD=8.4, range 15-51).

According to Sutherland [44], Port Colborne nickel refinery workers exposed to dusts from cupola furnaces for more than 6 months, to dusts from sinter furnaces for more than 3 years, or to dusts from calciner furnaces for more than 5 years had an increased risk of developing nasal or lung cancer. The occupational histories of workers at the nickel refinery who developed cancer between 1930 and 1974 indicate, however, that increased risks of developing lung and nasal cancer may not be limited to workers exposed to dusts and fumes from cupola, sinter, or calciner furnaces, and that nickel refinery workers in all exposure groups may have an increased risk of developing lung or nasal cancer. Of the workers who developed cancer between 1930 and 1974, 8 (22%) of the 36 who developed nasal cancer, and 36 (40%) of the 90 who developed lung cancer had worked near cupola, sinter, and calciner furnaces combined for less than 6 months. According to the occupational histories presented in Tables XV-3 and XV-4, 6 (17%) of the 36 workers who developed nasal cancer were never employed as cupola, sinter, or calciner furnace workers. Most of the workers who developed nasal or lung cancer were employed in many positions at the nickel refinery, and thus were exposed to dusts and fumes from more than one process. None of the workers who developed lung or nasal cancer were

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employed only near the cupola, sinter, or calciner furnaces. However, one worker with nasal cancer (case 33) and 5 workers with lung cancer (cases 2, 4, 24, 43, 61) were employed only in nondusty occupations; one worker with nasal cancer (case 22) was employed only in electrolysis operations; another with nasal cancer (case 10) was employed only on the anode furnaces; and three workers with lung cancer (cases 13, 14, and 88) were employed only in other dusty occupations. If the 36 workers who developed nasal cancer are classified according to the occupation in the nickel refinery in which the longest time was spent, then 10 (29%) were sinter furnace workers, 9 (25%) were electrolysis workers, 6 (17%) were calciner furnace workers, 6 (17%) were in occupations that were not dusty, 2 (6%) were anode furnace workers, 2 (6%) were in occupations with exposure to other dusts, and 1 (3%) was a cupola furnace worker. If the 90 workers who developed lung cancer are classified according to the occupation at the nickel refinery in which the longest time was spent, then 21 (23%) were electrolysis workers, 18 (20%) were in occupations that were not dusty, 17 (19%) were in other dusty occupations, 15 (17%) were sinter furnace workers, 12 (13%) were calciner furnace workers, 5 (6%) were anode furnace workers, 1 (1%) had spent an equal amount of time as a calciner and as a sinter furnace worker, 1 (1%) had spent an equal amount of time as an electrolysis worker and in an occupation that was not dusty, and none were cupola furnace workers. The risks of developing nasal cancer and lung cancer by occupation or exposure group cannot be assessed for these workers since the expected number of cases of nasal and lung cancer in each exposure group was not provided in either report [44,41]. The data indicate, however, that all nickel refinery workers may have an increased risk.

The available data [41] are not adequate to estimate the concentrations of airborne nickel to which workers in various occupations at the Port Colborne nickel refinery may have been exposed. It appears, however, that the concentration of airborne nickel and other compounds · and the types of airborne nickel compounds to which workers were exposed varied in different operations at the refinery. Cupola furnace workers handled sulfides of nickel and copper. Sinter and calciner furnace workers were exposed to airborne nickel, including at least nickel subsulfide and nickel oxide at relatively high concentrations, to traces of other substances such as arsenic or coke, and to sulfur dioxide. Anode furnace workers were probably exposed to airborne nickel oxide, to traces of other elements, and possibly to airborne nickel metal. Electrorefining tanks contained nickel sulfate and boric acid until the 1940's, when nickel chloride was also added [23]. Mists of nickel salts and possibly nickel hydrides were formed above the tanks, their composition being dependent on operating conditions such as current density and temperature. At Port Colborne, electrolysis workers would have been exposed to other airborne compounds from auxiliary operations in the electrorefining area. These operations included the formation of secondary anodes from anode slimes, and the purification of electrolytic solutions including both the cementation of copper in which nickel powder was added and cobalt precipitation in which nickel carbonate was added [10]. Recently, a limited amount of electrorefining has been done at Port Colborne by the electrowinning* process [10] during which workers might be exposed to airborne nickel subsulfide.

Exposure to traces of arsenic and coke may have somewhat increased the risk of developing lung cancer for nickel refinery workers. In a

review of the epidemiologic literature on the association between occupation and the development of cancer, however, Cole and Goldman [75] indicated that workplace exposure to arsenic has not been associated with the development of nasal cancer in any occupational group. They indicated that an association between workplace exposure to coke and the development of nasal cancer had been suggested. but they did not consider this relationship to have been established. Therefore, the available epidemiologic data indicate that workplace exposure to airborne nickel has increased the risk of developing cancer of the respiratory organs, particularly cancers of the nose, in nickel refinery workers.

The risk of death from lung and nasal cancer in workers at a nickel smelter complex in Copper Cliff, Ontario, has also been studied by Sutherland [45,46]. According to Inco, pentlandite*, an ore containing nickel, has been processed at this complex since it opened in 1888 [41]. Originally, this sulfide ore was smelted at Copper Cliff by processes that included outdoor heap roasting, blast furnace smelting, and converting*. When supplies of high grade ores became depleted, beneficiation by froth flotation was introduced. In 1930, an ore concentrator and an Orford process plant were built and outdoor heap roasting was abandoned. In 1948, slow cooling was introduced as a replacement for the Orford process and acid leaching, and a new sintering plant was installed at Copper Cliff to replace the old unit at Port Colborne. Sintering continued for 15 years at Copper Cliff until 1962, when the conversion to fluid bed roasters, begun in 1960, was completed [23].

In November 1960, a single high-volume sample of total dust (82.1 cu m of air over a period of 40 hours) was collected in the Copper Cliff

sinter plant [41]. The concentration of total dust in the air was 46 mg/cu m. From 1950 to 1961, a series of 34 samples of the dust escaping the sinter plant through roof monitors showed that it was composed of 60.9% nickel (SD=15.4) and 4.2% copper (SD=2.9). These findings were corroborated in June 1976, when 10 settled dust samples were taken from the old sinter plant and analyzed. The samples contained 62.3% nickel (SD=10.3), 12.6% sulfur (SD=8.2), 3.2% copper (SD=1.5), 0.54% cobalt (SD=0.18), 0.132% arsenic (SD=0.15), and 21.2% other elements. No other quantitative data are available with which to estimate worker exposure at the Copper Cliff sinter plant. The Inco report [41] speculated that the concentrations of trace elements such as arsenic may have been greater in airborne dust than in settled dust. According to Inco, the temperatures used for the oxidization of nickel may revolatilize trace elements such as arsenic so that smaller airborne particles would tend to contain a greater amount of these trace elements than larger particles.

In 1969, Sutherland [45] reported an epidemiologic study designed to assess the risk of death from lung cancer in sinter furnace workers at the Copper Cliff nickel smelter complex. The sintering process and the furnaces used at Copper Cliff and at Port Colborne were essentially the same [41]. The company provided lists of persons employed at the sinter plant on May 1, 1952, May 1, 1956, and August 1, 1961; in addition, the company provided lists of persons employed as mechanics from 1954 to 1961 or as electricians from 1948 to 1961 who had been employed for the majority of their time at the sinter plant. Sutherland identified 212 men employed at the sinter plant from 6 months to 5 years, 128 men employed from 5 to 10 years, and 143 men employed for more than 10 years from these lists. Not

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all of the workers employed between 6 months and 5 years, however, were identified by this procedure, and Sutherland did not discuss the comparability of the group of 212 men included in the study to all men employed from 6 months to 5 years. Deaths in the 212 men employed from 6 months to 5 years and the 271 men employed for more than 5 years are therefore considered separately for this review. The dates of birth, dates and places of employment in the company, and dates and places of death, if known, were taken from company employment and insurance records. The number of deaths in all the workers in the study was determined from the company's life insurance records, and the causes of death and ages at death were taken from death certificates. Deaths of sinter plant workers from five causes were determined. These included: lung cancer; other cancer; vascular disease, including heart disease and cerebral hemorrhage; other diseases; and accidents, poisonings, and violence. The number of expected deaths for each category was determined from the corresponding age-, time-, and cause-specific death rates for men in Ontario.

Sutherland [45] found that all but one of the deaths from cancer occurred in workers employed at the sinter plant for at least 5 years. The number of deaths and the O/E ratios of deaths in all five categories for workers employed at the sinter plant for at least 5 years are shown in Table III-9.

TABLE III-9

DEATHS IN WORKERS EMPLOYED AT THE SINTER PLANT
IN COPPER CLIFF, ONTARIO*

Cause of Death	O	E	O/E
Lung cancer	6	0.55	10.91
Other cancer	1	1.64	0.61
Vascular disease	2	5.92	0.34
Other diseases	3	2.05	1.46
All diseases	12	10.16	1.18
Accidents, poisonings, violence	5	2.51	1.99
All causes	17	12.67	1.34

*271 workers employed for at least 5 years and traced between 1948 and June 1968

Adapted from Sutherland [45]

In sinter plant workers employed for at least 5 years, the O/E ratio of deaths from lung cancer was 10.9:1 [45]. The average interval between first exposure and diagnosis of, or death from, lung cancer was 15.5 years, and the shortest interval was 8.3 years for the seven workers in the study and two other workers not included in the study who were later found to have developed lung cancer. The one worker in the study who developed nasal cancer had been employed at the sinter plant for 14.3 years and there was an interval of 17.3 years between first employment and death. This

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death was listed in Table III-9 as a death from cancer in sites other than the lung. The O/E ratios of death from other diseases; from all diseases; from accidents, poisonings and violence; and from all causes were elevated in sinter plant workers [45], although none of the O/E ratios were statistically significant. Fewer deaths from cancer in other sites and from vascular diseases occurred than were expected, but these ratios were not statistically significant either. Because of the length of time the sinter furnaces were used at Copper Cliff and the length of the followup period in this study, the longest possible interval of employment in the sinter plant was 15 years, and the longest possible interval between first exposure and death was 20 years.

The one death from nasal cancer should have been compared to an expected number of deaths from nasal cancer, rather than to the expected number of deaths from cancer in all sites combined, particularly since nasal cancer occurs rarely in the general population. Furthermore, the number of deaths in the 483 sinter plant workers in the study may have been underestimated, since deaths in former workers ineligible for pensions were not identified.

Sutherland [45] did not indicate the extent to which these workers were exposed to fume or dust from sinter furnaces and did not attempt to identify the cancer-causing agents to which these workers may have been exposed. The group was small, and the average duration of exposure and the interval between first exposure and death were short for an epidemiologic study of cancer, but the study nevertheless makes it clear that workers exposed to dust and fume from sinter furnaces where impure nickel sulfides were oxidized had an increased risk of death from lung cancer.

McEwan [56,57] described a monitoring program designed to identify cases of lung cancer in workers formerly employed at the Copper Cliff sinter plant. Chest X-ray and sputum cytology monitoring programs were described, and the findings of the sputum cytology program in 1973, 1974 [56,57], and 1975 [56] were presented. Four cases of lung cancer in former sinter plant workers who were still with the company were found by chest X-ray examinations conducted in 1969, 1970, and 1972 [56]. The chest X-ray program was then expanded, and after 1972, postero-anterior and lateral X-rays were taken every 6 months. McEwan [56] indicated that X-ray monitoring programs had not improved lung cancer survival rates, so a sputum cytology monitoring program was initiated to identify cases of lung cancer at the in situ or early invasive stage when medical intervention was more likely to be successful. Former sinter plant workers living in the area who were no longer employed by the company and workers who had worked in the sinter plant for short periods, eg, repairmen and electricians, were also included in the program after 1972. Employment histories were obtained from the company and a questionnaire which included inquiries on smoking habits and recent respiratory symptoms or illnesses was completed for each former sinter worker in the program [56]. All slides were reviewed by at least two persons, and slides with abnormal cytology were reviewed by a cytopathologist who considered that malignant cells "may be desquamated from a lesion that is still intraepithelial and may remain so for a period of time, occasionally measured in years." Workers with sputum samples having evidence of at least moderate dysplasia were sent to a physician for a more thorough examination of the respiratory tract, including chest X-rays and bronchoscopy. If no lesion was found,

bronchoscopy with multiple brushings and biopsies were repeated at 3-month intervals until a lesion was located.

The initial results of the 1973, 1974, and 1975 sputum cytology screening programs are shown in Table III-10 [56]. The most severe findings from each sample are reported. McEwan reported that many of the workers took part in all three surveys, although some workers were added and others did not participate in subsequent years. Workers with a diagnosis of lung cancer, based on earlier sputum cytology samples, were not included in the results of surveys in subsequent years.

The findings reported by McEwan [56,57] suggest that cigarette smoking is also associated with the development of abnormal sputum cytology in former sinter plant workers. Malignant cells were found in the sputum of smokers and former smokers, but nothing exceeding severe dysplasia was found in the sputum of any nonsmoker. According to McEwan, malignant cells were found in the sputum of 11 of the 412 former sinter plant workers examined between 1973 and 1975. Of these 11 workers, 4 had successful lobectomies, 2 had successful pneumonectomies, and 1 died following surgery; tumors had not yet been found in 4 workers when the study concluded, 1 of whom refused further treatment. All of the lung tumors identified were squamous-cell carcinomas at an early invasive stage, and only one had spread beyond the operated area.

Because the relevant data were not presented, the possible association of abnormal sputum cytology with duration of exposure at the sinter plant, the possible synergistic relationship between cigarette smoking and dust exposure in the sinter plant, and changes in sputum cytology in workers in each successive survey cannot be ascertained from

TABLE III-10

SPUTUM CYTOLOGY IN FORMER WORKERS AT THE SINTER PLANT
IN COPPER CLIFF, ONTARIO

Year and Group	Findings*						
	Malig-nancy	Severe Dysplasia	Moderate Dysplasia	Mild Dysplasia	Nega-tive	Unsatis-factory	Total
1973							
Smokers	4	2	7	33	32	0	78
Former Smokers**	0	1	4	10	5	1	21
Nonsmokers***	0	0	0	5	4	1	10
Total	4	3	11	48	41	2	109
1974							
Smokers	4	4	11	28	96	6	149
Former smokers**	1	0	2	8	17	5	33
Nonsmokers***	0	0	1	7	30	1	39
Total	5	4	14	43	143	12	221
1975							
Smokers	0	7	32	55	94	12	200
Former Smokers**	0	3	9	13	27	8	60
Nonsmokers***	0	3	5	10	13	10	41
Total	0	13	46	78	134	30	301

* 1973--most severe finding from 12 slides, 4 from each of 3 samples;
  1974, 1975--most severe finding from 5 slides of the blended 3-day sample
**Have not smoked in 10 years
***Includes pipe and cigar smokers

Adapted from McEwan [56,57]

these reports [56,57]. McEwan's study nevertheless suggests the value of a sputum cytology screening program for the detection of lung tumors at an early stage of development in groups with an increased risk of developing lung cancer.

Downdraft traveling-grate sintering machines similar to those used at Copper Cliff were also used at nickel sinter plants in Port Colborne, Coniston, and Falconbridge, Ontario [41]. In the sintering process used at Port Colborne and Copper Cliff, impure nickel sulfides were oxidized at temperatures of about 1,650 C. The sintering process was used at an earlier stage in the refining process at the plants in Coniston and Falconbridge. In these plants, about one-half of the sulfur was removed from the nickel ore or concentrate at temperatures of 1,000-1,100 C. The sintering plant at Coniston, which operated from 1914 to 1972, was dusty, but it was considered by Inco to be less dusty than the sintering plants at Port Colborne and Copper Cliff. The discharge end of the sintering machine was particularly dusty, and the few men working there always wore dust masks [41]. The area where flue dust from the smelter was dumped into receiving lines was also quite dusty. More efficient dust-collecting equipment was installed throughout the Coniston plant between 1968 and 1969. After 1968, the mixed feed of limestone, flue dust, fine ore, and ore concentrates was pelletized, and fine ore was no longer used. From an analysis of high-volume dust samples, Inco concluded that the total dust concentrations at the Coniston sintering plant were 5-125 mg/cu m even after improvements in ventilation and processes were instituted in 1968-1969.

In June 1976, analysis of eight samples of settled dust removed from horizontal surfaces in the Coniston sinter plant showed that it was about 6% nickel, 2% copper, 0.026% arsenic, and 33% sulfur [41]. Since improvements in working conditions were made in 1968-1969, Inco thought it reasonable to assume that concentrations of airborne nickel of at least 3-5 mg/cu m were common at the Coniston sinter plant throughout the first 50 years of its operation. Samples of settled dust from the the Port Colborne and Copper Cliff sinter plants were about 50-60% nickel. The nearly tenfold difference in the percentage of nickel in the settled-dust samples was related to the percentage of nickel in the feed to the sintering machines. The nickel concentrate used as feed in the Coniston sinter plant was about 5-15% nickel, while the impure nickel sulfide used as feed at the Port Colborne and Copper Cliff sinter plants was about 75% nickel. Inco claimed that no cases of nasal cancer have been identified and that the incidence of cancer of the respiratory organs has not been excessive in workers at the Coniston or Falconbridge sinter plants [41]. No data, however, were presented.

In 1971, an epidemiologic study by Sutherland of workers in several departments at the Copper Cliff nickel smelter complex was reported [46]. About 800 workers who had been employed in the complex for at least 5 years at the end of 1950 were selected by the company. About 200 workers were selected from each of the following four areas: converter furnace department, mill and separation departments, the copper refinery division, and an underground nickel mine. These groups were apparently chosen because they were generally exposed to lower concentrations of dust and fume than those who worked at the Copper Cliff sinter plant. Sutherland

indicated that exposure to sulfur dioxide and to metal dust and fumes was greatest in the converter furnace department, less in the mill and separation departments, still less in the underground mine, and least in the copper refinery division. Only 831 of the 842 workers selected by the company were included in the study since Sutherland considered the occupational histories of 11 workers to be inadequate. Although the study divided the workers into 12 groups, they are combined in this review into the five groups listed below:

(1) Converter furnace: Men who worked for at least 5 years in the converter furnace department.

(2) Mill and separation: Men who worked for at least 5 years in the mill and separation department.

(3) Copper refinery division: Men who worked for at least 5 years as mechanical, yard, transport, or tank-house workers in the copper refinery division.

(4) Underground mine: Men who worked for at least 5 years in an underground nickel mine.

(5) Mixed: Men who worked for at least 5 years at the nickel smelter complex, but who worked in one of departments listed above for less than 5 years. This group includes Sutherland's other eight exposure groups.

Deaths of workers and pensioners were identified by reviewing the company's life insurance records for 1950-1967, and the age at death and cause of death were taken from death certificates. The expected number of deaths in each group was determined from age-, time-, and cause-specific death rates for men in Ontario by procedures similar to those used in

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earlier studies by Sutherland [45,44]. By the end of the study period, the 831 men in the cohort had accumulated a total of 13,537 years at risk, 12,141 while employed and 1,396 while on pension. During the period of this study, the average length of employment for the workers was 14.6 years and the average time from the start of the study period until death or the end of the study period was 16.3 years.

The number of years at risk, the numbers of observed and expected deaths, the O/E ratios of deaths from lung cancer, all other cancers, other respiratory diseases, and all causes of death in each of the five exposure groups are listed in Table III-11 [46]. The number of deaths from all causes combined and from all cancers other than lung cancer were slightly less than expected, and the number of deaths from lung cancer and from other respiratory diseases was slightly greater than expected [46]. The O/E ratios of deaths in all exposure groups combined were 1.2:1 for lung cancer but the ratio was not statistically significant and the deaths did not appear to to be concentrated in any of the exposure groups. The O/E ratio of deaths from other respiratory diseases of 2.5:1 in converter furnace workers was the only statistically significant ratio found. The lack of significant findings in this study is probably related primarily to the small number of deaths expected in each of the exposure groups.

Sutherland did not comment on these results or draw any conclusions from this study [46]. Since the procedures used to select the workers were not discussed, it is not evident whether the group of workers included in the study was a random sample. Since deaths of workers in the study were identified from the company's life insurance records, deaths of former workers ineligible for pensions were not included. The study was limited

to workers employed in 1950, so the duration of observation for many of the workers may have been quite short, particularly for an epidemiologic study of deaths from cancer. However, the number of deaths from lung cancer and from other respiratory diseases was slightly greater than expected in Copper Cliff workers who were included in this study.

TABLE III-11

DEATHS IN WORKERS AT NICKEL SMELTER IN COPPER CLIFF, ONTARIO*

Exposure Group	Years at Risk	Lung Cancer			Other Cancers			Other Respiratory Diseases			All Causes		
		O	E	O/E	O	E	O/E	O	E	O/E	O	E	O/E
Converter furnace	3,609	3	2.54	1.18	5	6.99	0.72	6	2.36	2.54	50	49.71	1.01
Milling and separation	1,438	1	0.79	1.27	2	2.29	0.87	1	0.78	1.28	12	16.55	0.73
Copper refinery division**	3,134	4	2.24	1.79	5	6.28	0.80	0	2.11	0	35	44.69	0.78
Underground	3,251	3	2.24	1.34	6	6.13	0.98	2	2.05	0.98	40	43.74	0.91
Mixed exposure	2,106	0	1.24	-	3	3.41	0.88	1	-1.11	0.86	20	24.74	0.81
Total	13,537	11	9.05	1.22	21	25.10	0.84	10	8.41	1.19	157	179.43	0.88

*831 workers employed at least 5 years and traced between 1950 and 1967
**Tank house, mechanical, and yard workers

Adapted from reference 46

Environmental data for past exposures were not available for these workers. Recent data are available for some areas, but since new equipment had been installed in these areas, environmental concentrations of dust and fume were probably greater in earlier years [41]. Dust measurements in the Sudbury district where the Copper Cliff smelter complex is located indicate

that underground miners were recently exposed to nickel at concentrations of 0.006-0.04 mg/cu m using a personal sampler with a cyclone. High-volume samples were taken recently, and they showed concentrations of airborne nickel to be 0.17-15.3 mg/cu m in the matte separation area, undetectable to 2.8 mg/cu m in the mill area, and 0.03-0.2 mg/cu m in the converter furnace area [41]. No other environmental data were reported. It appears, however, that all four groups were exposed to lower concentrations of airborne nickel dust and fume than sinter furnace workers.

(d)   United States

In 1976, Enterline [47] reported to NIOSH on an epidemiologic study of a group of retired workers from a plant in Huntington, West Virginia, where nickel alloys are produced. Deaths that occurred before the end of 1971 were identified in company records for a group of 815 men who retired from the plant between 1941 and 1970. Before 1955, workers could retire either at 65 with a service pension or at any age with a disability pension.   Starting in 1955, an optional early-service pension plan allowed workers to retire at the age of 60. Of the 815 retired workers over 60 years of age, 515 had retired with a service pension, and 300 had retired with a disability pension and had lived to at least age 60. Enterline indicated that the 190 salaried employees included clerical workers, inspectors, foremen, engineers, laboratory workers, and management personnel, all of whom probably had received less exposure to nickel than the 629 workers paid by the hour. The average length of employment was about 30 years for salaried workers and 27 years for hourly workers.

From company records, Enterline [47] determined that 328 of the 815 pensioners (40%) had died before the end of 1971. Death certificates were

obtained for all but two of these workers, and deaths were classified by cause according to the seventh revision of the WHO classification [70].

The expected numbers of deaths from several causes were estimated using age- and time-specific death rates for white men in the United States. The numbers of observed and expected deaths and the O/E ratios of deaths from several causes in both salaried employees and hourly workers are shown in Table III-12.

The O/E ratios of deaths from nasal cancer and lung cancer were increased for retired hourly workers but not for retired salaried workers [47]. For retired hourly workers, the O/E ratio of deaths from nasal cancer was 15.4:1. Of two deaths from cancer of the ethmoid sinuses, both occurred in the 1960's. One worker who died from nasal cancer was a 62-year-old man who had been a bricklayer and had retired after 20 years of employment in 1948 on a disability pension because he had heart disease. The other worker who died from nasal cancer was a 62-year-old man who had, for 27 years, until shortly before his death, been a laborer in a wide variety of jobs, none of which, according to Enterline, appeared to involve unusual exposure to nickel. The O/E ratio of deaths from lung cancer was higher in retired hourly workers than in retired salaried workers, but neither ratio was statistically significant.

In addition, Enterline [47] found that the O/E ratios of deaths from several causes were greater in retired workers who died between the ages of 60 and 64 than in those who died at the age of 65 or over. In retired workers who died between the ages of 60 and 64, the O/E ratios were 3.1:1 for lung cancer (8 observed, 2.6 expected, P<0.05), 2.0:1 for all causes of cancer (18 observed, 8.8 expected, P <0.05), and 1.3:1 for heart disease

TABLE III-12

**DEATHS IN WORKERS RETIRED FROM A NICKEL ALLOY PLANT
IN HUNTINGTON, WEST VIRGINIA***

Cause of Death	ICD Number**	Hourly Workers			Salaried Workers			All Retired Workers		
		O	E	O/E	O	E	O/E	O	E	O/E
Cancer of the nose	160	2	0.13	15.38	-	-	-	-	-	-
Cancer of the lung, bronchus, trachea, and pleura	162-163	14	10.1	1.39	3	2.8	1.07	17	12.9	1.32
Cancer of the digestive system	150-159	14	16.0	0.88	5	4.5	1.11	19	20.5	0.93
Other cancer	-	15	17.6	0.85	7	5.2	1.35	24	22.8	1.05
Other diseases of the respiratory system	470-527	8	15.1	0.53	2	4.3	0.47	10	19.4	0.52
Cerebral vascular lesions	330-334	35	28.2	1.24	10	8.1	1.23	45	36.3	1.24
Coronary heart disease	420	92	96.4	0.95	37	27.6	1.34	129	124.0	1.04
Other heart disease	-	19	22.9	0.83	7	6.4	1.09	26	29.3	0.89
Other causes	-	47	48.1	0.98	9	13.9	0.65	56	62.0	0.90
All cancer	140-205	47	43.9	1.07	15	12.5	1.20	62	56.4	1.09
All heart disease	400-443	111	119.3	0.93	44	34.0	1.29	155	153.3	1.01
All causes	-	248	254.6	0.97	80	72.8	1.10	328	327.4	1.00

*815 workers, including 190 salaried employees and 625 employees paid by the hour who retired between 1941 and 1970 and who died before the end of 1971
**Classification number from the seventh revision of the WHO classification of causes of death [70]

Adapted from Enterline [47]

(26 observed, 20.4 expected). In retired workers who died at the age of 65

or over, the O/E ratios of deaths were 0.87:1 for lung cancer (9 observed,

10.3 expected), 0.92:1 for all causes of cancer (44 observed, 47.6

expected), and 0.97:1 for heart disease (129 observed, 132.9 expected).

The reason for this dramatic difference in the O/E ratios of deaths for the

two age groups is not clear. The group of retirees between the ages of 60

and 64 may have contained more disabled workers than did the group of those

aged 65 or over, or the pension records might have been inconsistent or

incomplete.

Although it is difficult to interpret the results of this preliminary

study [47], the two deaths from nasal cancer and the increased, though not

statistically significant, O/E ratio of deaths from lung cancer in retired

hourly workers suggest that these workers at the Huntington nickel alloy

plant may have had an increased risk of death from cancer of the

respiratory organs. Enterline suggested that differences in the O/E ratios

of deaths from heart disease in salaried and hourly workers may be related

to differences in the degree of physical activity required in their jobs.

A more comprehensive epidemiologic study of all workers at the nickel alloy

plant is needed to determine conclusively if these workers had an increased

risk of developing cancer of the respiratory organs.

A preliminary study of deaths in workers and pensioners at the

Huntington nickel alloy plant was reported by Inco in 1976 [41]. The study

included men who were on the company payroll on January 1, 1948, and who

had been employed at the plant for at least one year. There were 1,852

workers in the cohort, and in 1948, 1,634 were actively employed (88%), 16

were receiving service pensions (1%), 126 were receiving disability

pensions (7%) and 76 had been laid off and later recalled to active employment (4%). About 10% of the workers had terminated employment for reasons other than death or retirement before the end of 1974. The number of years at risk for the these workers was included until employment was ended, but accounted for only 3% of the total of nearly 40,000 years at risk for all workers between 1948 and 1975. Of the 1,852 workers, 1,132 were first employed between 1922 and 1939 (61%), and 720 were first employed between 1940 and 1947 (39%). In 1948, the average age of the cohort was 43 years.

Workers were classified into exposure groups according to their complete work histories since the plant opened in 1922 [41]. Workers were included in a pure exposure group unless they had been employed for more than one year in another exposure area. In this review, the four mixed exposure groups from the original report have been combined into one group. The exposure groups are listed below:

(1) Furnace: Men who worked in areas where nickel was melted and cast, or near the calciner furnaces (between 1922 and 1948, nickel-copper sulfide was converted to nickel-copper oxide in calciner furnaces).

(2) Pickling: Men who worked in areas where nickel metal bars were dipped in acid baths to remove nickel oxide formed on the surface during heating and cooling and to give the bar a clean finish.

(3) Grinding dust: Men who worked in areas where nickel oxide was removed from the surface of a bar of nickel metal by grinding, chipping, or polishing.

(4)   Office: Men who worked in offices, laboratories, or in the yard.

(5)   Mixed: Men who worked in more than one exposure group for more than one year.

Workers and pensioners in the study who died between January 1, 1948, and December 31, 1974, were identified by reviewing company records [41]. Death certificates were obtained, and the causes of death were classified according to the WHO classification [70]. The number of years at risk was determined for workers in each exposure group, each 5-year duration of exposure group, each 10-year age group, and each 5-year period. To determine the expected number of deaths in each group, the number of years at risk was multiplied by the appropriate age- and time-specific death rate for white men in the US between 1949 and 1970. Of the 1,852 workers, 608 had died before the end of 1974 (33%), the average age at death was 67 years, and the average interval between their first employment and death was 34 years [41]. The average age of the 1,244 workers in the study who were alive at the end of the study period was 64 years, and the average interval between first employment at the nickel plant and the end of the study period was 38 years.

The number of observed and expected deaths and the O/E ratio of deaths from cancer of the respiratory organs, all sites of cancer, and all causes for each of the five exposure groups are shown in Table III-13 [41]. For all of the nickel alloy plant workers in the study, the O/E ratio of deaths was 0.75:1 for all causes combined, 0.73:1 for all causes other than cancer (483 observed, 644.54 expected P<0.05), 0.05), 0.88:1 for cancer in all sites combined, and 0.97:1 for cancer of the respiratory organs [41].

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TABLE III-13

DEATHS IN WORKERS AT A NICKEL ALLOY PLANT IN HUNTINGTON, WEST VIRGINIA*

Exposure Group	Number of Workers	Cancer of Respiratory Organs			All Cancer			All Causes		
		O	E	O/E	O	E	O/E	O	E	O/E
Furnace dust	118	3	2.47	1.21	12	8.37	1.43	52	46.55	1.12
1-19 yr	-	0	0.49	-	2	2.05	0.98	11	12.94	0.85
20 yr or more	-	3	1.98	1.51	10	6.32	1.58	41	33.61	1.22
Pickling	225	5	5.62	0.89	11	20.31	0.54	92	116.77	0.79
1-19 yr	-	0	0.95	-	3	4.21	0.71	26	27.09	0.96
20 yr or more	-	5	4.67	1.07	8	16.10	0.50	66	89.68	0.74
Grinding dust	139	3	4.00	0.75	16	14.99	1.07	73	87.32	0.84
1-19 yr	-	0	0.66	-	2	2.85	0.70	17	18.06	0.94
20 yr or more	-	3	3.34	0.90	14	12.14	1.15	56	69.26	0.81
Office	110	0	2.10	-	2	7.27	0.28	30	41.32	0.73
1-19 yr	-	0	0.21	-	0	0.82	-	4	5.40	0.74
20 yr or more	-	0	1.89	-	2	6.45	0.31	26	35.92	0.72
Mixed	1,260	29	26.89	1.08	84	91.02	0.92	361	514.54	0.70
1-19 yr	-	2	4.24	0.47	17	18.16	0.94	87	120.48	0.72
20 yr or more	-	27	22.65	1.19	67	72.86	0.92	274	396.06	0.69
Total	1,852	40	41.08	0.97	125	141.96	0.88	608	806.50	0.75
1-19 yr	-	2	6.55	0.81	24	28.09	0.85	145	183.97	0.79
20 yr or more	-	38	34.53	1.10	101	113.87	0.89	463	622.53	0.74

*1,852 workers employed in 1948 and traced between 1948 and 1974

Adapted from Inco [41]

According to Inco, the decrease in the risk of death from all causes other than cancer in nickel alloy plant workers may have been related to selective factors for diseases such as heart disease that favor the working population over the total population. In workers in the furnace dust exposure group, the O/E ratios of deaths from all causes, from all causes of cancer, and from cancer of the respiratory organs were slightly increased but not statistically significant; the O/E ratios were 1.1:1 for all causes, 1.4:1 for all sites of cancer, and 1.2:1 for cancer of the respiratory organs. Deaths from cancer of the respiratory organs do not account for all of the slight excess of deaths from cancer in the furnace dust group, since the O/E ratio of deaths from nonrespiratory cancers was 1.5:1. In workers in the mixed exposure group who were employed for more than 20 years, the O/E ratio of deaths from cancer of the respiratory organs was 1.2:1, slightly elevated. In none of the exposure groups, however, did the O/E ratio of deaths from cancer of the respiratory organs differ significantly from 1.0.

Inco noted that two of the deaths from cancer of the respiratory organs were caused by nasal cancer [41] (apparently these deaths were also identified in an epidemiologic study of deaths by Enterline [47]). One of the workers was in the furnace dust exposure group, the other in the mixed exposure group. Inco suggested that both deaths from nasal cancer were related to exposure resulting from calcining operations, which were terminated at Huntington in 1948 [41]. A third worker died from nasal cancer in 1976. Inco reported that this worker apparently was not exposed to dusts and fumes from calciner furnaces and contended that this case of nasal cancer was unrelated to workplace exposure.

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This preliminary epidemiologic study [41] does not conclusively determine whether nickel alloy plant workers have an increased risk of death from cancer of the respiratory organs or from cancer in other organs. Within each exposure group, the numbers of both observed and expected deaths from cancer of the respiratory organs were too small to permit a reliable estimate of the O/E ratio of deaths. Two of the three deaths from nasal cancer were probably related to work in areas near the calciner furnaces. Furthermore, since deaths from nasal cancer are quite rare in the general population (between 1950 and 1969, the death rate from nasal cancer in white men in the United States, adjusted to the age distribution of the 1960 population, was 0.43/100,000 [76]), the third death from nasal cancer in the cohort of 1,852 nickel alloy plant workers also may have been related to workplace exposure, and thus may not represent the normal incidence of death from nasal cancer in the general population.

The death rate from lung cancer is not uniform throughout the United States. Between 1950 and 1969, the death rate from lung cancer in white men adjusted to the age distribution of the US population in 1960 was 37.98/100,000 for the United States, 35.18/100,000 for West Virginia, and 32.11/100,000 for Cabell County, West Virginia, where the nickel alloy plant is located [76]. To determine if the risk of death from cancer of the respiratory organs is elevated in workers in the nickel alloy plant in West Virginia, the number of observed deaths in these workers should also be compared with the expected number of deaths estimated from death rates for the population of West Virginia or the population of the region. Including workers on the payroll before 1948 in the study cohort would increase the number of both observed and expected deaths and thus increase

the reliability of the O/E ratios. Inco noted that this epidemiologic study is preliminary and that this cohort of nickel alloy plant workers will be studied in more detail [41].

The information on past operations at the Huntington nickel alloy plant provided by Inco [23,41] was limited. Between 1922 and 1948, impure copper-nickel sulfides, containing nickel subsulfide, were crushed and ground, and then oxidized at temperatures of 600-1,200 C in refractory-lined mechanically agitated calciner furnaces similar to those used at Clydach, Wales, and at Port Colborne, Ontario [41]. A few measurements of the concentration of airborne dust in the nickel alloy plant were made between 1939 and 1945. Airborne dust was sampled by a midget-impinger technique in the calciner building and the adjacent melt shop, and the results were expressed as mppcf. The concentration of airborne dust in mg/cu m was estimated from the measurements in mppcf, using a conversion factor of 7 for the calciner building and 5 for the melt shop. The derivation of these conversion factors was not discussed in the report. From two measurements, taken in 1939 and 1945, the concentrations of airborne dust near the ball mill where impure copper-nickel sulfide was ground and crushed were estimated to be 58 and 72 mppcf or 400-500 mg/cu m. From four measurements, the concentrations of airborne dust between the calciner furnaces were estimated to range from about 0.4-3.3 mppcf or 3-25 mg/cu m between 1939 and 1945. The fine dust from the calciner furnaces, where impure copper-nickel sulfides from Canada were oxidized, contained 45% nickel. The fine dust from calciner furnaces, where impure copper-nickel sulfide from New Caledonia was oxidized between 1941 and 1948, contained about 70% nickel. In the melt shop, one reading in 1939

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indicated that the concentration of airborne dust between two electric arc furnaces was 32.6 mppcf or about 163 mg/cu m, and four measurements indicated that the concentration of airborne dust in other areas of the melt shop ranged from 0.25-7.8 mppcf or about 1.3-39 mg/cu m in 1939-1942.

From these data on particle counts and the nickel content of dusts, it was estimated that workers near the calciner furnaces were exposed to about 5-15 mg/cu m of airborne nickel and to about 10-20 mg/cu m of total airborne dust; workers near the grinding and crushing machines were exposed to about 20-350 mg/cu m of airborne nickel, and to about 50-500 mg/cu m of airborne dust; and workers in the melt shop were exposed to about 5-150 mg/cu m of airborne dust [41]. Although Inco did not estimate it, the percentage of nickel in airborne dust near the furnaces in the melt shop would presumably reflect the high percentage of nickel in most of the alloys produced at this plant. Even though the data on the concentrations of airborne dust and the estimates of the concentrations of airborne nickel are limited, they seem to suggest that the concentration of airborne nickel near the calciner furnaces in the Huntington nickel alloy plant were in the same range as those near the calciner furnaces installed at the Clydach nickel refinery in the 1930's.

(e)   USSR

In 1970, Saknyn and Shabynina [58] reported the results of an epidemiologic study of deaths from cancer in a USSR plant where nickel oxide ore was processed. The authors indicated that there were three major operations at the nickel plant: preparation and drying of the ore, roasting and smelting operations, and recovery of cobalt and arsenic. Sulfur was added to process nickel oxide ores in the USSR [10] and Saknyn and

Shabynina [58] indicated that workers engaged in roasting and smelting operations were exposed to dusts containing nickel sulfides as well as nickel oxides. The authors apparently used company records to identify workers who died from cancer between 1955 and 1967. They determined the age- and sex-adjusted death rates from cancer in nickel plant workers and in the population of the city adjoining the plant, but they reported only the ratio of the cancer death rates in these two populations. Saknyn and Shabynina noted that the age- and sex-adjusted death rate from cancer in workers at the nickel plant was 1.5 times greater than that in the adjoining city. The death rate from cancer of the lungs in workers at the nickel plant was 1.8 times greater than that in the adjoining city, and the average duration of employment of nickel workers who died from lung cancer was 13 years. They also noted that the death rate from sarcomas, mostly osteosarcomas and pulmonary sarcomas, was 6.2 times greater in nickel workers than it was in the adjoining city and that the death rate from stomach cancer was elevated, but these findings were not reported in detail. The authors did not present information on the number of workers at the nickel plant, their occupational histories, the procedures used to identify deaths in workers or in the general population, or the numbers of observed and expected deaths in nickel workers. Because this information is lacking, the study suggests but does not adequately demonstrate that workers engaged in roasting and smelting nickel oxide ore may have an increased risk of death from cancer.

In 1973, Saknyn and Shabynina [59] analyzed the death rates from cancers of the lung and stomach and from sarcomas in workers at the plant studied in 1970 and in three additional nickel refineries. The same

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methods were used and similar results were found.

In 1960, Tatarskaya [49] investigated changes in olfactory function and in the nasal mucosa of 486 workers in USSR plants that refined nickel electrolytically. On the basis of their occupational histories, Tatarskaya divided the workers into four groups: electrolysis workers; workers in the cleaning section; persons who occasionally worked in the cleaning and electrolysis sections, eg, technicians and installers; and administrative personnel. The majority of the workers had been employed at the refinery for at least 5 years, and nearly two-thirds of them were under 40 years of age. Reexamination of 223 of the workers were conducted 1.5 years after the initial examination, and the 50 workers with the most severe damage to the nasal mucosa were examined three times in the same 1.5 year period. Tatarskaya reviewed symptoms and morphologic changes in the nose, pharynx, and larynx, as well as changes in olfactory function. Olfactory function was assessed qualitatively by determining whether workers could detect the odor of ammonium hydroxide, vinegar, tincture of valerian, 70% alcohol, or a 10% solution of cocaine. Anosmia was diagnosed if the worker failed to detect the odor of any substance, including ammonia; and hyposmia was diagnosed if the worker was unable to detect one or more of the test substances.

Tatarskaya noted that symptoms changed in number and kind with the duration of employment and were not related to age [49]. In the first few days and weeks of work in the electrolysis and cleaning shops, workers complained of sneezing, a sense of constriction in the nose, and runny nose. Later, nasal hemorrhages occurred in some workers, then either stopped or became rare or slight. As the duration of employment increased,

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the number of workers with complaints of dryness of the nose, formation of crusts, and olfactory disorders increased. Pain in the upper respiratory tract and difficulty in nasal breathing were also noted. The author observed that the number and severity of changes in respiratory tract mucosa also increased as the duration of exposure increased and were not related to age. Morphologic changes were most common in the nose, followed by the pharnyx and larynx. So-called subatrophic, atrophic, and dry rhinitis were noted in 10-16% of the workers, and chronic catarrhal rhinitis was noted in about 5% of the workers. Erosions, perforations, and ulcers were limited to the nose; 13% of the workers had erosions, 6% had perforations, and about 1.4% had ulcers. About 10% of the workers had subatrophic pharyngitis and about 3% had atrophic pharyngitis. About 3% of the workers had chronic tonsillitis, and about 3% had chronic laryngitis. Tatarskaya claimed that 160 workers (32.9%) had anosmia and 149 workers (30.6%) had hyposmia, but he reported that there was no definite relationship between the morphologic condition of the nasal mucosa and the degree of olfactory impairment.

On the basis of changes in morphology of the upper respiratory tract seen in workers examined more than once, Tatarskaya [49] concluded that, in most workers, erosion of the nasal septum showed no clear tendency to progress as the duration of employment increased. Only one case of erosion of the septum progressed to perforation in the 1.5 years between observations. Erosions and superficial ulcers tended to heal while workers were on vacation, but the damage reappeared in some cases. The author reported that the size and shape of nasal perforations did not change significantly in the 1.5-year observation period. Tatarskaya concluded

that exposure to an aerosol produced by the nickel compounds (primarily nickel sulfate) used in electrorefining caused damage to the nasal mucosa similar to that caused by exposure to aerosols containing chromium, fluoride, and arsenic. In addition, exposure to aerosols from solutions of nickel compounds seemed to affect olfactory function independently of effects on the morphology of the nasal mucosa.

Although Tatarskaya [49] divided the nickel workers into four occupational groups, the data were presented for all groups combined. If information had been presented on the concentrations of airborne nickel, duration of employment, and diagnostic procedures, and if there had been a control group, the significance of Tatarskaya's findings could be more adequately assessed. The extent of damage to the nasal mucosa and to olfactory function, however, seemed to have been fairly extensive, considering that all workers, including those with apparently minimal or intermittent exposure, were included in the analysis. Moreover, Tatarskaya's findings indicate that exposure to aerosols of nickel compounds produced or used in electrorefining can cause mild to severe changes in the morphology of the nasal mucosa, as well as changes in olfactory function.

In 1970, Kucharin [50] conducted on an examination of the nasal cavities and sinuses of 458 workers in a nickel electrorefining plant in the USSR. The author stated that 347 of the workers had been exposed to nickel in electrorefining operations for at least 10 years, while 111 workers were employed in auxiliary work; but he reported findings for only 302 of the 458 workers. Kucharin noted that the concentrations of airborne nickel ranged from 0.02 to 4.5 mg/cu m in the electrolysis and cleaning

departments, where workers were also exposed to chlorine and sulfuric acid fumes and to high temperatures. The workers were given an undescribed clinical examination, and the nasal cavities and sinuses were examined using both rhinoscopic and radiographic procedures. The radiographic findings were compared with the rhinoscopic findings to estimate the extent of damage in the nasal cavities and sinuses. Disorders of the nose were grouped, apparently on the basis of radiologic findings, into three categories: acute sinusitis; chronic sinusitis; and cysts or cystlike lesions. Rhinoscopic findings were grouped into five categories; subatrophic changes of the nasal mucosa, atrophic changes of the nasal mucosa, erosions, perforations, and nasal polyps. Of the 302 workers on whom Kucharin reported, 199 (66%) had aberrations of the nasal cavities and sinuses detected by X-ray, 145 of whom (73%) also had associated findings in the rhinoscopic examination. Some complained of bleeding, dryness, formation of scales, or pain in the nose. Those with nasal erosions or perforations complained of periodic nosebleeds, stuffiness of the nose, frequent colds, and mucous discharge. However, not all of the workers with microscopic nasal lesions such as erosions and perforations reported symptoms. Of the 251 workers with chronic sinusitis, 104 (41%) had nasal erosions, 66 (24%) had subatrophic changes of the nasal mucosa, 17 (7%) had atrophic changes, 16 (6%) had nasal perforations, and 8 (3%) had nasal polyps. The pattern of microscopic changes was similar in the 31 workers with cysts or cystlike formations and the 17 workers with acute sinusitis. Olfactory function was reduced in 98 of the 215 workers with chronic sinustis (45%), while somewhat fewer of the workers with acute sinusitis or cysts were affected.

Kucharin [50] did not explain how workers had been selected for the study, nor was the extent or duration of exposure considered. Diagnostic procedures were not adequately described, and no basis was given for classification either by radiographic or rhinoscopic procedures. The results were not reported for all workers, and it is unclear if workers with more than one symptom or type of lesion were counted in several groups. Since electrolysis and cleaning department workers were exposed to other potentially harmful compounds, such as chlorine and sulfuric acid fumes, the information in this report is insufficient to establish that the symptoms and the microscopic lesions of the nose in electrolytic nickel refinery workers resulted specifically from exposure to nickel. Although the etiologic agents cannot be determined from this study, its findings do indicate that exposure to airborne compounds in the electrolysis and cleaning departments of a nickel refinery may cause damage to the nasal cavities even when the concentration of airborne nickel was reported to be at or below 4.5 mg/cu m.

(f)   Other Countries

In 1965, Tsuchiya [60] reported an epidemiologic study comparing death rates from cancer, particularly lung cancer, in the population with death rates in workers in various occupations in Japan. A questionnaire was sent to the health supervisors of 200 randomly selected industries from all Japanese industries with more than 1,000 employees. There was good agreement between the general population of Japan and the different occupational groups studied for the relative frequencies of different types of cancer with the exception of lung cancer. Therefore, Tsuchiya concluded that reports from the industrial health supervisors were reasonably

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reliable and that the sample was fairly representative of the working population. The industries were divided into 12 groups according to exposure to substances considered by Tsuchiya to be potential carcinogens, eg, benzene, aniline, X-rays, nickel, and chromium, but the procedures used were not reported. The number of deaths from stomach, liver, and lung cancer in each of the 12 exposure groups was compared with the expected number of deaths derived from age-adjusted death rates for the entire sample. Tsuchiya identified 19 deaths from lung cancer in industries using nickel (chemical forms unspecified), and reported that the number of deaths was significantly greater than expected (P<0.01).

In the second part of the study, the number of deaths in all Japanese industries handling nickel or chromium was compared with the number of deaths in all Japanese industries that did not handle nickel or chromium [60]. The number of observed and expected deaths was not adjusted by age, but only deaths in workers between the ages of 20 and 59 were considered. Tsuchiya found 22 deaths from lung cancer in workers in industries handling nickel or chromium; the O/E ratio was 2.2:1 (P<0.05). Since data from industries that handle either nickel or chromium were combined, the proportion of deaths from lung cancer that may be associated with exposure to nickel cannot be determined from these data. The results of the first part of the study suggest, however, that workers in industries that handle nickel have an increased risk of death from cancer of the lungs.

In 1959, Rockstroh [61] described 45 confirmed cases of lung cancer that occurred between 1928 and 1956 in workers at a nickel smelting plant in Germany where nickel-arsenide ore was processed. In addition, 39 cases of defects in the nasal septa were found in an examination of 90 workers at

the plant, and 2 cases of skin cancer were reported in an 11-year period. Rockstroh noted that workers were exposed to nickel, arsenic, cobalt, copper, bismuth, and benzopyrene at the nickel smelting plant, although data were not presented. Because only 2 cases of skin cancer, the type of cancer usually associated with exposure to arsenic, were found, whereas 45 cases of lung cancer were diagnosed, Rockstroh concluded that arsenic was not the only cancer-causing agent to which workers at the nickel smelter were exposed.

Animal Toxicity

(a)   Carcinogenicity

(1)   Inhalation or Intratracheal Exposures

Kasprzak et al [77], in a study reported in 1973, administered 5 mg of nickel subsulfide suspended in 0.1 ml of 5% sodium carboxymethyl cellulose in a single intratracheal injection to each of 13 male Wistar rats weighing about 200 g. The mean particle size was 10 μm (range 1-30) and penetration into the small bronchioles and alveolar spaces was verified by microscopic examination of lungs of other rats similarly exposed. All the rats survived through the observation period of 15 months and were subsequently killed for examination. One liver tumor, without metastases, was seen. The lungs of nine of the rats, including the rat with the liver tumor, were unaltered, but the lungs of the other four showed peribronchial adenomatoid proliferation, and two of these had inflammatory reactions in the bronchial walls.

In another study with nickel subsulfide, Ottolenghi et al [78] reported the effects on Fischer rats of both sexes following its

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In another study with nickel subsulfide, Ottolenghi et al [78] reported the effects on Fischer rats of both sexes following its

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inhalation. A group of 226 rats was exposed to respirable nickel subsulfide dust (95% of the particles were smaller than 1.5 μm) at an average nickel concentration of 0.97 mg/cu m (SD=0.18), and 241 controls were exposed to filtered air. The exposure period was 6 hours/day, 5 days/week, for 78-84 weeks. Hexachlorotetrafluorobutane, an agent used to induce pulmonary infarction, was also injected intravenously (iv) into one-half of the control and treated animals. The authors reported that this agent had no effect on the induction of tumors in these rats. Surviving animals were observed for 30 weeks before being killed. All animals were necropsied except 18 treated and 26 control animals, which were lost because of advanced autolysis or cannibalism. There was no difference in 1st-year mortality between the treated and control group; however, the mortality of the treated animals increased rapidly in the final 26 weeks of exposure, resulting in a significant difference (P<0.01) in survival by the end of the observation period. Fewer than 5% of the exposed rats survived for 108 weeks, whereas 31% of the controls survived. Nickel subsulfide-treated rats began to lose weight after 60 weeks of exposure. At the conclusion of the study, the differences in weight between control and treated rats averaged 65 g for females and 50 g for males. At necropsy, animals exposed to nickel subsulfide exhibited abscessed, consolidated, and spotty lungs. Typical hyperplasia in both the bronchial and bronchoalveolar segments of the lung was observed in 133 of the 208 nickel subsulfide-treated rats and in 46 of 215 controls. Hyperchromatism of the epithelial cells or proliferation of columnar and cuboidal cells were observed in 106 treated rats and in 28 control rats. Squamous metaplastic changes of the bronchial and bronchoalveolar portions of the lung were also

observed more frequently in nickel subsulfide-treated rats (18.3%) than in controls (4.6%). Benign epithelial tumors (8 bronchial and 7 alveolar adenomas) were found in 15 treated rats; the only tumor in this classification in the control group was described as an alveolar papilloma. Fourteen treated rats had malignant tumors, 10 of glandular type (adenocarcinomas), 3 of surface epithelial origin (squamous-cell carcinomas), and 1 of fibrous tissue origin (fibrosarcoma), but only one malignancy was found in a control animal. Ottolenghi et al [78] concluded that nickel subsulfide was a pulmonary carcinogen when inhaled by rats and hypothesized that its carcinogenicity was related to its low water solubility.

Farrell and Davis [79] reported in 1974 the results of a study designed to determine the effects of various particles, including nickel oxide, carbon, ferric oxide, aluminum oxide, and cobalt oxide, on diethylnitrosamine (DEN) carcinogenesis. Combinations of DEN and particles were given to 5 groups of 50 Syrian hamsters equally matched by sex. Four other groups received DEN alone and 6 additional groups served as controls. The DEN was administered subcutaneously and the particles by intratracheal instillation. DEN (a total of 6 mg) or saline was given once a week for 12 weeks; this was followed by 30 equal weekly administrations of a particulate substance for a total dose of 120 mg. All the animals were observed for up to 68 additional weeks. In the 200 animals which received DEN alone, there were three nasal tumors, one of which was malignant. In the 250 animals given both particles and DEN, there were 13 tumors of the nasal cavity, 9 of which were malignant. Other tumors of the respiratory tract did not differ among the groups. In the hamsters treated with nickel

oxide alone, there were no tumors in the respiratory tract and no excess of tumors at other sites. Animals given nickel oxide and DEN had four nasal tumors and no excess of other tumors compared to groups given DEN. Nickel oxide increased the number of nasal tumors produced by DEN, but not significantly more than the other particles used in the study.

Wehner et al [80], in 1975, described the results of a nickel oxide inhalation study. A group of 102 two-month-old male Syrian golden hamsters received lifespan exposures (up to 2 years) to a respirable aerosol (median diameter, 0.3 μm) of nickel oxide at a concentration of 53.2 mg/cu m (SD=11.1), for 7 hours/day, 5 days/week. Half of the animals were also exposed for 10 minutes three times daily to cigarette smoke. Fifty-one additional animals were exposed to cigarette smoke and sham dust; another group of 51 control hamsters was exposed to sham smoke and sham dust. The first evidence of a nickel oxide effect was the accumulation of nickel oxide particles on the alveolar septa. Accumulation was noted in macrophages aggregated near small bronchioles, lymph vessels, and blood vessels. Animals which died soon after the initiation of the exposures were examined microscopically; emphysema and particles of nickel oxide, often filling entire alveolar spaces, were noted, but little cellular response was seen. Animals which survived longer showed an increasing cellular response characterized by inflammation, macrophage proliferation, and bronchial and bronchiolar epithelial hyperplasia. Three malignant tumors, two osteosarcomas and a rhabdomyosarcoma of the thoracic skeletal muscle, were observed in nickel oxide-exposed animals. The control animals did not develop these tumors. Differences in survival or body weight related to nickel oxide exposure alone were not recorded. The authors [80]

concluded that, whereas lung lesions (massive pneumoconiosis) developed from chronic exposure to nickel oxide, "neither a significant carcinogenic effect of the nickel oxide nor a cocarcinogenic effect of cigarette smoke" was found.

Kim et al [81], in an unpublished inhalation study, exposed male Wistar rats to various combinations of nickel and iron dusts. The 287 rats were divided into three treatment groups (77, 76, and 67 animals) and one control group (67 animals). Group I was exposed to nickel powder at a concentration of 87.3 μg/cu ft (SD=8.06) (3.1 mg/cu m). Group II was exposed to a mixture of equal weights of nickel powder, "Dust C" (24.1% nickel sulfate, 68.7% nickel sulfide (Ni2S3), and 7.2% nickel oxide), hematite (Fe2O3), and pyrrhotite (FeS); the total nickel concentration was 59.5 μg/cu ft (SD=5.60) (2.1 mg/cu m), and the iron concentration averaged 53.2 μg/cu ft (SD=5.70) (1.9 mg/cu m). Group III was exposed to an iron mixture (iron, hematite, and pyrrhotite) at an iron concentration of 85.0 μg/cu ft (SD=6.50) (3.0 mg/cu m). Within each group, subgroups were exposed from 7 to 16 months over a 10-26 month period; identical exposure schedules were used for all three dust combinations. Particle sizes were predominantly (98%) less than 2 μm. All animals were exposed 6 hours/day, 5 days/week. In Group I, 3 of 60 examined rats had lung tumors (two carcinomas and one lymphosarcoma); in Group II, there was 1 squamous-cell carcinoma of the lung in the 61 rats that were examined; in Group III, 3 of 58 rats had lung tumors (2 carcinomas and 1 papillary adenocarcinoma), and, in the 55 control animals, 1 lung carcinoma was found. Twelve of 40 rats in Group I and 11 of 36 rats in Group II had granulomas in the lungs, compared to only 1 of 55 control rats and 3 of 58 animals in Group III.

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The authors [81] concluded that under the conditions of the experiment, there was no evidence that lung cancer was the result of a direct carcinogenic action of the inhaled dust.

Hueper [82], in 1958, reported a study of the carcinogenic potential of elemental nickel. A total of 222 animals were exposed to 99% pure nickel, 4 μm or less in size, at a concentration averaging 15 mg/cu m for 6 hours/day, 4 or 5 days/week, for 24 months or until death. Guinea pigs (32 males, 10 females), Wistar rats (50 males, 50 females), Bethesda rats (60 females), and C57 black mice (20 females) were exposed. By the end of the 1st year, 45% of the guinea pigs, 64% of the Wistar rats, 52% of the Bethesda rats, and 85% of the mice had died. All of the exposed animals died by the end of the 2nd year. Microscopic examination of the guinea pigs showed that signs of lung irritation (edema, hemorrhage, hyperemia, and leukocytic infiltration) were common. In addition, areas in the bronchioles and alveoli contained an increase in the number and size of unusually shaped and hyperchromatic epithelial cells. These areas also showed accumulations of adenomatoid cell formations which extended into adjacent areas as exposure progressed. In six of the animals the lungs contained circumscribed areas sufficiently atypical to be described as microcarcinomas or minature adenocarcinomas. A multicentric anaplastic alveolar carcinoma was found in one guinea pig lung. The only metastatic lesion found in the guinea pigs was a tumor, suspected by the author to have originated in the lung, observed in a lymph node near the bladder; however, the primary tumor was never located. Five of nine control guinea pigs of similar age also showed small adenomatoid peribronchial cellular accumulations but not of the degree or frequency seen in the treated

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animals. The author [82] stated that the frequency, extent, and number of adenomatoid lesions in the guinea pigs increased with the length of exposure. In rats, the lungs of 15 of 50 examined animals showed "rather numerous" adenomatoid lesions or accumulations. Chronic paranasal sinus inflammations accompanied by ulcers were also noted in a majority of the rats. The mice showed general hyperemia and hemorrhagic lesions, probably from irritation, but no mucosal or adenomatoid lesions such as were found in guinea pigs and rats. Although suggestive lesions were found in rats and guinea pigs, the data presented are not a clear indication of carcinogenicity attributable to elemental nickel.

Hueper and Payne [83] injected by thoracotomy 0.02 ml of a suspension containing finely powdered metallic nickel (2 g/10 ml) in a 10% gelatin solution. Twenty female and 14 male 3-month-old Bethesda Black rats were given nickel injections in the right lung. Control animals were not mentioned. Eight of the animals died within 72 hours after exposure. One year later the procedure was repeated on the 23 survivors, and all of the animals were dead 24 months after the initial exposure. Three malignant tumors were observed: a spindle-cell sarcoma of the right lung, probably related to treatment, and two squamous-cell carcinomas, one in the uterine endometrium and another in the skin of the cheek, possibly not related to treatment. Pigmented fibrous tissue, sometimes containing areas of bronchiolar adenomatosis, developed in many of the injected lungs. Since no controls animal were used, no comparison with expected results can be made.

Hueper and Payne [83] also tested in rats and hamsters the carcinogenic potential of powdered nickel, particle size 1-3 μm, inhaled

with sulfur dioxide and powdered limestone. The limestone was added to prevent the nickel particles from forming conglomerates and also to dilute the nickel content and decrease its toxicity. Chamber concentrations of nickel were not specified; the animals were exposed for over 6 hours/day to a mineral mixture (3-4 parts nickel to 1 part limestone for the hamsters and 1 part nickel to 1 part limestone for the rats) fed into the chamber at 50-65 g/day, along with sulfur dioxide at a concentration of 20-35 ppm. One hundred male hamsters and 120 rats (60 males, 60 females) were exposed, and all died in a 24-month period. Control animals were not mentioned. Cancers of the lung were not observed in either the rats or the hamsters; hamster lungs showed scarcely any effects attributable to exposure. Although many of the rats exhibited inflammatory "fibrosing" changes with bronchiectasis, squamous-cell metaplasia of the epithelial lining, and peribronchial adenomatosis, none of the lesions was definitely malignant.

(2) Oral Administration

In 1974, Schroeder et al [84] described an investigation in which 52 male and 52 female Long-Evans rats were exposed from weaning until death to an unspecified soluble nickel salt at a concentration of 5 ppm nickel in their drinking water. A similar group of rats served as controls. The drinking water for the treated and control rats consisted of deionized spring water with the following essential metals: zinc, 50 ppm; manganese, 10 ppm; copper, 5 ppm; chromium, 5 ppm; cobalt, 1 ppm; and molybdenum, 1 ppm. The authors [84] estimated that the diet of both treated and control rats contained 0.44 μg nickel/g of food. They stated that the average daily nickel consumption of adult rats was 2.6 μg of nickel for controls and 37.6 μg for treated animals. No difference in

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survival between nickel-treated and control rats was noted. The experimental group developed three sarcomas, two carcinomas, and eight benign tumors. The controls had six sarcomas, three carcinomas, two lymphomas, and six benign tumors. A slight increase (13.3%) above controls in the incidence of focal myocardial fibrosis was observed in the rats that received nickel. Schroeder et al [84] concluded that nickel at 5 ppm in drinking water was nontoxic, nontumorigenic, and noncarcinogenic and adversely affected neither longevity nor growth in rats.

In another experiment, Schroeder et al [85] reported that, of 74 Swiss mice given nickel acetate over their lifespan at 5 ppm in drinking water, 10 developed tumors; tumors were also noted in 33 of 104 control mice. Because the diet in this study [85] was subsequently considered to be chromium deficient, Schroeder and Mitchener [86] repeated the experiment in 1975. In the latter study, they reported on the life-term effects of nickel on 108 male and female Swiss mice given drinking water containing 5 ppm of nickel as nickel acetate. Fourteen tumors were noted in 81 necropsied treated animals and 19 tumors were noted in 88 necropsied control animals.

The results of these three studies [84-86] suggest that nickel ions, at a dose of 5 ppm in the drinking water, do not cause increases in the incidence of tumors in mice and rats. No studies were found to evaluate the carcinogenic potential of nickel at higher levels.

(3)   Intramuscular Injection and Implantation

Numerous investigators have reported injection- or implantation-site rhabdomyosarcomas and fibrosarcomas in laboratory animals treated with nickel or its compounds. Gilman and Ruckerbauer [87] observed

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a 40-70% tumor incidence in rats and mice injected with dust taken from a flue in a Canadian nickel refinery. The major components of that dust were later tested individually by Gilman [88]. No injection-site tumors in rats treated with nickel sulfate were found, but tumor incidences of 23-35% in two strains of mice and 41% in rats injected with nickel oxide and 33-53% in two strains of mice and 80% in rats injected with nickel subsulfide were reported.

Nickel subsulfide has subsequently been found to be a very potent inducer of injection-site sarcomas [89-94]. Herchen and Gilman [89] reported that 32 days of exposure were required for a 250-mg nickel subsulfide disc, implanted in the thigh muscles, to induce tumors. Gilman and Herchen [90] also reported that physical shapes of nickel (powder, chips, disc, or diffusion chamber) affected the latency period but not the incidence of injection-site tumors. Sunderman et al [91] reported a dose-response relationship, ie, 4 of 15 rats developed tumors at a dose of 0.6 mg, 11 of 15 at 1.2 mg, 13 of 15 at 2.5 mg, and 15 of 15 at 5 mg.

Nickel powder has also been injected into laboratory animals [94-100]. Furst and Schlauder [95] reported that rats were much more sensitive to tumor induction by injection with nickel than were hamsters. Hueper [96] reported that mice did not develop tumors when administered nickel powder suspensions by intramuscular (im) or iv injection, but that intrafemoral injection of nickel powder induced injection-site tumors in 27 of 100 rats. In rabbits, one of six developed a tumor from intrafemoral injection, but no tumors were noted in 10 rabbits given six weekly iv injections of nickel. In another study, Hueper [97] observed 4 injection-site tumors in 25 rats given intrafemoral injections of nickel and none in

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20 rats given intranasal injections of nickel.

Nickel acetate induced tumors in 3% of the rats given three 7-mg muscle implants [101] and in 22% of the rats injected with 35 mg [99]. No injection-site tumors were noted in animals injected with 5.6 or 22.4 mg of nickel monosulfide* [94]. One rat in each group of 35 animals given three 7-mg injections of nickelic oxide or anhydrous nickel acetate developed a tumor [101]. Ten injection-site tumors were observed in 35 rats over a period of 20 months after three 7-mg injections of nickel carbonate [101]. Nickel chloride, nickel sulfate, and nickel ammonium sulfate did not produce injection-site tumors when given in three 7-mg doses [101]. Nickel fluoride and nickel hydroxide have also been reported to produce injection-site tumors [102].

(4)   Other Routes of Exposure

Jasmin and Riopelle [103] studied nickel subsulfide-induced renal carcinomas in young (120-140 g) female Sprague-Dawley rats. Nickel subsulfide (5 mg) in saline or in glycerin was injected into each pole of the right kidney; glycerin was also injected intrarenally into one control group, and nickel subsulfide (10 mg) was given iv to another. All animals were observed for 12 months and palpated regularly. No renal carcinomas were observed in 20 rats given iv nickel subsulfide or in the 16 glycerine-injected animals. In the intrarenally injected groups, nickel subsulfide in glycerine produced renal carcinomas in 7 of 16 examined animals, and nickel subsulfide in saline produced 11 carcinomas in 24 animals. The control groups showed no tumors remote from the injection sites; eight mesentery tumors, four lung tumors, and one liver tumor were noted as

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extensions of primary tumors in the animals injected intrarenally with nickel subsulfide.

In a second experiment, Jasmin and Riopelle [103] studied the effect of other metals injected intrarenally. Glycerin (control), nickel subsulfide, nickel monosulfide, metallic nickel, cobalt sulfide, cobalt, chromium, cadmium, lead, or gold was injected into both poles of the right kidney of Sprague-Dawley rats (16-20 rats were autopsied for each metal). Doses of 5 mg of each metal in 0.05 ml of glycerin were used. No renal carcinomas developed in any rats except those injected with nickel subsulfide (7 of 16). Two rats in the nickel subsulfide group also developed mammary growths, and 1 of 20 rats injected with metallic nickel had a rhabdomyosarcoma at an unspecified site.

Stoner et al [104] investigated the production of lung adenomas in strain A mice given multiple intraperitoneal (ip) injections of 13 metallic compounds, one of which was nickel acetate. Three groups of 20 mice received nickel acetate 3 times weekly for 8 weeks in doses totaling 72, 180, and 360 mg/kg. Three control groups were used: one group was given the vehicle, another group was treated with a positive carcinogen (urethane), and a third group received no treatment. All mice were killed 30 weeks after the first injection, and the average number of lung tumors/mouse was determined. The average number of tumors/mouse was 0.42 in the vehicle control group, 21.6 in the urethane controls, and 0.28 in animals given no treatment. At a nickel acetate dose of 360 mg/kg, there were 1.26 tumors/mouse (P<0.01); at 180 mg/kg, 0.71 tumors/mouse; and at 72 mg/kg, 0.67 tumors/mouse. The increases in tumors/mouse at the 180 and 72 mg/kg doses were not statistically significant.

Furst et al [105] injected 5 mg of nickel powder intrapleurally into 10 Fischer rats. The procedure was repeated at monthly intervals for a total of five treatments. Control animals received saline injections. Two intrapleural tumors were noted in the nickel-treated animals; no tumors were found in the controls. The first nickel-induced tumor appeared in just over 100 days.

Hueper [97] reported the results of intrapleural injections of nickel powder. Five monthly injections of 50 mg of nickel in suspension were given to 25 rats. Four site tumors were noted 17 months after the beginning of the experiment. Hueper [96] later reported that no site tumors developed in 50 mice given single intrapleural injections. A dose of 0.02 ml of 0.6% suspension of powdered nickel in a 2.5% gelatin-saline solution was used.

Shafer [106] reported an attempt to induce tumors in the submaxillary salivary glands of 25 rats by implantation of a 25% nickel-lanolin paste. No tumors developed in the 66-week observation period.

(b)   Mutagenic Effects

The mutagenic potential of inorganic nickel compounds has not been adequately studied. McCann et al [107] have commented that the Ames Salmonella-microsome test is not suitable for metals because of the large amounts of magnesium salts, citrate, and phosphate required in the minimal medium.

Buselmaier et al [108] tested the mutagenicity of 16 pesticides, including nickel chloride, in the host-mediated assay. NMRI-strain mice were injected ip with histidine-dependent strain G46 Salmonella typhimurium or leucine-dependent strain a21 Serratia marcescens. Immediately after

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injection of one of the strains of bacteria, six mice received a subcutaneous nickel chloride injection of 50 mg/kg. Three hours later, the mice were killed; the bacteria were recovered and cultured for 4 days, and back-mutants were counted. In neither test was nickel chloride found to be mutagenic, nor was it mutagenic in the same bacterial strains on plate tests.

Green et al [109] described in 1976 the use of a simplified fluctuation test involving the measurement of reversion to tryptophan independence by tryptophan-dependent Escherichia coli, strain WP2. Nickel chloride at concentrations of 5, 10, and 25 μg/ml of medium did not increase reversion to tryptophan independence.

Demerec et al [110] reported in 1950 a study of mutation to streptomycin nondependence in streptomycin-dependent E. coli (B/r/Sd-4). The bacteria were washed to remove streptomycin, exposed to nickel sulfate or nickel nitrate for 1-24 hours (exact details not given), and plated on streptomycin-deficient medium. After 7 days, the number of mutant colonies was counted. Nickel sulfate and nickel nitrate were reported as "not mutagenic"; no supporting data were provided.

In 1970, Corbett et al [111] reported the effects of nickel sulfate on bacteriophage T4. T4-infected E. coli were treated with nickel sulfate (300 μg/ml) during phage replication. Mutations in the rII DNA segment were determined through the use of permissive (E. coli B) and nonpermissive (E. coli KB) hosts. Nickel sulfate was toxic but not mutagenic in this system.

Lindegren et al [112], in 1958, observed nickel-ion induction of respiratory deficiency in yeast cells. Respiration-sufficient yeasts, ie, those with red color and containing less than 1% respiration-deficient cells under normal conditons, were grown in media containing 0.013, 0.025, 0.038, 0.050, or 0.075% nickel chloride hexahydrate. Haploid (14061), diploid (F-2), and tetraploid (11294 x 11296) strains of yeast were used. Respiratory deficiency in all three strains, identified by the white color of the cells, was observed on the medium containing the 0.05% concentration (46-65% of the cells deficient). The 0.075% medium was lethal to all cells. The authors [112] stated that this deficiency may result either from destruction or inactivation of a cytoplasmic granule or from a gene mutation. The high frequency of deficiency and its relative independence of ploidy suggested to the authors [112] that the respiratory deficiency produced by nickel chloride was a cytotoxic effect rather than a gene mutation.

Nishioka [113] tested 0.05 ml of 0.05 M nickel chloride solution in the Rec assay with negative results. Although this assay does not measure mutagenic effects directly, it indicates qualitatively the ability of a chemical to induce DNA changes by measuring its inhibiting effect on growth of recombination-deficient Bacillus subtilis, strain M45, relative to the inhibition of growth in recombination-positive B. subtilis, strain H17.

In 1963, Komczynski et al [114] reported the effects of nickel chloride, nickel sulfate, and nickel nitrate on cell mitosis in the root of the broad bean (Vicia faba). Five concentrations (0.1, 0.01, 0.001, 0.0001, and 0.00001%) of each salt were tested. All of the nickel salts produced more abnormal cell divisions than were found in water-treated

controls. The nitrate salt was most effective, and the number of abnormal divisions increased slightly with the strength of the nitrate solution. Aberrations included abnormal arrangement of chromatin, grossly deformed cells, extra micronucleoli, and the appearance of small granulations of nuclear chromatin in the cytoplasm. The authors stated that these abnormalities are evidence of cell nuclei disturbances.

Von Rosen [115,116], in review papers, reported that nickel salts exhibited only weak genetic action on pea (Pisum abyssinicum) rootlets. Details of the studies were not given.

(c)   Teratogenicity and Other Effects on Reproduction

In 1972, Ferm [117] cited previously unpublished data from his laboratory in a review of the teratogenic effects of metals on mammalian embryos. He presented data from the iv injection of nickel acetate into golden hamsters on the 8th day of pregnancy. Results are summarized in Table III-14 [117]. The author [117] reported that "a few general malformations in some of the surviving embryos" were noted, but details were not given. Lack of information on the malformations and on their frequency in various litters makes interpretation of or conclusions from this study uncertain.

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TABLE III-14

EMBRYOCIDAL EFFECTS OF NICKEL ACETATE ON GOLDEN HAMSTERS

Amount Injected in mg/kg	Number of Pregnant Hamsters	Total Number of Embryos	Number of Embryos Resorbed	Total Number of Surviving Embryos	Number of Normal Embryos	Number of Abnormal Embryos
2	2	24	0	24	22	2
5	2	22	1	21	20	1
10	5	56	22	34	32	2
20	5	55	10	45	44	1
25	6	68	59	9	5	4
30	3	33	33	0	-	-

Adapted from Ferm [117]

Sunderman et al [118] recently reported in an abstract the fetal toxicity of nickel chloride administered im to Fischer rats on the 8th day of gestation. Groups of 12, 11, 12, and 13 rats were given nickel at 8, 12, 16, and 0 mg/kg. The dams were killed on the 20th day of gestation and live and dead fetuses were counted. The average number of live fetuses/dam was 9.7 in controls; 8.9 at the 8 mg dose; 7.7 at 12 mg (P<0.001); and 7.0 at 16 mg (P<0.01). The ratio of dead fetuses to the total number conceived was 2/128 in controls; 6/113 at 8 mg (P<0.05); 8/93 at 12 mg (P<0.01); and 19/103 at 16 mg (P<0.001). No fetal malformations were found at any treatment level. The authors concluded that im injections of nickel chloride caused fetal mortality at doses which did not cause maternal mortality.

The effect of hydrated nickel chloride on the developing chick embryo was described in 1952 by Ridgway and Karnofsky [119]. LD50 doses of nickel

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chloride were injected into the yolk sac of 4-day embryos or into the yolk sac and onto the chorioallantoic membrane of 8-day embryos. The LD50 doses, determined in unreported trials, were 0.20 mg/egg for 4-day eggs, 2.38 mg/egg for 8-day yolk-sac-injected eggs, and 0.33 mg/egg for 8-day chorioallantoic-membrane-injected eggs. Although the toxicity varied with the age of the embryo and the route of exposure, the authors [119] reported that no developmental abnormalities were produced in chick embryos surviving the LD50 doses.

Timourian and Watchmaker [120] exposed sea urchin eggs to nickel chloride solutions and noted their subsequent development. Embryos were exposed at fertilization and followed through the developmental process. Nickel was incorporated into the fertilized egg more rapidly than certain other divalent ions. Early development, through the blastula stage, was not affected by nickel chloride concentrations up to 10 mM. However, gastrulation (normally occurring 18-20 hours after fertilization) was completely arrested in 10 mM solutions; gastrulation started in a few embryos, but was not completed in a 1 mM solution; and it only reached mid-development in a 0.1 mM solution. Eggs in 10 μM and 1 μM solutions completed gastrulation at the same time as controls. However, many of the embryos completing gastrulation were affected at later stages; at 10 μM, there were cell malformations, and at 1 μM, the prism stage was affected. In another test, embryos not exposed until the gastrula stage was reached were less affected than cells exposed at fertilization. Although nickel chloride did not grossly affect pregastrula development, the authors [120] concluded that, since it was absorbed in early stages, there were subtle effects on early morphologic development.

In 1971, Schroeder and Mitchener [121] described the effects of soluble nickel salts on reproduction in Long-Evans rats. Five pairs of weanlings were given nickel salts at 5 ppm in their drinking water. In previous experiments, Schroeder et al [84] had found that this concentration of soluble nickel salts had no effect on survival or growth of rats. In the present study [121], the litters which resulted from the subsequent mating of the treated rats formed the F1 generation. The F1 rats also received nickel in their drinking water and were mated to produce an F2 generation. The same procedure was repeated in the production of an F3 generation. Control animals received deionized water without nickel and were similarly raised through the F3 generation. Criteria used to estimate toxicity included intervals between litters, age when a pair produced its first litter, male-female ratio, number of runts (large head and small body), deaths, stillborn offspring, failure to breed, and congenital abnormalities. There was no effect on the interval between litters or the age at which the pair produced the first litter. In the treated F1 generation, 9.1% of the pups died and 30.6% were runts; in the treated F2 generation, 10.2% of the pups died and 5.1% were runts; and in the treated F3 generation, 21% of the pups died and 6.2% were runts. One dam from the F1 generation died; no other maternal deaths were reported. The average litter size in the nickel-treated rats decreased from 11.0 pups in the F1 generation to 8.1 in the F3 generation; the male-female ratio in these litters also decreased markedly, from 1.2 in the F1 to 0.44 in the F3 generation. In the controls there was one runt in the F2 generation and one pup died in the F3 generation; there were no changes in litter size or in the male-female ratio. The authors [121] concluded that nickel at 5 ppm

in the drinking water affected reproduction in rats.

Hoey [122], in 1966, reported the effects on rat testes of subcutaneous injections of nickel sulfate. Five albino rats were injected with nickel sulfate at 0.04 millimole/kg. Microscopic examination, 18 hours after a single injection, indicated that marked damage (central tubular shrinkage and hyperemia) had occurred in all testicular tissue except the interstitial tissue. Degeneration of the spermatozoa in the epididymis was noted. Four other animals received up to 30 daily injections of nickel sulfate at 0.04 millimole/kg, and one was killed on each of days 2, 10, 21, and 30. Although the interstitial tissue, the body of the epididymis, the Sertoli cells, and spermatogenesis were affected in the early stages of treatment, full spermatogenesis was restored by the end of the injection series. Three additional rats received a 10-day series of injections at the same dose as the other groups; although some morphologic changes occurred, function was not affected at the end of the series. When examined by X-ray after injection of a contrast medium, the testes of another rat given a single dose showed slight enlargement of the lymphatic channels with hemorrhages in some areas. The author [122] concluded that no irreversible damage resulted from any of the test conditions.

In 1972, Waltschewa et al [123] reported the effects of nickel sulfate on the testes of rats. Thirty 5-month-old male albino rats were administered, through an esophageal tube, nickel sulfate at 25 mg/kg daily for 120 days. Ten similar males served as controls. At the end of the treatment, the rats were caged for 24 hours with female rats in estrus, and the number of pregnancies was subsequently determined. The male rats were killed, and their testes, liver, and kidneys were microscopically examined.

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Examination of liver sections showed increased lactate dehydrogenase concentration, decreased DPN-diaphorase concentration, and signs of degenerative cell damage. Degenerative cellular changes were also noted in the convoluted tubules of the kidneys. The authors [123] stated that changes in the liver and kidneys were relatively slight and noncharacteristic. Testicles of the treated rats were smaller than those of the controls. The findings from microscopic examination included interstitial cell proliferation and transparent vessel walls. The number of spermatozoa and their precursors in the testicular canaliculi was reduced. Succinodehydrogenase and steroid 3-beta-dehydrogenase concentrations in the testes were decreased. The authors [123] reported that none of the female rats placed with treated males were impregnated; three of six females mated successfully with control males. The authors concluded that nickel sulfate selectively damaged the testes of rats, which resulted in inhibition of spermatogenesis leading to a loss of procreative capacity.

Kar and Sarkar [124] reported in 1960 on their investigation of the effects of nickel on the action of testosterone and estrogen. Gonadectomies were performed on 18 male and 18 female albino rats. After a 15-day period to permit total regression of the accessory genital organs, 12 male rats were given im injections of 62.5 μg of testosterone propionate daily for 4 days, and 12 female rats were given the same dose of estradiol dipropionate. Six rats of each group also received nickel acetate subcutaneously at 0.04 millimole/kg/day for the same period. A three-group comparison was thus provided for each sex: (a) castrate only, (b) castrate with sex hormone, and (c) castrate with sex hormone and nickel acetate.

The animals were killed the day after completion of treatment. The seminal vesicles, ventral prostate, levator ani muscle, and uterus were weighed. Nickel acetate appeared to inhibit the androgenic action of testosterone, since the seminal vesicle, ventral prostate, and levator ani muscle of the nickel-treated males weighed less than those of males treated with testosterone only. The administration of nickel acetate approximately doubled the uterine-weight response to estrogen. These effects of nickel acetate on hormone action could be attributed either to alteration in the relative rate of metabolism of testosterone and estrogen or to interference with the sensitivity of the target tissues to the hormones.

Kamboj and Kar [125] investigated the effects of nickel nitrate injected into one testis of rats and subcutaneously in mice. Six albino rats received single injections of 0.08 millimole of nickel nitrate/kg in the left testis and of sterile distilled water in the right testis. Nine Swiss mice were injected subcutaneously with a 0.2 ml solution of nickel nitrate daily for 30 days, resulting in a total nickel nitrate dose of 0.08 millimole/kg. Eighteen control mice received distilled water subcutaneously. The rats were killed 2 or 7 days after the single injection and the mice were killed 2, 7, or 30 days after their last injection. Testes of both species were weighed and examined microscopically. A reduction in the weight of the treated testes was observed in treated animals of both species but was more marked in rat testes, which weighed half as much as untreated testes at 7 days. Treated rat testes had focal necrosis and hemorrhage. Cellular exfoliation and lysis occurred in the cellular elements in 2 days; at day 7, indications of regeneration of the interstitium were noted. No effect on spermatozoa in

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the ductus deferens was observed in rats. Treated mice had no necrotic changes in the interstitial tissue of the testes. However, shrinkage of the tubules and spermatogenic arrest at the primary spermatocyte or spermatogonial stages were noted.

Malaviya and Saraswat [126] studied the effects of nickel chloride on the reproduction of guinea pigs. Male guinea pigs, two at each dose, were injected subcutaneously in the intrascapular region with nickel chloride at doses of 1, 0.001, or 0.0001 mg/kg daily for 15 days. The test animals and a similar group of controls were then mated with fertile females. The females mated to the test animals did not differ from those mated to the controls in the period of gestation, number of litters or offspring, weight of offspring, or offspring development.

(d)   Other Effects

(1)   Acute Toxicity

The LD50's for some inorganic nickel compounds in several species of animals have been determined. The results are listed in Table III-15 at the end of this chapter. Initial signs of toxicity following the ip injection of nickel acetate into rats and mice included diarrhea, respiratory difficulty, and lethargy [127]. Intestinal adhesions with whitish mucous layers covering the viscera were noted upon microscopic examination [127]. In rats, oral LD50 doses of nickel chloride produced depression of the nervous system, edema of the mucous membranes of the mouth and nose, viscous transparent diffusions from the oral cavity, hyperemia of the nose and outer ear, lacrimation, bleeding from the nose, and diarrhea in rats [128].

(2)   Respiratory System

Belobragina and Saknyn [129] reported in 1962 the results of their studies with dust obtained from nickel production areas. Samples of dust were administered intratracheally to 81 white rats at doses of 50 mg/animal. The animals were killed, and their lungs were examined microscopically, 3, 6, 9, or 12 months after treatment. No controls were reported. Dust from the roasting shop, which contained 33.4% nickel oxide, 31.0% nickel sulfide, silicon dioxide, and iron and aluminum oxides, caused high initial mortality (22 of 37 animals died in 5 days); after 6 months, connective tissue nodes were formed and slight sclerosis was present. Another dust, from the electric furnace shop, which contained 95% nickel oxide, produced diffuse sclerosis after 6 months. Rats were also exposed to this dust at a concentration of 80-100 mg/cu m in an inhalation chamber 5 hours/day for up to 12 months. After 6 months, areas of emphysema began to appear, and moderate sclerosis was present after 12 months. For both dusts, hyperplasia of the lungs and peritracheal lymph nodes was observed. According to the authors [129], intratracheal and inhalation exposures to nickel oxide dusts produced similar results.

Selivanova and Ponomarkov [130], in 1963, reported the effects of nickel powder inhalation on dogs. Five dogs were exposed for 10 minutes/day for up to 6 months to nickel powder at a concentration of 5-6 mg/cu m. The animals were kept for observation up to 19 months. No changes were noted in the weight or general condition of the dogs. However, within 2-3 months of the initiation of the exposures, the blood showed a decrease in leukocyte counts, primarily in neutrophils. Necropsy of one dog which died early (time not specified) showed nickel particles

evenly distributed in the lung tissue; nickel was also present in liver and kidney tissues. In two dogs examined 12 months after the beginning of the experiment, the nickel in the lungs was combined into conglomerates around the bronchi and vessels, and there were indications of an interruption in blood flow in the small vessels of the lungs. In two dogs observed for 19 months, pulse and respiration rates were consistently increased. By the end of the 6-month exposure, slight fluctuations in the electrocardiogram were noted, and these increased in the postexposure period, indicating gradual development of cardiac insufficiency. Microscopic examination showed the development of coarse-fiber tissue. The authors [130] concluded that pneumosclerosis had gradually developed in the lungs after inhalation of nickel powder causing cardiac insufficiency. Since controls were not used and the ages of dogs were not given, it is not possible to determine if the effects were the result of nickel exposure.

In 1972, Bingham et al [131] reported pulmonary responses of Wistar rats to inhalation of respirable aerosols (less than 1 μm in diameter) of nickel chloride and nickel oxide. The average concentrations, measured as nickel, at which the animals were exposed were 109 μg/cu m for nickel chloride and 120 μg/cu m for nickel oxide. Controls were exposed to filtered air. The period of exposure was 12 hours/day, 6 days/week, for up to several months. After the last exposure, the lungs were excised and cells collected by lavage and counted. After 2 weeks of exposure, the average numbers of cells were 3.5 million/g of lung in controls, 5.1 million/g of lung in nickel chloride-exposed rats, and 9.8 million/g of lung in nickel oxide-exposed rats. After 4-6 weeks of exposure, the number of cells washed from nickel oxide-exposed animals had increased to more

than 11 million/g of lung. Findings from microscopic examinations of lungs of rats exposed to nickel oxide for 2 weeks included accumulation of macrophages in the alveolar spaces, hypersecretion in the bronchial epithelium, and lymphocyte infiltration of the alveolar walls and perivascular spaces. After longer exposures, lymphocytic infiltration and the number of intraalveolar macrophages were found to have diminished, and focal thickening of the alveolar walls was also observed. Findings in rats exposed to nickel chloride included mucus secretion, hyperplasia, and peribronchial lymphocytic infiltration. Alveolar macrophages, however, were less abundant than in the lungs of rats that had inhaled nickel oxide. Washings from the lungs of rats exposed to both compounds, and particularly nickel chloride, were viscous and cloudy. Bingham et al [131] concluded that inhalation of nickel oxide and nickel chloride at concentrations as low as 0.1 mg/cu m induced some pathologic changes and produced an increase in the number of alveolar macrophages.

An unpublished report by Clary [132] outlines preliminary results following exposure of rats to airborne nickel chloride at a concentration of 1 mg/cu m, measured as nickel. Thirty exposed and 30 control male rats were used. Guinea pigs were also used but results were not included in this preliminary report. Exposures were 5 days/week for 3 months, at which time half of the animals were killed, or for 6 months. The exposure and control groups showed no difference in serum biochemistry, body weights, or liver glucose levels. Findings at necropsy for both the animals killed at 3 months and 6 months included increased lung weights and nickel accumulation in lungs and kidneys. Most control animals had mild to moderate bronchitis and bronchiolitis at 3 months; in addition, 7 of 15 had

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moderate fibrosis (average score=1+). Exposed animals had about the same incidence and severity of bronchitis and bronchiolitis as control animals; however, fibrosis in the alveolar ducts was more marked (average score=3+) and occurred in all 11 examined animals. Signs of irritation in the exposed animals included proteinaceous material in alveolar spaces and proliferation of type II granular pneumocytes. No signs of metaplasia were observed. The lungs of the control and exposed rats killed at 6 months were similar to animals killed and examined at 3 months. In the exposed rats there were slightly greater numbers of foamy macrophages and more interstitial fibrosis than observed in controls. In both cases, examination of the liver, kidneys, or pancreas revealed no lesions.

In 1972, Wehner and Craig [133] reported on the retention of nickel oxide in the lungs of Syrian golden hamsters. Eight 3-month-old male hamsters were exposed 6 hours/day, 5 days/week, for 3 weeks at a mean concentration of 39 mg/cu m. The animals were killed 4 days after the last exposure, and the lungs were analyzed for nickel; assuming a mean inhalation volume of 60 ml/minute, the authors calculated that 19.3% of the theoretical dose was retained in the lungs. In a final report on the study [134], the lungs of these animals were described as having mild to significant interstitial inflammatory reactions, congestion, and emphysema. Liver cells showed mild degenerative changes; kidneys were normal.

Wehner and Craig [133] also exposed 34 hamsters of both sexes to nickel oxide at a concentration of 61.6 (SD=30.3) mg/cu m. Seventeen of these animals were also exposed to cigarette smoke. The animals were exposed 4 hours/day, 5 days/week, for 3 months. Control animals were mentioned but not described. From 16 animals that were killed 4 days after

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the last exposure, the authors calculated that 19.7% of the theoretical nickel oxide dose was retained in the lungs of the hamsters. The final report [134] provided details of a microscopic examination of the lungs of these animals. No differences were reported between animals exposed to nickel oxide and those exposed to nickel oxide and smoke. Nickel oxide particles were phagocytized and concentrated in the macrophages in massive accumulations throughout the lungs. Blood cells accumulated in several parts of the lung interstitium, and there were occasional points of hemorrhage and edema. The kidneys showed mild glomerular congestion, hypertrophy of the endothelial lining of Bowman's capsule, and occasional proteinaceous casts. The livers were normal.

(3)   Endocrine and Enzyme Systems

Kadota and Kurita [135] investigated the effect of nickel chloride on the blood glucose level of rabbits. They reported that 7 of 11 rabbits injected iv with nickel chloride at 10 mg/kg showed transient hyperglycemia 1-4 hours after injection. All seven rabbits that received 15 mg nickel chloride/kg exhibited pronounced hyperglycemia, but the glucose level returned to normal within 24 hours. Histologic examination of pancreases taken from four rabbits 1 hour after injection of nickel chloride at 15 or 20 mg/kg indicated alpha-cell destruction, degranulation, and some necrosis of beta cells.

Mikhaylov et al [136] exposed 64 male white rats to nickel dust which contained sulfides (20.9%) and oxides (55.4%) of nickel. The animals were exposed at 70 mg/cu m, 4 hours/day, for 4 months. After 3-4 months, body weights were significantly less than those of control animals. At the same time, decreases in the concentrations of sugar and glycogen in the blood

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and liver were noted. The authors [136] also reported that intratracheal administration of this dust in doses of 40-180 mg/kg produced liver congestion and necrobiotic areas.

Horak and Sunderman [137] have reported the effects of nickel chloride, administered ip, on the plasma glucose and serum insulin concentrations of female Fischer rats. Nickel chloride produced hypoglycemia in fasting rats 2 hours after injection of 1-17 μmol/kg (about 0.13-2.2 mg/kg) and hyperglycemia 0.5 and 1.0 hours after injection of 17-85 μmol/kg (about 2.2-11.0 mg/kg). The authors [137] also reported the effect of nickel chloride on plasma concentrations in hypophysectomized or adrenalectomized rats (compared to effects in sham-hypophysectomized or sham-adrenalectomized rats). The hyperglycemic responses to injections of nickel chloride were suppressed but not completely inhibited by the adrenalectomy. Adrenergic blockade did not affect the hyperglycemic influence of nickel. Exogenous insulin (1-5 units/kg) antagonized the hyperglycemic effect of nickel chloride (68 μmol/kg or 8.8 mg/kg), but the effect was not entirely overcome. Increases in serum immunoreactive insulin levels were observed 1 hour after injection of nickel chloride at a concentration of 34 μmol/kg (about 4.4 mg/kg) and the increases persisted 0.5-3 hours after the injection of 68 μmol/kg. The authors [137] concluded that the hyperglycemic effects of nickel were antagonized by exogenous insulin and suppressed by adrenalectomy and hypophysectomy, and that the insulinogenic response of the pancreas to hyperglycemia was unimpaired by nickel. These observations, along with the finding that adrenergic blockade was ineffective against nickel-induced hyperglycemia, suggest that this hyperglycemia may not be caused by stimulation of the adrenal glands.

Clary [138] reported the effects of intratracheally injected nickel on glucose metabolism in rats. Twenty male albino rats were given an oral dose of 600 mg of 14C glucose and challenged with 0.5 mg of nickel. Five rats were killed immediately after the injection and others were killed hourly up to 3 hours after the injection. Twenty-four additional rats, in groups of three, were given various combinations of 0, 0.25, 0.5, or 1 mg of nickel and 0, 0.25, 0.5, or 1.0 units of insulin; the animals were then killed 30 minutes after the injection. In the initial test, glucose and 14C concentrations in serum increased after nickel administration, whereas insulin and liver 14C concentrations decreased. In the second test, 0.5 mg of nickel given with 0.25 units of exogenous insulin had no effect on serum glucose concentrations. Other combinations of nickel and insulin resulted in increased or decreased serum glucose levels, depending on the nickel-to-insulin ratio. The author [138] concluded that the increase in glucose probably reflected the influence of nickel on the production or secretion of insulin. He hypothesized that nickel did not influence insulin directly, but rather affected pituitary hormone secretions which control insulin concentrations.

LaBella et al [139] observed that iv injection of nickel (as nickel chloride) resulted in a decrease of serum prolactin, a hormone secreted by the pituitary. A single injection of nickel chloride containing 100 μg or 200 μg of nickel was administered to urethane-anesthetized rats which had been treated with chlorpromazine. Prolactin concentrations in controls after 30 minutes averaged 113 ng/ml of serum, whereas prolactin concentrations were 72 ng/ml in rats treated with 100 μg of nickel and 66 ng/ml in rats given 200 μg. LaBella et al [140] also reported in vitro

results showing that nickel ion inhibited prolactin release from incubated bovine pituitary fractions.

Sobel et al [141] administered a nickel chloride saline solution to 18 guinea pigs by ip injection at a dose of 4 μmol/100 g (about 5 mg/kg). Eighteen controls received an injection of saline only. Urinary corticoid excretion in guinea pigs injected with nickel chloride was almost twice that of controls.

Yeliseyev [142] exposed 50 male white rats to a hydroaerosol of nickel chloride, 24 hours/day for 6 months at nickel concentrations of 500, 5, 1, or 0.2 μg/cu m. A control group was exposed to an aerosol of tap water. Inhalation of nickel chloride at 500 and at 5 μg/cu m resulted in a reduction of the iodine-fixing function of the thyroid gland relative to controls. No changes were observed with concentrations of 1 or 0.2 μg/cu m. Yeliseyev [142] also investigated the effect of nickel chloride on an unspecified number of rats given doses of about 5, 0.5, 0.05, or 0.005 mg/kg/day in their drinking water. A control group received tapwater only. Oral ingestion of nickel at 5 or 0.5 mg/kg resulted in reduction of the iodine-fixing function of the thyroid, as compared to controls, whereas a dose of 0.05 mg/kg caused an increase in this function during the 1st month, a return to normal at the 2nd month, and a decrease at the 3rd and 6th months. No change was observed at a dose of 0.005 mg/kg. The author concluded that inhalation was a more dangerous route of administration than oral ingestion, and that oral ingestion of nickel at 0.05 mg/kg of body weight and inhalation at 0.005 mg/cu m were isoeffective, threshold doses.

Iodine retention in the thyroid has also been studied in dogs exposed to nickel powder [130]. Five dogs were exposed by inhalation to nickel

powder at a concentration of 5-6 mg/cu m, 10 minutes/day, for 6 months. Radioactive iodine (131I) was used to measure the rate and extent of iodine retention. The normal 24-hour accumulation of 131I in the thyroid was 22% of the administered dose. Three months after exposure to nickel began, 35% of the iodine administered was retained; after 7 months, 41%; and after 12 months, 44%. At the end of the 19-month study, retention had returned to normal.

Shvayko and Tsvetkova [143] reported the influence of orally administered nickel on the thyroid function of white rats. Nickel chloride, in nickel doses of 1, 25, and 100 mg/kg/day, was mixed with the food given to 89 male rats over a period of 3.5-4 months. The rats receiving 1 mg/kg showed greatly decreased iodine uptake as measured with radioactive iodine. Iodine uptake was increased at the 25 mg/kg dose but gradually decreased at the 100 mg/kg dose.

Apparent conflicting trends of iodine uptake in these studies [130,142,143] and their implications to thyroid function need clarification before conclusions can be drawn on the appropriateness of these studies to an occupational health standard.

(4)   Skin

The potential for skin absorption of inorganic nickel has not been thoroughly studied. In 1960, Choman [144] published the results of autoradiographic studies on the percutaneous absorption of nickel chloride by two rats. The concentration of the nickel chloride solution was 0.1% and the pH was 6.5. Labeled 63-nickel chloride was applied to shaved areas on the backs of the rats and left for 60 minutes. The animals were killed, the skin at the application site was removed, and autoradiographs were

prepared. Four hours later, radioactive nickel chloride was applied to another section of skin removed from the dead rats, and after 60 minutes, an autoradiograph was prepared. Nickel chloride was absorbed only to a depth of 25 μm in both animals whether applied before or after death. The penetration depth of 25 μm suggested to the author [144] that nickel chloride contacted only the first layer of the epidermis and was not absorbed through the skin. Pretreatment of rat skin with a detergent, sodium lauryl sulfate, facilitated nickel chloride penetration to an average depth of 425 μm in living rats.

Norgaard [145] measured the amount of radioactive nickel absorbed through the dorsal skin of guinea pigs and rabbits in 24 hours. The fur was removed by chemical depilation from a 5- x 5-cm area from each of two animals of both species, and radioactive nickel (57Ni, apparently as a solution of nickel sulfate) was applied. Following application, excess moisture was evaporated, and the area was covered. The animals were killed after 24 hours, and the radioactivity in the urine, blood, liver, and kidneys was measured. The amounts of activity in all four tissues varied, but the amounts were not convertible to absolute amounts of nickel in the tissues, as only samples of each tissue were taken. This study showed that nickel applied to the skin of guinea pigs and rabbits was absorbed and distributed.

Nickel chloride (30% in aqueous solution) has been tested for acute skin irritation potential [146]. Six albino rabbits were given 0.5 ml of the solution on intact and abraded skin. The sites were occluded, and the development of erythema and edema was scored at 4, 24, and 72 hours after the beginning of exposure. A slight erythema was noted at the abraded

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sites after 4 hours of exposure; all other observations were negative. The primary irritation score was 0.2, meaning that nickel chloride in this standard test was not corrosive.

Kolpakov [147] studied the toxicity of nickel sulfate solution applied to the dorsal skin of white rabbits. The fur was removed by chemical depilation from a 10- x 10-cm area of each animal's back, and a 20% solution of nickel sulfate was applied on a gauze compress. Five rabbits were treated on intact skin; in six rabbits, the epidermis was destroyed with fine emery paper, and nickel sulfate was applied to three, with three kept as controls; and, in the last group, an unspecified organic solvent was first applied for 6 days, followed by nickel sulfate (three animals) or physiologic saline (three animals). After removal of the compress, sections of skin, liver, kidneys, and lungs were removed and examined for the presence of nickel. In the rabbits with intact skin, no nickel was detected in the liver, lung, or kidney sections and there were no signs of toxicity. In the animals whose skin had first been abraded, toxic signs (convulsions and salivation) appeared within 2-3 hours, and all the animals died within 7-10 hours. Nickel was detected in the skin, liver, kidneys (particularly in the medullar portion), and lungs. No effects were noted in the control animals. In the rabbits pretreated with an organic solvent, death occurred within 7 hours, and nickel was again detected in all tissue sections. No deaths occurred in the control rabbits treated with organic solvent only.

(5)   Kidneys

In 1975, Gitlitz et al [148] reported the results from ip injection of nickel chloride in female albino Fischer rats. Nickel chloride in sterile sodium chloride solution was injected in doses of 4 ml/kg containing 2, 3, 4, or 5 mg of nickel. Each dose level was tested on groups of five or six rats, and five control animals were injected with the vehicle only. Within 2 days of the injection, all the test doses caused significant increases (P<0.01) in the urinary excretion of protein, ie, proteinuria, which is evidence of kidney damage. Amino acid excretion was not altered at the 2 mg/kg dose, but histidine, 1-methylhistidine, and sarcosine excretion was affected by a 3-mg/kg injection. In doses of 4 and 5 mg/kg, nickel chloride affected the excretion of all acidic, neutral, and basic alpha-amino acids except aspartic acid. Plasma levels were monitored to determine whether increased urinary amino acid excretion was a result of increased plasma levels, but no increases were noted. Pathologic alteration of the renal tubules were found in one of five rats killed 48 hours after ip injection of 4 mg of nickel/kg. Electron microscopy in these rats also showed fusion of the foot processes of epithelial cells in renal glomeruli. This effect appeared to be reversible.

(6)   Eyes

A commercial nickel chloride product has been tested in rats for eye irritation potential [146]. The proprietary formula was reported to contain 30% nickel chloride in aqueous solution. Three albino rats were given 0.1 ml of the solution in an unwashed eye; the other eye served as a control. The development of irritation was scored according to the tissue involved (cornea, conjunctiva, or iris) and the intensity of irritation.

The irritation score for nickel was 19.6 out of a possible 110.0 points. This score was classified as mildly irritating.

(e)   Metabolism

Wehner and Craig [133] reported the results of pulmonary deposition and clearance studies with nickel oxide in hamsters. Ninety-two 2-month-old male Syrian golden hamsters were exposed to nickel oxide at 73.5 mg/cu m for two consecutive 7-hour periods. Immediately after exposure, four randomly selected animals were killed, and tissues from the lungs, liver, kidneys, and gastrointestinal tract were analyzed for nickel by atomic absorption spectrophotometry. Subsequent groups of four animals were killed at increasing intervals, the last group 155 days after the exposure. Nickel oxide was only slowly removed from the lungs; by the 6th day after exposure, more than 70% of the nickel oxide was still present. Only small amounts of nickel oxide were found in the liver, gastrointestinal tract, or kidneys at any time.

Wehner and Craig [133,134] studied the uptake of nickel oxide from the gastrointestinal tract of hamsters. Nickel oxide, 5 mg in suspension, was administered by gavage to six hamsters. Twenty-four hours later, the animals were killed, and tissues were analyzed for nickel by atomic absorption spectrophotometry. There was no increase over control values in the nickel content of the lungs, liver, kidneys, or carcass of the experimental animals.

Clary [138] studied the distribution of radioactive nickel chloride administered intratracheally to 30 male albino rats. A 63-nickel chloride solution containing 1 mg of nickel was injected into each animal, and the amount of nickel in various organs was determined 6 hours after injection.

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The authors stated that the kidneys showed the greatest concentration of nickel/g of tissue, followed by the lungs, adrenals, liver, pancreas, spleen, heart, and testes. Other tissues had only a very low nickel content. All tissues had much lower levels 24 hours after injection. By 72 hours, 90% of the nickel dose had been excreted, mainly in the urine (75%).

Ho and Furst [149] compared oral and ip administration of radioactive nickel chloride in rats. Female Fischer-344 rats were given doses of 9.12, 2.28, or 0.57 mg of nickel ion by stomach tube or ip injection. Regardless of the quantity of nickel given orally, the entire amount was excreted in 48 hours, 3-6% in the urine and the rest in the feces. Animals given nickel chloride by ip injection excreted only 1-2% of the nickel in the feces and the rest in the urine. Maximum excretion was reached 1 hour sooner in ip-injected rats than in the orally treated animals.

Sunderman [150] reported the tissue distribution of nickel in rabbits after iv injection of radioactive nickel chloride. Rabbits killed 2 hours after a single injection of 4 μmol/kg (about 0.52 mg/kg) had the greatest concentration of nickel/g of tissue in the kidneys, followed by the pituitary, serum, lungs, heart, and liver, with the lowest concentration in the hypothalamus. Rabbits killed 24 hours after the last of 34-38 daily injections of 75 nmol/kg/day (about 9.7 μg) showed similar results, with the highest concentrations in the kidneys and the pituitary, but blood levels were reduced and spleen levels were elevated.

Sunderman and Selin [151] investigated the metabolism of radioactive nickel chloride in rats after iv injection. An average of 86.7% of the administered dose was excreted in the urine within 24 hours, and only 0.5%

was excreted in the feces. After 4 days, 92.8% of the injected dose had been recovered.

Chen et al [152], using colorimetric analysis for nickel determinations, reported that rats injected im with 60 mg of nickel acetate excreted 95% of this compound in the urine within 2 weeks. Rats injected with 60 mg of nickel powder, however, still excreted nickel after 6 weeks.

Wase et al [153] injected radioactive nickel chloride into mice and determined the distribution of nickel. Fifty-six adult male mice were administered 102 μg of nickel as nickel chloride by ip injection. Most of the nickel was excreted in the urine and feces by 8 hours after the injection, with fecal excretion predominating. The kidneys contained the highest concentration of nickel, followed by the lungs and plasma. The authors [153] also noted that, at 72 hours after injection, the lungs still retained almost 40% of the nickel initially found there.

(f)   Essentiality of Nickel

A growing body of evidence suggests that nickel has an essential physiologic role in animals. According to Sunderman and coworkers [154] in 1972, this evidence included (1) the finding that serum nickel concentrations appeared to be controlled within relatively narrow ranges [155,156]; (2) identification of a metalloprotein which contained nickel [156-158]; (3) the observation that serum nickel concentrations are altered by several human diseases [159-161]; and (4) results of a preliminary study of induced nickel deficiency in chicks [162-164]. Nielsen [165,166] has reviewed the literature on the essentiality of nickel and concluded that nickel met the requirements for essentiality. In 1975, it was concluded in the NAS-NRC report [3] that nickel partially satisfied established criteria

for essentiality. Unequivocal demonstration that nickel deprivation produced abnormalities that could be cured or prevented by nickel administration was still lacking [3].

Since the publication of these reviews, Nielsen et al [167] have reported results which show additional support for nickel essentiality in chicks. Nielsen et al [168], as well as Schnegg and Kirchgessner [169], have demonstrated, in three-generation studies, nickel deficiency in rats. Schnegg and Kirchgessner [169] stated that the daily nickel requirement for the normal growth of rats was presumably near 50 ppb. This information neither supports nor refutes the premise that a safe exposure level for dermal contact with or inhalation of nickel can be determined, and it should be interpreted as the conclusions of the individual authors rather than those of NIOSH.

Correlation of Exposure and Effect

No reports on the acute toxicity of inorganic nickel in humans have been found. LD50 data in animals for several nickel compounds are summarized in Table III-15 [127,128,136,137,170-174].

Studies of electrolysis workers in nickel refineries in the USSR have shown erosions [26,49,50] and perforations [49,50] of the nose and impairment or loss of the sense of smell [49]. In one study [49], it was noted that symptoms changed in number and kind with duration of employment, but erosions of the nasal septum did not tend to change with age or progress to perforations over the 1.5-year study period. Similar findings have not been reported in other nickel refineries. In a Norwegian refinery, however, atypical epithelial changes were noted in 17% of the

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nasal tissue samples removed from nickel workers by biopsy [72].

Some workers exposed to nickel, particularly those who had skin contact with nickel solutions, developed dermatosis [27-29]. The only recent report giving the incidence of occupational dermatosis for nickel workers was a study from the USSR in which 1.8-6.2 cases/100 workers were observed [26]. In a 1926 report [18], dermatosis in a nickel refinery was most prevalent in workers handling nickel salts and solutions; heat and humidity were contributing factors. A recent report [27] also noted that more cases of nickel dermatitis were observed in workers around heated electroplating tanks than were observed in workers employed in cold plating.

Cuts and abrasions [28,29] and the use of degreasing agents [28] have been observed to be predisposing factors in the development of dermatitis. Additional evidence is available from animal studies. In rats administered nickel chloride on intact skin, nickel penetrated only to the first layer of the epidermis; on skin treated with sodium lauryl sulfate, nickel penetrated much further [144]. Nickel was not found in the organs of rabbits administered nickel sulfate on intact skin, but if the skin was first abraded or treated with an organic solvent, nickel was found in the liver, kidneys, and lungs [147].

Poor work practices, such as the failure to wear gloves, have been cited as contributing to the development of dermatitis [27,29]. Once sensitivity to nickel has been developed, it has persisted, and workers have had to be transferred to areas where additional contact with nickel was unlikely [29,30].

Asthmatic disease has been reported in persons with nickel dermatitis [52,53]. In one case, eosinophilia was diagnosed [53]. Although these case reports are insufficient to permit any conclusions concerning occupational exposure to nickel, it appears that a few persons who become sensitive to nickel may develop lung complications.

Inhalation studies in animals have demonstrated adverse lung effects from exposure to inorganic nickel. Rats exposed to nickel chloride at a concentration of 0.1 mg of nickel/cu m for 12 hours daily for several weeks developed hyperplasia and showed peribronchial lymphocytic infiltration and mucus secretion [131]. Rats exposed to nickel chloride at 1 mg of nickel/cu m for 6 months had increased lung weights, and nickel appeared to exacerbate preexisting lesions [132]. Sclerosis has been reported in dogs [130] and rats [129], although no definite conclusions could be drawn from these experiments because of the lack of controls.

In parts of several long-term inhalation studies designed to assess the carcinogenicity of nickel and its compounds, other effects were also noted. Hamsters exposed to nickel oxide at a concentration of 39 mg of nickel/cu m for three weeks developed inflammation and congestion of the lungs and emphysema [134]. The lungs of rats and guinea pigs receiving lifespan exposure to elemental nickel at an average concentration of 15 mg/cu m had excessive adenomatoid lesions; in rats, the majority had chronic paranasal sinus inflammation and ulceration; and in guinea pigs, edema, hemorrhage, and hyperemia were common [82]. In a similar experiment, hamsters showed little effect from exposure to metallic nickel [83]. Rats exposed to nickel subsulfide at a concentration of about 1 mg/cu m for approximately 80 weeks had abcessed, consolidated lungs with

varying degrees of hyperplasia or metaplasia [78]. In humans, only two reports of pneumoconiosis were found [54,55], and they are inadequate to assess the possibility of adverse lung effects in humans from exposure to inorganic nickel. Considering the number and degree of changes observed in animal studies, especially when these resulted in cancer, a more thorough study of respiratory organ effects other than cancer is needed in humans.

Nickel chloride injected ip has caused proteinuria and aminoaciduria in rats [148]. Nickel may accumulate in human kidneys [175] and it has been shown to accumulate in the kidneys of animals [138,150]. These studies are only suggestive of kidney effects and further studies are needed to determine if adverse effects of exposure to inorganic nickel may result in functional changes in the kidneys.

Animal exposures to inorganic nickel have produced a variety of endocrine [130,138] and enzymatic [136,138] changes. The iodine-fixation rate [130] and the levels of insulin [138], glucose [137,138], and glycogen [136] were reportedly affected. These effects are difficult to extrapolate to humans, since none of these effects has been investigated in workers exposed to nickel.

Inorganic nickel has not been adequately tested for ocular toxicity. Nechiporenko [67] has reported eye damage in electrolysis workers, but the extent of exposure was not reported. An animal study [146] also suggests that nickel chloride (30% in proprietary solution) may be mildly irritating to the eyes.

Carcinogenicity, Mutagenicity, Teratogenicity, and Effects on Reproduction

     (a)   Carcinogenicity

Epidemiologic studies indicate that workers engaged in operations in which nickel is processed have increased risks of developing cancer of the nose [35,37,39-41,43,44,47], lungs [35,37,39-41,43-46], larynx [41,43], and possibly the kidneys [44 and E Pedersen, written communication, December 1976]. Environmental data on the concentrations of airborne nickel or on the chemical compositions of nickel compounds to which workers were exposed were not provided in any of the epidemiologic studies on nickel workers. However, based on estimates of the concentrations of airborne nickel in the past [41] and information on the processes used to refine nickel [10,23,36,41], it appears that workers who developed lung or nasal cancer were exposed to mixtures of many different nickel compounds, and that the risks of developing lung and nasal cancer were greatest for workers employed in operations which had the highest concentrations of airborne nickel.

An increase in the number of deaths from nasal cancer in nickel workers was first noted in 1932 in workers at a nickel refinery in Clydach, Wales [21]. Epidemiologic studies by Doll et al [39,40] have shown that the risks of death from lung and nasal cancer were highest in workers first employed at the Clydach nickel refinery before 1925 and have decreased substantially for workers beginning employment in subsequent years. In the most recent study, Doll et al [40] reported that, as of the beginning of 1972, the O/E ratio of deaths from lung cancer had decreased from 7.0:1 in workers first employed before 1925 to 1.9:1 in workers first employed after 1925. The O/E ratio of deaths from nasal cancer was 329:1 for workers

first employed before 1925. No deaths from nasal cancer have been identified in workers first employed after 1925, but nasal cancer was listed as an associated cause of death for one worker first employed in 1929 [40].

In epidemiologic studies, Hill [35] and Doll [37] found that process workers were more likely to die from lung or nasal cancer than nonprocess workers. In one study [37], the risks of death from lung and nasal cancer were significantly greater in both process and nonprocess workers than in the general population of England and Wales. Doll [37] reported that, as of 1956, the O/E ratio of deaths from nasal cancer was 297:1 in process workers and 119:1 in nonprocess workers, and the O/E ratio of deaths from lung cancer was 7.1:1 in process workers and 3.4:1 in nonprocess workers.

In 1958, Williams [38] found that concentrations of nickel, but not of arsenic, were elevated in the lungs of two Clydach nickel refinery workers. The concentrations of nickel were 90 and 120 ppm of dry tissue, compared to an average nickel concentration of less than 5 ppm in the lungs of two comparison groups. In contrast, the concentrations of arsenic were less than 0.2 ppm in the lungs of the two nickel workers and the lungs of both comparison groups.

In a study of 507 workers employed in one department at the Clydach refinery for 15-25 years, Morgan [36] found that deaths from nasal cancer and lung cancer occurred most frequently in calciner furnace workers, especially those who cleaned the flues, and in copper sulfate process workers, followed by other furnace workers, crushing and grinding department workers, and workers transporting matte to the Mond (carbonyl) process area. Morgan [36] reported that Clydach nickel refinery workers

began to wear gauze masks in 1922; Inco recently reported that workers always wore double gauze masks [41]. The efficiency of these double gauze masks ranged from 70 to 95%, but the masks were less efficient for smaller-sized particles (less than 4 μm) [41]. The most recent epidemiologic study by Doll et al [40] has shown that the risk of death from nasal cancer in Clydach nickel refinery workers has decreased with the year of first employment more rapidly than the risk of death from lung cancer. This finding indicates that larger particles were probably associated with the development of nasal cancer and smaller particles were probably associated with the development of lung cancer. The gauze masks first worn by Clydach workers in 1922 appear to have been the most significant factor in reducing worker exposure to airborne dust at this refinery.

No information was found on specific nickel compounds to which Clydach workers were exposed. However, a substantial amount of information was available on processes used to refine nickel and how they were changed over the years [10,23,36,41]. The assumption that workers were exposed to dusts and fumes of materials present in the operations in which they were employed is reasonable and permits some qualitative estimates of the nickel compounds involved. Quantitation is not possible, since nickel sulfides, escaping into the air as burning particles, were probably at least partially converted to nickel oxides; thus, exposure to nickel oxide may have been greater than the nickel oxide content of the feed material would suggest. Additionally, some contaminants are more volatile than nickel so that higher concentrations of these elements would be possible [41].

Initially, feed material at Clydach was a nickel-copper sulfide matte containing 40-45% nickel [23]. Workers in the calciner sheds were exposed

to dusts from the crushing and grinding of the matte and to nickel sulfides and nickel oxides emitted during the high-temperature oxidation process. Workers extracting copper and transporting the leached matte to the carbonyl sheds were exposed to calcined nickel oxide dusts and, before 1925, to arsenic present in the acid used for leaching [36]. Since material from the carbonyl sheds was returned for reprocessing [41], calciner workers were also exposed to materials added during the process. After 1933, the sulfur content of the feed was decreased, and, in 1945, the feed was changed to nickel oxide [36]. Thus, the forms of nickel to which workers were exposed have varied over the years.

Some monitoring data are available for limited areas of the Clydach refinery. In 1932, changes in calciners appeared to have lowered sulfur dioxide levels from about 25 ppm to about 1.5 ppm, although total dust concentrations remained high [41]. Based on an estimate of 70% nickel in the dusts, there were roughly 20 mg of airborne nickel/cu m in the calciner sheds in 1949. However, wide variations were reported [41] and employee exposures cannot be estimated. No data were available to estimate worker exposure in the pre-1925 conditions and the percentages of contaminants in dusts are not available.

In 1950, Loken [42] reported three cases of lung cancer in workers employed at a nickel refinery in Kristiansand, Norway, where matte from nickel sulfide ore was processed [10]. Two of the workers had been employed in the roasting kiln area and the third had worked in shearing nickel and as a foreman of an unspecified department. The concentration of nickel in the lungs of one of the affected workers from the roasting kiln area was reported to be quite high, 2.8 mg/g of dry tissue, although the

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worker had not worked at the refinery for 10 years prior to the determination.

An epidemiologic study by Pedersen et al [43] has shown that workers in many occupations at the Kristiansand nickel refinery had an increased risk of developing cancer of the respiratory organs. The risk was greatest in roaster and smelter workers and in electrolysis workers, but workers employed in other process departments at the nickel refinery also had an increased risk. In roaster and smelter workers, the O/E ratios of cases were 50.0:1 for cancer of the nose, 10.0:1 for cancer of the larynx, and 4.8:1 for cancer of the lung. In the electrolysis department workers, the O/E ratios of cases were 30.0:1 for cancer of the nose and 7.2:1 for cancer of the lung; no cases of cancer of the larnyx were identified. In process workers in other departments, the O/E ratios of cases were 10:0:1 for cancer of the nose, 5.0:1 for cancer of the larynx, and 4.6:1 for cancer of the lung. In nonprocess workers and workers in unspecified processes, the O/E ratios of cases were 20.0:1 for cancer of the nose and 1.5:1 for cancer of the lung; no cases of cancer of the larynx were identified. The risk of developing lung cancer was highest in electrolysis workers employed at the refinery for at least 15 years (O/E ratio of 23.4:1) [43]. In addition, three cases of kidney cancer have been reported in workers at this refinery (E Pedersen, written communication, December 1976). Pedersen et al [43] showed that increased risks of developing cancers of the nose, larynx, and lung were not limited to workers engaged in the roasting and smelting of nickel ore. At the Kristiansand nickel refinery, the risk of developing lung cancer was greater in electrolysis workers than in roaster and smelter workers; the overall risk of developing cancer of the respiratory organs

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was significantly greater in all nickel refinery workers than in the general population of Norway. Dust from nickel sulfide or oxide was present in the roasting and smelting departments, while aerosols of nickel chloride and sulfate were predominant in electrolysis areas; nickel oxide and sulfate were found in copper-leaching areas (E Wigstol, written communication, April 1977).

In 1965, Tatarskaya [48] reported two cases of nasal cancer in workers engaged in the electrolytic refining of nickel in the USSR. Epidemiologic studies [58,59] from the USSR suggest that workers engaged in processing nickel oxide ore have an increased risk of death from cancer at several sites. Because of methodologic deficiencies, however, interpretation of these studies [58,59] is difficult. In addition, sulfur was added in the process [10], so no extrapolation of the results can be made to other nickel oxide ore refineries using different processes.

In an epidemiologic study of deaths in workers and pensioners at a nickel refinery in Port Colborne, Ontario, Sutherland [44] found that, between 1930 and 1957, the O/E ratios of deaths in nickel workers were 37.1:1 for nasal cancer and 2.2:1 for lung cancer. Sutherland's study was updated by Inco in 1976 to include deaths that occurred in Port Colborne workers between 1930 and 1974 [41]. In the updated study, the O/E ratios of deaths for these workers were 51.1:1 for nasal cancer, and 1.9:1 both for cancer of the lung and for cancer of the larynx. The occupational histories of 36 workers who had developed nasal cancer and of 90 workers who had developed lung cancer as of June 1976 [41] indicated that deaths from lung and nasal cancer were not limited to calciner, sinter, or cupola furnace workers [41]. Of the 36 workers who developed nasal cancer, one

was employed only in occupations that were not dusty, one was employed only as an electrolysis worker, one was employed only as an anode furnace worker, and three others were never employed as calciner, sinter, or cupola furnace workers. The 90 workers who developed lung cancer were also employed in different occupations at the refinery. The expected number of deaths in each exposure group was not provided, but, based on the occupational histories of these 126 workers, it appears that deaths from lung and nasal cancer in Port Colborne nickel refinery workers were not limited to any one exposure group. In addition, 3 deaths from kidney cancer were identified in a group of 225 electrolysis workers [44], suggesting that these workers may also have an increased risk of developing kidney cancer, since kidney cancer is rare in the general population.

The available information on nickel refining processes [10,23] and limited environmental data [41] were used to estimate the major airborne contaminants at the Port Colborne nickel refinery. Cupola furnace workers handled mixed copper and nickel sulfides. Impure nickel sulfides, containing nickel subsulfide, were oxidized in sinter and calciner furnaces at temperatures of 600-1,650 C [41]. Workers near these furnaces were probably exposed to high concentrations of nickel subsulfide and nickel oxide dust and fume. Area monitoring in the sinter plant at Port Colborne indicated an average total dust concentration of about 340 mg/cu m, estimated to contain about 50% nickel [41]. Since nickel oxide was reduced to nickel in anode furnaces [23], workers near these furnaces were exposed to airborne nickel oxide and possibly to elemental nickel. Electrolysis workers at the Port Colborne refinery were probably exposed primarily to mists of nickel salts and hydrides emitted from the electrolysis tanks,

which contained nickel sulfate and boric acid until the 1940's, when nickel chloride was also added [23], and to other nickel compounds, including nickel metal and nickel carbonate, used in the purification of the electrolytic solution. Some electrolysis workers, particularly those engaged in cleaning anode scrap or operating the desulfurization furnace may have been exposed to high concentrations of nickel. High volume samples taken recently near electrolysis tanks had an average concentration of 0.11 mg/cu m of airborne nickel, although one personal sample had a concentration of 8.13 mg/cu m of airborne nickel [41].

In workers at a sinter plant in Copper Cliff, Ontario, Sutherland [45] found that the risk of death from lung cancer was elevated. One death from nasal cancer was also identified in the sinter plant workers studied by Sutherland. These workers were exposed to dusts and fumes at concentrations similar to those observed in the Port Colborne sinter plant [41]. In an epidemiologic study [46] of deaths from cancer in four other occupational groups at the Copper Cliff nickel smelter complex, Sutherland found that the O/E ratio of deaths from cancer of the respiratory organs was slightly elevated in all four groups combined (converter furnace workers, mill and matte separation workers, underground miners, and copper refinery workers), but it was not significantly greater than in the population of Ontario.

No data on exposures were available for these groups. Recent data suggest that miners are exposed to nickel at concentrations between 6 and 40 μg/cu m and that concentrations of airborne nickel now range from undetectable to 2.8 mg/cu m in the mill area, 0.17-15.3 mg/cu m in the matte separation area, and 0.03-0.2 mg/cu m in the converter furnace area.

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Preliminary epidemiologic studies [41,47] suggest that some workers at a nickel alloy plant in Huntington, West Virginia, may have had an increased risk of death from cancer of the respiratory organs. Between 1922 and 1948, nickel-copper sulfide matte, including nickel subsulfide, was oxidized in calciner furnaces similar to those used at Clydach, Wales, and at Port Colborne and Copper Cliff, Ontario [41]. Three deaths from nasal cancer, those of a bricklayer, a laborer [47], and a worker with no apparent exposure to dusts from the calciner furnaces [41], have been identified in these workers. The risk of death from cancer of the respiratory organs was slightly elevated but not statistically significant in retired hourly workers (O/E ratio 1.57) [47], although it was not elevated in all workers (O/E ratio 0.97) [41]. Limited area samples in the calciner sheds contained 5-15 mg of nickel/cu m near the furnace and 20-350 mg/cu m near the grinders. In the melt shop, area samples contained 5-150 mg of total dust/cu m, probably largely nickel [41]. These studies [41,47] suggest that Huntington nickel alloy plant workers may have had slightly elevated risks of developing nasal and lung cancer. It cannot be determined from these preliminary studies, however, if nickel alloy plant workers other than those who were exposed to dust and fume from calciner furnaces would also have an increased risk of developing cancer of the respiratory organs.

Three case reports suggest that exposure to airborne nickel in occupations other than those in nickel refineries may also be associated with the development of cancer of the respiratory organs [62-64]. A case of lung cancer was reported in a 36-year-old man engaged in grinding and polishing nickel-plated material [63], a reticulosarcoma of the nasal fossa

was reported in a 59-year-old woman who electroplated cutlery with nickel [62], and a squamous-cell carcinoma of the nasal cavity was recently reported in a 35-year-old man employed in a nickel stripping operation [64].

On the basis of epidemiologic studies, it appears that the risk of developing cancer of the respiratory organs in nickel refinery workers is related to the extent of exposure to airborne dust, mist, or fume containing nickel. Based on occupational histories of workers who developed lung or nasal cancer, it appears that nickel workers who developed cancer of the respiratory organs were exposed to a mixture of airborne nickel compounds, including nickel subsulfide; nickel oxide; nickel metal; and to nickel salts, such as nickel sulfate, nickel chloride, and nickel carbonate. Exposure to airborne coke, arsenic, or other trace elements or compounds may contribute to the increased risk of developing lung cancer in nickel workers. However, exposure to coke, arsenic, or other trace elements has not been associated with the development of cancer of the nose [75].

The carcinogenic potential of individual nickel compounds has been tested in experimental animals. The experimental data are summarized in Table III-16 at the end of this chapter. Wistar rats did not develop lung tumors over a 15-month observation period after an intratracheal injection of 5 mg of nickel subsulfide [77]. However, rats developed benign and malignant tumors after about 80 weeks of exposure to nickel subsulfide inhaled at a concentration of 1 mg/cu m [78]. Nickel subsulfide has induced a high rate of injection-site tumors in rats [88,89,91] and mice [88]. Kidney carcinomas were found in 45% of rats injected intrarenally

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with nickel subsulfide [103]. Hamsters did not have a high rate of injection-site tumors after im injection of nickel subsulfide [95].

Inhalation of nickel powder produced no lung tumors in rats or mice and only a single tumor in guinea pigs [82]. Kim et al [81] found 3 lung tumors in 60 rats exposed to nickel powder by inhalation; 1 lung tumor was observed in 55 control animals. Rats and hamsters did not develop lung tumors when exposed to nickel powder by intratracheal instillation [83]. Lesions suggestive of potential tumor development were noted in several studies [82,83], but these studies did not show that elemental powdered nickel induced malignant tumors under the studied conditions. Nickel powder has also been injected by many other parenteral routes. Rats developed tumors at the site of im injection [99], intrafemoral implantation [96,97], and intrapleural injection [97,105]. Intrarenal injection of nickel did not produce kidney carcinomas in rats [103]. A tumor developed in 1 of 6 rabbits at the site of intrafemoral implantation, but no tumors developed in 10 rabbits exposed to nickel powder by iv administration. No injection-site tumors were induced in mice by iv, im, or intrapleural injections.

Hamsters did not develop lung tumors during lifespan inhalation exposure to nickel oxide; however, two osteosarcomas and one rhabdomyosarcoma were reported [80]. Intramuscular injection of nickel oxide produced injection-site tumors in rats and mice [88]. Rats also developed tumors at the site of nickel oxide implants [101].

Other nickel compounds have also been tested. Nickel carbonate, nickel fluoride, nickel hydroxide, and nickel-iron matte have induced injection-site tumors [94,101,102]. Nickel acetate reportedly induced

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tumors at the site of injection [99,101] and also lung adenomas [104];
nickel sulfate [100,101], nickel chloride [101], and nickel ammonium
sulfate [101] did not produce injection-site tumors. Nickel-monosulfide
injections did not cause kidney tumors in rats [103].

The experimental studies of the carcinogenicity of nickel and its
compounds in animals have not been particularly helpful in determining
whether or not all forms of nickel may cause tumors. The small nodules,
so-called "microcarcinomas," found by Hueper [82] in rats exposed to nickel
dust lend support to the conclusion that elemental nickel can cause tumors
when particle sizes are small enough for the dust to be airborne; in this
case, most particles were smaller than 4 μm. Many other experimental
studies in rodents have been less helpful, because of inadequate
experimental design, such as using exposure and observation periods that
are too short, or perhaps because of the insensitivity of many rodent
species or strains to the induction of tumors in the respiratory tract.

Injection-site sarcomas have been induced in rodents by many nickel
compounds, but the applicability of these studies to a recommendation for
workplace exposure to inorganic nickel is questionable. Injection-site
tumors have been induced by compounds that have not caused cancer in
animals by other routes of exposure, but it is not clear whether this lack
of association between the tumor-producing potential of some compounds by
implantation with this potential by other routes of exposure also applies
to metals and metal compounds. These data, however, justify recommending
precautions to keep nickel from getting into open wounds.

The 1976 edition of the Registry of Toxic Effects of Chemical
Substances, published by NIOSH, lists nickel refinery dust as carcinogenic

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in humans. Several other nickel compounds are listed as suspected carcinogens in animals. This information was obtained from an IARC monograph on nickel [1]. These studies, together with additional investigations of the carcinogenicity of inorganic nickel, have been reviewed in this chapter.

(b)   Genetic Effects

In tests on a variety of microorganisms, eg, viruses [111], bacteria [108], and yeast cells [112], nickel salts gave no evidence of mutagenic activity. Tests on pea and bean root tips have suggested that nickel interferes with mitosis [114-116]. The positive results on plants may have little relevance to safety evaluations for human beings. No reports of mutagenicity tests for nickel in animals were found.

(c)   Teratogenicity and Other Effects on Reproduction

Nickel acetate administered iv in doses of 2-25 mg/kg on the 8th day of gestation produced undescribed abnormalities in hamsters [117]. No findings for control animals were reported. Chick embryos did not show abnormal morphologic development when nickel chloride was injected into the egg [119], but nickel chloride solutions interfered with sea urchin egg development [120]. In a recent abstract, Sunderman et al [118] reported fetal toxicity following im injection of nickel chloride into Fischer rats at doses of 12 and 16 mg of nickel/kg. No fetal malformations were noted. Administration of nickel acetate at a dose of 1 mg/kg/day for 15 days reportedly did not affect the reproductive process of male guinea pigs [126], but the study was not reported in sufficient detail.

Nickel salts produced testicular damage in rats and in mice given oral [123], subcutaneous [122], and intratesticular [125] doses of 10-25

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mg/kg. In one study, the effect was reversible [122]. In a three-generation study in rats, 5 ppm of nickel in the drinking water, which corresponded to an ingested nickel dose of about 37.6 μg/d for an adult rat [84], had adverse effects on reproduction [121]. Because of the lack of detail in this report, which ,summarized experimental results on seven metals, it is difficult to determine which parts of the reproductive process were affected. A decrease in the ratio of males to females in the litters and an increase in the number of runts suggests that an effect on gestation, perhaps on transplacental toxicity, occurred. The limited data presented do not clearly indicate whether there were effects on postnatal viability, such as those that might result from an effect on lactation. Studies that are more definitive than this report [121] are needed before these effects might be considered in a standard for workplace exposure to inorganic nickel.

No case reports or epidemiologic studies have been found which address the subject of reproductive or teratogenic effects in humans exposed to inorganic nickel. Single studies on several animal species suggest that some animals are susceptible to reproductive and possibly to teratogenic effects when given nickel by various routes of administration. Research is needed, including experimental animal studies and human epidemiologic studies, to determine whether nickel affects human reproduction.

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TABLE III-15

LD50 DATA FOR NICKEL

Compound	Species	Sex	Route of Exposure	LD50 (mg/kg)	Time of Death	Reference
Nickel acetate	Mouse	M	Oral	410	24-72 hr	127
"	"	F	"	420	"	127
"	"	M	ip	32	6-48 hr	127
"	"	F	"	32	"	127
"	Rat	M	Oral	360	24-72 hr	127
"	"	F	"	350	"	127
"	"	M	ip	23	6-48 hr	127
"	"	F	"	23	"	127
Nickel chloride	Mouse	-	"	26	-	170
"	Rat	F	"	11	1 wk	137
"	"	F	"	14	-	171
"	"	F	im	51	-	171
"	"	M	Oral	232	Several d	128
"	"	F	"	285	"	128
Nickel chloride hexahydrate	Mouse	-	ip	48	-	170
Nickel sulfate	"	-	"	38	10 d	172
"	"	M	"	21	30th d	173

TABLE III-15 (CONTINUED)

LD50 DATA FOR NICKEL

Compound	Species	Sex	Route of Exposure	LD50 (mg/kg)	Time of Death	Reference
Nickel perchlorate heptahydrate	Mouse	M	ip	100	4 min-12 hr	174
Nickel oxide (55.9%) and sulfide (20.9%) dusts	Rat	-	it*	110	Over 3 d	136
"	"	-	ip	690	"	136
"	Mouse	-	"	744	"	136

*Intratracheal administration

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TABLE III-16

TUMORIGENICITY OF NICKEL COMPOUNDS

Compound	Species	Route of Exposure	Dose (mg)	Dosage Schedule	% Tumors*	Reference
Nickel subsulfide	Rat	Inhal	1.0/cu m	78-80 wk Controls	14 <1	78
"	"	Tracheal	5.0/rat		0	77
"	"	im	20.0/site		80	88
"	Mouse	"	5.0/site		53	88
"	"	"	"		33	88
"	Rat	Implant	250.0/disc	0-32 d	0	89
"	"	"	"	64 d	27	89
"	"	"	"	128 d	73	89
"	"	"	"	256 d	73	89
"	"	im	0.6/rat		27	91
	"	"	1.2/rat		73	91
	"	"	2.5/rat		87	91
	"	"	5.0/rat		100	91
	"	"	10.0/rat		100	92
				Controls	0	92
"	"	"	10.0/rat		100	93
"	"	"	"		52	93
"	"	Renal	5.0/kidney		45	103
Nickel oxide	Hamster	Tracheal	4.0/rat	30 wk	0	79
	"	Inhal	53.2/cu m	Lifespan	3	80
	Rat	im	20.0/site		41	88
	Mouse	"	5.0/site		35	88
	"	"	"		23	88

TABLE III-16 (CONTINUED)

TUMORIGENICITY OF NICKEL COMPOUNDS

Compound	Species	Route of Exposure	Dose (mg)	Dosage Schedule	% Tumors*	Reference
Nickel oxide	Rat	Implant	7.0/rat	3 implants	3	101
Nickel sulfate	"	"	"	"	0	101
"	"	im	5.0/site		0	88
Nickel acetate	"	Implant	7.0/rat	3 implants	3	101
	"	im	35.0/kg		22	99
		ip	360.0/kg	3x/wk x 8 wk controls	1.26** 0.42**	104
Nickel powder	"	Inhal	2.9/cu m	Up to 26 mon Controls	5 2	81
"	Guinea pig	"	15.0/cu m	Up to 15 mon	2	82
"	Rat	"	"	"	0	82
"	"	Tracheal	4.0/rat	Repeated at 12 mon	6	83
"	Hamster	im	5.0/hamster	5 monthly	4	95
"	Rat	"	5.0/rat	"	76	95
"	"	"	28.0/rat	Killed at 7 mon	10	100
"	"	"	50.0/rat		66	99
"	"	"	3.6/rat		0	94
"	"	"	14.4/rat		20	94

TABLE III-16 (CONTINUED)

TUMORIGENICITY OF NICKEL COMPOUNDS

Compound	Species	Route of Exposure	Dose (mg)	Dosage Schedule	% Tumors*	Reference
Nickel powder	Rat	Renal	5.0/kidney	Both poles	0	103
"	"	Intra-pleural	5.0/rat	5 monthly injections	20	105
"	"	"	50.0/rat	"	16	97
"	"	Femoral	-		27	96
"	Rabbit	"	-		17	96
"	Mouse	iv	-		0	96
"	Rat	"	-	6 weekly injections	33	96
"	Rabbit	"	-	"	0	96
"	Mouse	im	-		0	96
"	"	Intra-pleural	-		0	96
"	Rat	im	28.3/rat		100	98
Nickel acetate	Mouse	Oral	5.0/liter	Lifespan	17	86
	"			Controls	22	
	"		"	Lifespan	14	85
	"			Controls	32	
Nickel carbonate	Rat	Implant	7.0/rat	3 implants	30	101
Nickel monosulfide	"	Renal	5.0/kidney	Both poles	0	103
	"	im	5.6/rat		0	94
	"	"	22.4/rat		0	94

*Percent of rats with tumors related to treatment; see text for details
**Data given in tumors/rat

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IV. ENVIRONMENTAL DATA AND ENGINEERING CONTROLS

Sampling and Analytical Methods

During industrial operations, nickel and inorganic nickel compounds may escape into the environment as dusts from grinding, cutting, and melting operations [23,176], as fumes where high temperatures are involved, and as mists where nickel solutions are used [26]. Routine sampling and analytical methods do not permit the identification of individual nickel compounds present in the occupational environment. Therefore, only sampling and analytical methods for total nickel are discussed here. A direct readout method for analysis of airborne nickel dust, fume, or mist has not been found.

No air sampling methods specific for total nickel determinations have been found. A variety of methods suitable for general particulate sampling have been used [13,23,176], and samples collected by these methods often contain large amounts of other metals and metallic compounds. In a nickel smelter or refinery, other elemental components present in the ore, eg, copper, iron, lead, arsenic, and other trace materials, may be present [10]. Samples from the battery-making industry frequently contain cadmium [177]. Other metals, particularly chromium, are used with nickel in the electroplating industry [178]. Thus, since no sampling methods are nickel-specific and other metals are often present, the analytical method must be specific for nickel.

Tada [179], in 1968, recommended the use of a midget impinger containing 5 ml of distilled water to sample water-soluble nickel compounds. A sample volume of 10 liters, collected at the rate

of 3 liters/minute, was recommended; the resulting sensitivity for nickel was reported as 0.1-3 mg/cu m. However, the use of impingers is not preferable to collection on a filter because of the inconvenience to the worker during sample collection and because of the unknown collection efficiency of an impinger with water for insoluble nickel dusts and fumes.

When gravimetric determinations of total dusts are performed concurrently with nickel analysis, filters are the preferred method of sample collection. However, when very low concentrations of nickel in the environment are being determined, the background concentration of nickel in the filter must be considered [180]. In 1972, Hwang [181] reported the following nickel concentrations in common filters: glass fiber filter, less than 0.08 μg nickel/sq cm; silver membrane filter, 0.1 μg nickel/sq cm; and organic membrane filter, 0.001 μg nickel/sq cm. Pate and Tabor [182], in 1962, reported 0.33 μg of nickel/37-mm glass-fiber filter. Because of their high nickel content, glass-fiber filters are not recommended for nickel sampling.

Membrane filters of many types have been used to collect particulate nickel [23,180,183]. Cellulose-ester membrane filters have been shown to contain very low amounts of nickel. Birks et al [184] reported 0.001 μg nickel/sq cm based on emission spectrographic analysis; Dams et al [185], using neutron activation analysis, reported the nickel content of these filters to be less than 50 ng/sq cm. Polycarbonate-membrane filters have also been used in sampling for airborne nickel [183], and a filter manufacturer [186] reports nickel concentrations of 0.007 μg/sq cm of filter. Polycarbonate-membrane filters, however, may cause digestion residue problems.

NIOSH's currently accepted sampling method for airborne metals uses a cellulose-membrane filter [187]. Although the cellulose-membrane filter may contain some contaminant nickel, the use of a blank filter for estimating background levels and a sufficiently large sample volume can overcome this potential problem. A sampling rate of 2.0 liters/minute and a filter pore size of 0.8 μm are recommended. The recommended sampling procedure is detailed in Appendix I.

To collect sufficient nickel for analysis by personal monitoring methods, a large sample volume must be used, generally requiring a sampling period approaching 6 hours. Because some operations may emit variable amounts of nickel into the workplace air, short-term sampling may be necessary to determine the need for engineering controls in particular cycles of an operation; high-volume samples may then be required to collect sufficient nickel for these determinations.

For many metals including nickel, particles collected on a filter can be analyzed by one of several methods. Nickel, if not already in solution, is dissolved and concentrated, this solution can be extracted and is finally analyzed. Lewis and Ott [188] have published a thorough review of the analytical chemistry of nickel. The analytical methods reviewed here are discussed in terms of their suitability for analysis of samples of airborne nickel.

Chromatographic methods of analysis for nickel have been developed. Circular, thin-layer chromatography was found to be semiquantitative for nickel, with a sensitivity of 0.03 μg/drop of test solution when extracted from a mixture of other cations [189]. Paper chromatography has been used in the analysis of nickel-chromium aerosols with a limit of detection of

0.5 μg/sample [190,191]. However, these determinations were based on visual comparisons with color standards.

The ring oven technique, initially a qualitative method but adaptable to semiquantitative analysis [192], is especially useful in area monitoring with a sequential tape sampler [3]. The method is inexpensive and has a limit of detection of 0.075 μg of nickel [193]. Its application to personal breathing-zone samples, however, is less practical.

Gas-liquid chromatography (GLC) has also been used for nickel analyses [194,195], eg, Barratt et al [194] measured nickel concentrations down to 0.1 μg/ml. Rodriguez-Vazquez [195] reviewed the applications of GLC to inorganic chemical analysis and mentioned three necessary conditions for the analysis of metals: the metal must be convertible to a volatile form; the volatile complex must be thermally stable; and the conversion must be quantitiative. Thus, GLC requires the measurement of a secondary nickel complex, the formation of which may introduce error into the analysis.

Investigators have also used activation analysis for the determination of nickel [196-198]. Although these methods are sensitive and do not destroy the sample, the requirements for elaborate equipment, the safety precautions necessary for use of an irradiating beam and radioactive sources, and the relatively small thermal neutron cross section of nickel make activation analysis undesirable for routine use. Activation analysis is primarily useful as a research method.

Polarographic methods have also been used to analyze nickel [199,200]. Polarography possesses the required sensitivity (2μg/sample [200]) and specificity for a variety of heavy metals; however, when this

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method is used for mixtures of metals, such as nickel and cobalt, as is common with air samples, quantitation becomes difficult [200]. Polarographic methods, therefore, depend on prior knowledge of the components of the samples.

Colorimetric methods of analysis for nickel have also been widely used [179,201]. Following the formation of a colored nickel complex, the complex is extracted, and the color intensity is determined with a spectrophotometer. Dimethylglyoxime and ammonium pyrrolidine dithiocarbamate have often been used as complexing agents. Sunderman [201] has reported the limit of detection as 0.04 μg/sample. For repetitive analyses, however, a less time-consuming procedure is desirable.

X-ray fluorescence spectrography has also been used for nickel analyses [184,202]. The method is sensitive and nondestructive. Detection limits of 0.037-0.18 μg nickel/sq cm have been reported [184]. Analysis is accurate and linear in the range from one to several hundred micrograms [202].

The use of the emission spectrograph is a widely reported and extremely accurate method of nickel analysis [176,180,203-205]. Sugimae [180] reported the working range of emission spectroscopy as 10-1,000 μg of nickel/g of sample; the relative standard deviation was determined to be 13.2% at a nickel concentration of 180 μg/g. A sample was analyzed by atomic absorption in 12 laboratories and found to contain 209-293 μg nickel/g (mean 264); Sugimae, using emission spectoscopy, reported 230 μg/g for the same sample. The use of this method has usually been restricted to high-volume samples [203,204].

Atomic absorption spectrometry (AAS), both flame and flameless, has been used to analyze metals in environmental samples [23,183]. Nickel, as well as other metals in the air, can be identified quickly and simply [206]. Advantages of AAS include minimal sample preparation, good selectivity, and relatively simple operating procedures. It is readily adaptable to the measurement of nickel in biologic media and combines good sensitivity with relatively low cost [207].

Begnoche and Risby [183] have reported the use of flameless AAS for the determination of metals, including nickel, in atmospheric particles. However, the authors reported that, because of the use of aqua regia, the graphite tube in their furnace became unreliable after four or five determinations without major modifications. Mitchell et al [208], in 1975, suggested that flameless methods should be used only to exploit their unique characteristic, excellent sensitivity with a small sample size. Otherwise, flameless methods were reported to be slow and interference prone and to require precise operator skills. These problems can be overcome and flameless methods may eventually be sufficiently well characterized for routine nickel determinations.

Flame AAS has been used extensively for the analysis of nickel in samples of airborne particulate matter [23,205,206]. Kneip et al [205] have proposed a tentative method for analysis of nickel. NIOSH has also proposed a similar method [187]. The reported working range of this method was 0.1-20.0 μg of nickel/ml of solution [205]. Hwang and Feldman [206] reported 101-108% recovery using flame AAS. This method was cited as having good selectivity, being simple to operate, requiring minimal sample preparation, and having high sensitivity [206]. Hwang [181] later reported

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a sensitivity of 0.05 μg/ml which gave a 1% absorption at the 232.0-nm line. Moreover, flame AAS is relatively free from sample carryover and memory effects; samples are easily nebulized; and a wide range of operating conditions is available [207].

This method has also been studied for interferences. Silica, beryllium, and antimony were noted to interfere when present in excess [205]. Sundberg [209] recommended an oxidizing flame to minimize the interferences found with hundredfold excesses of zinc, iron, copper, cobalt, and manganese. In unusual situations, therefore, other methods, such as the use of different reagents or centrifugation prior to analysis, may have to be used to overcome specific interferences.

In 1974, NIOSH reported a flame AAS method for the analysis of nickel [187], for which the range was specified as 0.2-20 μg/ml of solution. Further evaluation of this method has resulted in a revision of the lower end of this range, so that the NIOSH Division of Physical Sciences and Engineering now estimates that the lowest reliably detectable concentration of nickel with this method is about 1 μg/ml. This estimate was partially based on consideration of matrix effects and the requirement that the relative standard deviation be 10% or less. This method, as described in Appendix II, is recommended for determining compliance with the recommended TWA concentration limit. In almost all cases, complete dissolution of the residue after acid digestion can be attained if the sample is brought up to a total volume of 10 ml. Therefore, assuming the lowest limit of detection as 1 μg/ml, 10 μg of nickel must be collected for analysis. Since the longest sampling period readily attainable in a single work shift is about 6 hours and a sample flow rate of 2.0 liters/minute is recommended, a

sample volume of 700 liters is the maximum volume readily collected. The lowest air concentration of nickel which will result in the collection of 10 μg of nickel in a 700-liter sample volume is 15 μg/cu m. As an additional condition for analysis, the total signal for the sample must be at least double that of the blank. Use of a filter with a low nickel content and digestion in a minimum amount of acid should eliminate the potential problem of high nickel concentrations in blanks. Any other method used for the detection of nickel in order to determine compliance with the recommended TWA concentration limit must meet or exceed the requirements specified above.

Biologic Monitoring

Urinary nickel monitoring is suggested as a medical surveillance procedure, but a standard for nickel in urine has not been recommended because available data represent an assessment of populations rather than of individuals. The following discussion and the method of analysis outlined in Appendix III may be useful in those situations where biologic monitoring is being considered.

The flame AAS method recommended in Appendix III has been sufficiently tested to ensure its reliability [155,210]. The instrumentation is compatible with that of the recommended environmental monitoring method. Sunderman [207] has reviewed the uses of both flame and flameless AAS in clinical pathology, citing disadvantages and advantages of each method. Nickel concentrations in urine are extremely low and methods are rapidly being developed to adapt flameless AAS to the measurement of nickel in urine.

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At a subcommittee meeting of the International Union of Pure and Applied Chemistry [211], Mikac-Devic et al have recently reported an extremely sensitive and simple method for the determination of nickel in biologic fluids. Urine, serum, or whole blood were wet-digested, the pH adjusted, and a nickel-furil-dioxime complex extracted into an organic phase. The organic-phase nickel was analyzed in a flameless atomic absorption spectrophotometer. The method is extremely sensitive (0.2 μg/liter), sample preparation is not elaborate, and interferences should be minimal. The method is currently undergoing interlaboratory testing. Other direct flameless AAS methods were also reported by Anderson and Zachariasen and Bozic and Etier at that meeting [211]. These also are reported to be simple and sensitive methods for measuring nickel concentrations in biologic samples.

Normal values for nickel concentrations in a variety of biologic tissues have been reported. Nomoto and Sunderman [155] reported the results of AAS analysis of urine collected from 26 healthy subjects in central Connecticut. The mean concentration of nickel found in urine was 0.23 μg/100 ml (SD=0.14). Urinary nickel concentrations in men and women did not differ significantly. The mean urinary excretion of nickel was 2.4 μg/day (SD=1.1; range 1.0-5.6).

The results of Nomoto and Sunderman [155] were verified in 1972 by McNeely et al [212]. The mean concentration of nickel found in the urine of 20 healthy Hartford, Connecticut, subjects, not exposed to nickel in their workplace, was 2.0 μg/liter (SD=0.9; range 0.7-4.0). The mean daily urinary excretion of nickel was found to be 2.5 μg/day (SD=1.4; range 0.5-6.0). McNeely et al [212] were also able to correlate environmental and

urinary levels of nickel in this study. The average atmospheric concentration of nickel in Hartford was 36 μg/1,000 cu m. During the same period, the average atmospheric concentration in Sudbury, Ontario, was 533 μg/1,000 cu m. The mean concentration of nickel in the urine of 19 healthy Sudbury residents who did not work with nickel was 7.2 μg/liter (SD=3.9; range 2.1-16.5). The average daily urinary excretion of nickel was determined to be 7.9 μg/day (SD=3.7; range 2.3-15.7). The authors concluded that the significantly higher urinary nickel concentrations in Sudbury residents resulted from their exposure to much higher environmental levels of nickel.

Zachariasen et al [213] reported an average urine nickel concentration of 24 μg/liter (SD=4; range 16-35) in 8 healthy residents of Kristiansand, Norway, who were not exposed to nickel in the workplace.

Horak and Sunderman [214] reported that nickel in feces collected from 10 healthy Hartford, Connecticut, subjects, not exposed to nickel in their work, averaged 3.3 μg/g wet weight (SD=0.8; range 2.1-4.4) and 14.2 μg/g dry weight (SD=2.7; range 10.8-18.7). Fecal excretion of nickel averaged 258 μg/day (SD=126; range 80-540).

Nodiya [215] reported similar results in an investigation of nickel excretion in 10 healthy Russian vocational students. Total daily nickel ingestion was estimated at 280-300 μg. Fecal excretion of nickel averaged 257.85 μg/day (range 219-278) and urinary excretion averaged 29.07 μg/day (range 27.6-31.3).

Hohnadel et al [216] reported that sweating is a significant route of nickel excretion. An analysis of sweat collected during sauna baths from 48 healthy adults who did not work with nickel showed a mean concentration

of 52 μg of nickel/liter (SD=36) for arm sweat of men and 131 μg/liter (SD=65) of women. The total volume of arm sweat excreted averaged 23 ml (SD=12) in men and 7 ml (SD=3) in women.

Catalanatto et al [217] have reported the concentration of nickel in the parotid saliva from 38 healthy adults, who were employees of the University of Connecticut Health Center, and in Naval recruits in Chicago. None of the subjects worked with nickel and all subjects abstained from eating and smoking for at least 1 hour prior to sample collection. A flameless AAS technique was used to analyze the samples for nickel. The concentration of nickel in the saliva averaged 1.9 μg/liter (SD=1.0; range 0.8-4.5). No differences in the salivary nickel concentrations were found between men and women, health center employees and naval recruits, caries-free subjects and caries-prone subjects, and smokers and nonsmokers.

Schroeder et al [175] reviewed data from several sources on nickel in human tissue. He noted that nickel was reported as normally present in the tissues of most human infants. In addition, the lungs, liver, kidneys, and intestines of most stillborn fetuses usually contained nickel.

Concentrations of nickel in urine and plasma following workplace exposure to nickel also have been reported. Kemka [218] reported the results of spectrophotometric analysis of nickel in the atmosphere of a smelting plant and in the urine of the employees. The highest average concentration of airborne nickel, 0.349 μg/cu m, was found in the electrolysis section of the plant; the highest urinary nickel concentration found in electrolysis workers was 240.0 μg/liter (24.0 μg/100 ml). Urinary nickel concentrations of 10 randomly selected nonexposed subjects averaged 27.0 μg/liter (2.7 μg/100 ml).

In 1967, Klucik and Kemka [219] reported the concentration and the elimination rate of nickel in the urine of six electrolysis workers exposed to aerosols of nickel sulfate and nickel carbonate. Environmental nickel concentrations were reported to have ranged from 0.086 to 1.265 mg/cu m. The six workers were isolated in a hospital after a work shift, and the nickel concentration in 24-hour urine samples was determined by polarography. The control value, obtained from persons with no exposure to nickel in their work, was 9.8 μg/100 ml. First-day nickel concentrations averaged 26.4 μg/100 ml; in all workers but one, the concentration returned to the normal within 7 days. This worker showed increasing urinary nickel concentrations (12.5-22.5 μg/100 ml) over the 7 days. The authors suggested that the increasing elimination of nickel may have resulted from nickel retention in that worker.

Morgan [220] used a colorimetric method of nickel analysis to determine the concentration of nickel in the urine of workers in various departments of a nickel refinery. In the carbonyl process department, nickel concentrations in the urine ranged from 0.008-0.15 ppm (about 0.8-15 μg/100 ml). In those departments where workers were exposed only to raw materials and not to nickel carbonyl the following urine-nickel values were reported: furnaces--0.01-0.043 ppm (1-4.3 μg/100 ml); chemical precipitation plants--0.005-0.06 ppm (0.5-6 μg/100 ml); and calcination plant--0.002-0.05 ppm (0.2-5 μg/100 ml). Morgan [220] compared these data to those of control applicants for employment in the nickel plant aged 18-48 years, whose average urinary nickel concentration was 0.04 ppm (SD=0.02) (4 μg/100 ml).

Hogetveit and Barton [221], in 1975, presented plasma and urinary nickel data collected from workers at a nickel refinery in Kristiansand, Norway. Plasma nickel concentrations averaged 0.74 μg/100 ml in "tank house" electrolysis workers exposed to soluble nickel compounds and 0.6 μg/100 ml for 126 roasting and smelting department workers. These values were compared to those obtained from university students, which averaged 0.42 μg/100 ml. Four persons (anode-cleaning worker, smelting department worker, metal shop employee, and university volunteer) were monitored serially. Plasma and urinary nickel analyses were made every 10 days for 6 months. The nickel values dropped to nearly normal during a 2-week off-work period and increased during periods of overtime and increased production. The metalworker's plasma and urinary nickel values were lower than those of the two nickel refinery workers but were still above those the university student. The authors [221] concluded that workers exposed to soluble nickel compounds (electrolysis workers) had higher biologic nickel values, and that nickel concentrations decreased rapidly when an employee went on furlough or retired.

In 1975, Noreseth [222] compared worker exposures to airborne nickel, as measured by personal samplers, with the preshift and postshift urinary nickel concentrations of the same workers. The study included workers from the roasting, smelting, and electrolysis departments of a nickel refinery, and welders. Roasting and smelting department workers were potentially exposed to nickel concentrations of 1.3 mg/cu m (SD=0.3) as determined from 32 mean weekly determinations, but these workers wore respiratory protection; their urinary nickel concentrations averaged 6.6 μg/100 ml (SD=0.4) for 189 determinations. The electrolysis department workers were

exposed to 0.4 mg nickel/cu m (SD=0.3) (26 mean weekly values) and showed

13.2 μg nickel/100 ml (SD=0.85) of urine in 180 determinations. Six of 19

welders were exposed to nickel concentrations greater than 1 mg/cu m and 1

welder was exposed to as much as 5.4 mg nickel/cu m; 4 of 19 welders had

urinary nickel concentrations exceeding 10.0 μg/100 ml and the other 15

were below 10.0 μg/100 ml. Noreseth [222] also observed that welders had

urine excretion ratios similar to those of roasters and smelters; he

attributed this to exposure to similar chemical forms of nickel.

Electrolysis workers, although exposed at lower nickel concentrations, had

elevated excretion levels because their exposure was to soluble forms of

nickel such as nickel chloride or nickel sulfate. Although the exposure-

to-excretion ratios of welders were fairly well correlated (correlation

coefficient 0.85), this may have been due to a more uniform exposure than

that of other groups; the author stated that, on the whole, urinary

excretion of nickel was poorly correlated with an individual's exposure

and, therefore, of limited use in assessing the exposure of the individual.

Environmental Data

Nickel is ubiquitous in the environment. Varying amounts of nickel

are found in food, in the air, and in most soils. Schroeder et al [175]

analyzed several diets for nickel content, concluding that, based on the

various foods consumed, a 2,300 calorie diet with 100 g fat, 100 g protein,

and 250 g carbohydrate could have a nickel content varying from 3-10 to

700-900 μg. They also concluded that a rough estimate of the daily average

intake of nickel was 300-600 μg. The diets of four laboratory workers

contained 305, 340, 360, and 480 μg of nickel. A vegetarian diet would be

higher in nickel, since plants generally have a higher nickel content than do edible animal tissues.

It was estimated in a review of the health effects of nickel [3] that the average adult consumed 10 μg of nickel/day in drinking water. McNeely et al [212] reported that nickel in the municipal tapwater in Hartford, Connecticut, averaged 1.1 μg/liter. Tapwater in Sudbury, Ontario, had an average nickel concentration of 200 μg/liter [212].

Nickel concentrations in ambient air have also been reported [223-225]. Nickel concentrations in suspended particulate matter varied between urban and nonurban air [225]. Urban areas (217 stations) had an average nickel concentration of 0.017 μg/cu m; proximate nonurban areas (5 stations), 0.008 μg/cu m; intermediate nonurban areas (15 stations), 0.004 μg/cu m; and remote nonurban areas (10 stations), 0.002 μg/cu m. In 1968, the ambient air concentration of nickel in the Ironton, Ohio-Ashland, Kentucky-Huntington, West Virginia, area was reported [223]. Huntington, the site of a large nickel mill, had an ambient air nickel concentration of 1.2 μg/cu m, while the concentration at six sampling stations in other areas of the study averaged about 0.04 μg/cu m.

Environmental data for workplace exposures have been reported for several processes:

(a)   Smelting and Refining Operations

Recent environmental data have been reported for Sudbury and Port Colborne, Ontario, nickel smelting and refining plants [41]. Nickel concentrations of 0.006-0.04 mg/cu m were reported from an unstated number of respirable dust samples from underground mining operations. High-volume samples taken in the milling and ore-separating areas showed nickel

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concentrations of 0.0-2.8 mg/cu m. In processing departments, the following nickel concentrations were reported: reverberatory furnaces, 0.08-1.4 mg/cu m; roasters, 0.03-3.3 mg/cu m; converters, 0.03-0.2 mg/cu m; and matte separation, 0.17-15.3 mg/cu m. The number of samples was not reported.

In the Port Colborne electrolysis plant, high-volume sampling was done in 14 areas [41]. Nickel concentrations averaging 0.11 mg/cu m (SD=0.14, range 0.002-0.254) were reported. Personal samples were also taken. An average nickel exposure of 0.19 mg/cu m (range 0.11-0.27) was reported for three cementation operators. Other nickel exposures were reported for two cobalt precipitation operators (0.08 and 0.28 mg/cu m), one pressman (0.16 mg/cu m), one anode scrap washer (8.13 mg/cu m), and two tank cleaners (both less than 0.029 mg/cu m).

Klucik and Kemka [219] reported the concentration of nickel in the air over electrolysis tanks where nickel carbonate and nickel sulfate solutions were used. The mean environmental nickel concentration was 0.6 mg/cu m with a range of 0.086-1.265 mg/cu m.

In 1972, Sushchenko and Rafikova [26] reported concentrations of airborne nickel in an electrochemical refining plant. Electrolyte solutions contained 75-85% nickel in the anolyte and 74-79% nickel in the catholyte. For the years 1966-1970, the concentrations of hydro-aerosols of nickel salts were reported to have ranged from 0.035 to 1.65 mg/cu m. Highest concentrations of airborne nickel were found in the overhead-crane cabs and in the areas where the refined nickel was filtered from the solution.

(b)   Nickel Alloy Production

Information supplied to NIOSH indicated the concentrations of airborne nickel found in several nickel alloy casting and forming operations [23,176]. In one plant, where the percentage of nickel found in high-volume samples was used to estimate the percentage of nickel in nearby total-dust breathing-zone samples, the nickel concentrations in atmospheric pressure-melting operations were estimated to range from less than 0.1 mg/cu m to 0.6 mg/cu m. Vacuum melting produced nickel concentrations ranging from less than 0.1 to 0.2 mg/cu m. In another plant, the concentrations of airborne nickel in 60 samples from the melting and casting area ranged from 0.006 to 1.210 mg/cu m, with an average of 0.152 mg/cu m. For other areas, the number of personal samples, average concentration of nickel, and range were reported as: annealing, shearing, and shot-blasting, 8 samples, 0.253 mg/cu m average (range 0.005-0.830); cold rolling, grinding, annealing, and pickling, 9 samples, 0.098 mg/cu m average (0.0005-0.244); and grinding and chipping, 6 samples, 1.103 mg/cu m average (0.259-3.148). Four samples were taken for operators in the hot rolling, sawing, and flame cutting departments; nickel concentrations determined were 0.233, 0.630, 0.654, and 1.851 mg/cu m, respectively.

Grinding operations at these nickel-alloy production plants have also been monitored [23,176]. In one plant, for 16 samples taken from 1972 through 1976, the nickel concentrations averaged 0.610 mg/cu m. In the other plant, less than 0.1 mg for total particulate matter/cu m, with an assumed nickel percentage of 1.4%, was reported in the grinding and cutting department in 1970.

(c) Welding, Grinding, and Flame Spraying

Nickel-metallizing or flame-spraying is a common industrial process for rebuilding worn nickel parts [13 (pp 491-493)]. In samples from the breathing zones of metallizing workers, which were collected on a filter and analyzed by AAS, 103 μg of nickel /cu m (range 9-230) has been reported [226].

The welding of nickel-containing metals or the use of nickel-based welding electrodes can result in employee exposure to nickel. Where alloys with low nickel content were welded, air samples all contained less than 100 μg nickel/cu m [227]. However, the welding of steel with more than 10% nickel resulted in breathing-zone samples with nickel concentrations of 3.80 mg/cu m [228].

Environmental measurements from steel grinding and cutting operations have also been reported [228,229]. The grinding of steel containing more than 10% nickel produced an airborne nickel concentration of 240 μg/cu m [228]. Eleven samples taken in another grinding shop were all less than 100 μg/cu m [229]. Cutting stainless steel ingots resulted in a total dust concentration averaging 70.8 (range 11.3-167.9) mg/cu m; the dust was reported to contain 11.5% nickel [55].

(d) Other Operations

Donaldson [230] reported sampling results from a plant where water-soluble nickel compounds were manufactured. Samples were collected on a 0.8-μm, 37-mm Millipore filter at a sampling rate of 2 liters/minute and a sample volume of over 800 liters. The results were analyzed by AAS. The average nickel concentration for 29 employees was 0.244 mg/cu m (range 0.009-2.780).

In 1974, Cohen et al [231] reported the results of environmental sampling near an automated nickel-chrome plating operation. The mean concentration of nickel in 14 samples was 27.1 μg/cu m (range 8.9-71.2).

Battery production areas have also been sampled for nickel [177]. Area samples in a nickel-cadmium battery plant averaged 0.36 mg nickel/cu m (range 0.05-0.851) for 8 samples. Twenty-eight personal breathing-zone samples in the same plant had an average nickel concentration of 0.415 mg/cu m (range 0.06-2.42). Two additional samples contained nickel concentrations of 18.3 and 53.3 mg/cu m.

Tubich et al [232] reported the results of an environmental survey in an investment-casting operation. Nickel concentrations of 8-110 μg/cu m, with an average of 40 μg/cu m, were reported in the melting department. The concentrations of nickel in the grinding and welding areas of the investment castings operation were reported as 6-150 μg/cu m, with an average of 95 μg/cu m.

Nickel is also used to produce a catalyst used in the hydrogenation of fats and oils [233]. Environmental monitoring was conducted in one such catalyst plant. In 1974, seven area samples contained an average total nickel concentration of 0.15 mg/cu m (range 0.01-0.60) and five personal samples contained an average nickel concentration of 0.37 mg/cu m (range 0.19-0.53). In 1975, soluble and insoluble nickel fractions were determined separately. Two-hour area samples (approximately 60 cu m of air sampled) contained an average of 0.003 mg of soluble nickel/cu m (range 0.001-0.007) and an average of 0.288 mg of insoluble nickel/cu m (range 0.013-1.24). Breathing-zone samples were reported to contain average nickel concentrations of 0.003 mg/cu m (range 0.002-0.009) and 0.052

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mg/cu m (range 0.012-0.159) for soluble and insoluble nickel compounds, respectively.

Engineering Controls

Prevention of cancer and dermatitis resulting from exposure to inorganic nickel requires the protection of employees from the inhalation of, or skin contact with, nickel dusts and fumes. The use of well-maintained closed systems and the prevention of dust generation, when compatible with the operation involved, are the best methods of preventing exposure. In areas where the escape of inorganic nickel into the environment of the worker is likely, the use of a properly designed and maintained ventilation system will prevent the accumulation of airborne nickel dusts and fumes in excess of the recommended environmental limit. Good ventilation practices, such as those outlined in the current edition of Industrial Ventilation--A Manual of Recommended Practice [178], published by the American Conference of Governmental Industrial Hygienists, should be followed. Where exhaust ventilation is required, adequate makeup air, conditioned as needed for worker comfort, must be provided.

Local exhaust ventilation systems should be designed and operated in conformance with the American National Standard Institute's Fundamentals Governing the Design and Operation of Local Exhaust Systems (Z9.2-1971) [234]. Enclosures, exhaust hoods, and ductwork must be kept in good repair so that design airflows are maintained. Airflow should be measured at each hood at least twice a year, and preferably more often. Continuous airflow indicators (such as water or oil manometers) are recommended and should be properly mounted at the juncture of the fume hood and duct throat or in the

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ventilation duct and marked to indicate the desired airflow. Employers are encouraged to establish a schedule of preventive maintenance and servicing for all equipment necessary to keep the environmental levels of inorganic nickel at or below the recommended TWA concentration limit.

The use of bag burners and slurry-handling techniques can minimize employee exposure to powders and fine dusts [13 (pp 528-571)]. Fluid-bed roasters have been installed to minimize employee exposure during the refining of nickel ore [23]. Vacuum dust collection systems are efficient where a dusty nickel product is produced or where nickel dust is generated [235]. Enclosures over conveyors, the minimizing of free-fall vertical drops, and the use of vacuum packers for dusty operations should also be considered.

Electroplating operations and other operations involving open-surface tanks containing nickel in solution involve the potential release of nickel mists into the environment. Floating baffles of plastic chips or balls have been used to reduce environmental contamination from many open surface tanks [236] and might be considered where nickel solutions are used.

V. WORK PRACTICES

Increased risks of dermatitis from contact with nickel, especially with solutions of nickel compounds [28,29], and increased risks of cancer of the respiratory organs from airborne forms of nickel [43,44] are the primary hazards reported from workplace exposure to inorganic nickel. Workers may be exposed to dusts, fumes, mists, or liquids containing nickel. Operations most likely to generate airborne nickel particles include welding, grinding, melting, cutting, pyrometallurgic refining, and the handling of finely divided nickel compounds. In operations at temperatures approaching the melting points of the nickel compounds being used, nickel fumes may be generated. The production of nickel catalysts and nickel salts, hydrometallurgic refining, and the plating of objects with nickel involve potential exposure to liquids or mists containing nickel. Particularly in these operations, therefore, work practices, along with the engineering controls described in Chapter IV, must be directed toward reducing skin and eye contact with inorganic nickel and preventing inhalation of airborne nickel.

Enclosing materials, processes, and operations is completely effective only if the integrity of the system is maintained. Such systems must be inspected frequently by qualified persons for leaks, and any leaks must be repaired promptly. The condition of seals and joints, access ports, and other such potential release points require special attention. Similarly, points where excessive wear or stress occur must be inspected regularly. Scheduled preventive maintenance, which offers more protection

to the worker than maintenance performed only after problems arise, should be practiced.

Employers must limit access to areas where occupational exposure to nickel may occur to those employees needed for the process. Records of employees entering these areas must be made and included in the employees' permanent files. Signs warning of the hazards of entry into areas containing airborne nickel contamination must be prominently displayed.

To limit skin contact with nickel and to minimize the resulting risk of sensitization, as well as to prevent exposure of the employees and their families outside the workplace, workers occupationally exposed to inorganic nickel must wear work clothing, which must be changed daily and not worn outside of the workplace. Work clothing must consist of coveralls (or any other combination of clothing which offers the same protection, such as trousers and shirt or skirt and blouse), hat or other head covering, hose or other leg covering, and shoes. Gloves should be provided where necessary.

Workers exposed to liquids or solutions containing nickel must be provided with suitable protective equipment. Such equipment should include corrosion-resistant clothing (impervious boots, gloves, and aprons or coats), acidproof hoods, and splashproof goggles. Full-body protective clothing may be necessary where it provides the only practical means of ensuring healthful working conditions [237]. Skin abrasions increase the risk of dermatitis [29]; therefore, protective clothing and gloves should be of sufficient strength to reduce the likelihood of such contact. In operations involving high temperatures or molten metal, both personal protective equipment and work clothes should be sufficiently flame

retardant to adequately protect employees.

Change rooms, lockers, showers, and protective clothing, where needed, must be provided for and used by employees occupationally exposed to nickel. Employees must wear the protective clothing provided by the employer, change clothing in rooms containing lockers which allow for the separation of street and work clothing, and shower after the work shift.

While there have been no reports of effects on workers' families due to inorganic nickel brought into the home, it is good practice to collect clothing worn by employees at the job site and to have the employer launder the clothing. Clothing must be stored and laundered to prevent exposure of those handling the soiled clothing [237].

Employees occupationally exposed to inorganic nickel must not eat, handle, or store food in the work area. While evidence of the oral toxicity of nickel is limited, animal studies [121,123] indicate adverse effects on reproduction from orally administered nickel. While these effects are nonspecific and therefore may or may not have an impact on man, they do indicate a toxic action of ingested nickel. Good practice requires the limitation of absorption of heavy metals in any form. Similarly, smoking and the carrying of uncovered smoking materials in the work place must be prohibited and employees should be instructed to wash their hands before smoking outside the workplace. Hogetveit and Barton [221] have observed that employees who eat outside of nickel work areas have lower urine and plasma levels of nickel.

Frequent washing of exposed skin is the most effective means of preventing dermatitis in operations where the employees are exposed to solutions or liquids containing nickel. Nonimpervious clothing that

becomes contaminated during the work shift must be changed and not worn again until the nickel is removed from the clothing. Washrooms convenient to production areas must be provided for all employees occupationally exposed to nickel. Employees must be required to wash prior to any eating or smoking, before breaks and lunch periods, and at the end of the work shift.

The employer must provide a respiratory protection program. The requirements for such a program are listed in 29 CFR 1910.134 and 30 CFR 11. A clean and well-maintained supplied-air or self-contained respirator must be available to each employee required to wear a respirator in his work. Workers who are expected to use respirators for entry into an area of overexposure to nickel must be trained in respirator use as well as in other emergency activities the worker may be expected to perform.

Where nickel-containing dusts are generated, it is important that they be removed by vacuum rather than swept or blown away [235]. Where there is no danger from electrical equipment or high-temperature furnaces, water may be used to wash away accumulated dusts, provided a fine mist of water is first applied to prevent dusts from becoming airborne. Prompt cleanup of spills and dusts, repair of all leaks and equipment, and proper storage of material must be emphasized to all supervisory personnel, and employees must be properly trained in these procedures. Spills of nickel solutions may be neutralized, if appropriate, then washed with water [238] into a sanitary sewer (if in accordance with local, state, and federal regulations) or an impoundment pond.

Workers involved in maintenance operations may be exposed to inorganic nickel through unusual or nonroutine tasks. Maintenance

personnel must be given thorough training in the use of local exhaust ventilation, respirators, and other necessary protective devices. Employees entering vessels or enclosed spaces where airborne nickel may be present must follow proper entry procedures, including the use of adequate respiratory protection, as required.

Nickel solutions may be acidic; therefore, when eye contact occurs, employees should immediately and thoroughly rinse the affected eye with water for 15 minutes [239]. If a solution is corrosive due to chemicals other than nickel, a physician should be consulted. Abrasions and wounds should be kept covered; but if, in spite of precautions, abraded skin is exposed to inorganic nickel, the area must be washed immediately with mild soap and water, and cleaned by debridement if necessary. If intact skin is exposed to inorganic nickel, the area should be washed with mild soap and water.

Nickel metal and alloys, although highly resistant to corrosion, should be stored so as to prevent formation of any surface contamination which may be released into the environment during subsequent handling. Acids which corrode nickel must not be stored with nickel products or compounds. Storage containers of inorganic nickel should be labeled, and, if solutions are stored, adequate dikes for the containment of spills must be provided. Reduced nickel catalysts should be stored in non-oxidizing atmospheres to prevent fire [233]. Finely divided or reduced nickel compounds also must not come into contact with gases containing carbon monoxide which may result in the formation of nickel carbonyl [13 (pp 495-527)].

VI. DEVELOPMENT OF STANDARD

Basis for Previous Standards

A Threshold Limit Value (TLV) of 1 mg/cu m (1,000 μg/cu m), measured as nickel, for workplace exposure to nickel metal dusts or fumes and to soluble nickel salts was proposed by the American Conference of Governmental Industrial Hygienists (ACGIH) in 1964, and adopted in 1966. The 1966 Documentation of the Threshold Limit Values [240] contains information supporting this TLV. The increases in deaths from lung and nasal cancer in nickel refinery workers in Norway, Wales, and Canada were noted, but a specific carcinogenic agent was not implicated. Experimental studies by Hueper [82,96,97] and Gilman and Ruckerbauer [87] were cited. Hueper reported that finely divided nickel metal powder produced injection-site tumors in the pleural cavities, muscle tissues, and other tissues of rats and guinea pigs [96,97], and that inhalation of 15 mg/cu m of powdered nickel produced lung tumors in these species [82]. Gilman and Ruckerbauer [87] reported that injection-site tumors were produced in rats and mice injected with dust from the effluent stack of a nickel refinery in Ontario. The 1966 Documentation [240] also noted that dermatitis ("nickel itch") was common in nickel platers. The TLV Committee emphasized, however, that a TLV of 1 mg/cu m for nickel dusts or fumes and for soluble nickel salts, measured as nickel, was probably too high to prevent dermatitis or sensitization caused by soluble nickel salts. The 1971 edition of the Documentation [241] does not differ in substance or conclusion from earlier editions.

A change in the TLV for soluble nickel salts from 1 mg/cu m to 0.1 mg/cu m, measured as nickel, was proposed by the TLV Committee in 1974 and adopted in 1976 [242]. The TLV Committee also has proposed a short-term exposure limit of 0.3 mg/cu m for a 15-minute exposure to soluble nickel salts [242]. The proposed Documentation of the Threshold Limit Values [243] indicated that three soluble nickel salts, nickel chloride, nickel sulfate, and nickel nitrate, are of industrial importance. A report by Bingham et al [131], indicating that inhalation exposure to nickel chloride at a concentration of 0.1 mg/cu m, measured as nickel, for several weeks caused hyperplasia and increased mucus secretion in the lungs of rats, was cited in the proposed Documentation [243]. An unpublished report by Clary [132] was also cited, indicating that inhalation of nickel chloride at a nickel concentration of 1 mg/cu m for 6 months produced increases in lung weight and in the cellular vascularity of the walls of the alveoli of rats and guinea pigs and aggravation of preexisting, reversible lesions in the lungs. Dermatitis in nickel platers and effects on glucose metabolism in animals were also mentioned [243].

In 1976, the Committee proposed a TLV of 1 mg/cu m, measured as nickel, for workplace exposure to dusts and fumes of insoluble inorganic compounds from nickel sulfide ore-roasting operations [243]. The 1976 Documentation [243] cited studies by Loken [42], Saknyn and Shabynina [58], Morgan [36], and Sutherland [44] which indicated to the ACGIH that lung and nasal cancers were associated primarily with exposure to high levels of dusts and fumes generated by the high-temperature calcination and sintering of impure nickel subsulfide. The ACGIH considered inconclusive the results of animal experiments designed to reproduce the nasal and lung cancers seen

In nickel workers [78,80]. They stated in the Documentation [243], however, that cancers continue to be found in workers exposed to nickel subsulfide before 1960. Fluid-bed roasting was introduced in Canada in 1960 and no cancers have been found in workers first exposed since that time. The TLV committee concluded that, since 16 years is insufficient time to evaluate the effects of that process change on the development of cancer in nickel workers, their recommendation of 1 mg/cu m must be tentative.

Standards for occupational exposure to nickel compounds in other countries are listed in Table V-1 [244-246].

The Federal Republic of Germany published standards [247] and documentation [248] for occupational exposure to breathable dusts of metallic nickel, nickel sulfide, nickel sulfide ores, nickel oxide, and nickel carbonate, as they may develop in manufacturing and processing. Based on epidemiologic studies by Doll [37] and Shaknyn and Shabynina [58] and animal experiments by Hueper [82,96,97], nickel was classified as a substance known to be capable of producing cancer in humans and for which, therefore, no safe maximum workplace concentration could be established [248].

The present US standard (29 CFR 1910.1000) for workplace exposure to nickel metal and soluble nickel salts measured as nickel is an 8-hour TWA concentration limit of 1 mg/cu m (1000 μg/cu m). This standard is based on the TLV for workplace exposure adopted by the ACGIH in 1968.

TABLE VI-1

OCCUPATIONAL ENVIRONMENTAL LIMITS
FOR NICKEL IN FOREIGN COUNTRIES

Country and Compound	μg of nickel/cu m
Bulgaria	
Nickel and its oxides	500
German Democratic Republic	
Nickel metal*	500
Japan	
Nickel metal	1000
Rumania	
Nickel, soluble compounds	500
Sweden	
Nickel metal*	10
USSR	
Nickel metal*	500
Nickel monoxide and sulfide dust	500
Nickel metal and soluble compounds**	500

*From Winell [245]
**From Roschin and Timofeevskaya [246]

Other data adapted from <u>Permissible Levels of Toxic Substances in the Working Environment</u> [244]

<u>Basis for the Recommended Standard</u>

(a)   Permissible Exposure Limits

Deaths from lung cancer and nasal cancer in nickel workers were first reported in 1932 [21], but the agents causing these cancers still have not been conclusively identified. Epidemiologic studies have shown that workers engaged in refining nickel from sulfide ore [35,37,39-41,43-45]

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have an increased risk of death from cancer of the respiratory organs. Some of these cancers have been associated with furnace work [43-45]; the high-temperature calcination and sintering of nickel sulfides, in particular, have been implicated [36,44,45]. However, occupational histories (Tables XV-3 and XV-4) of workers who developed cancer of the respiratory organs at one nickel refinery [41] show that some of these cancers occurred in cupola and anode furnace workers, in electrolysis workers, and in workers in other dusty operations as well. Auxiliary operations, including the crushing and grinding of nickel matte and the cleaning of calciner flues, have also been implicated [36]. In a refinery where nickel was purified electrolytically, increased mortality from lung and nasal cancer was observed in workers whose longest employment had been in the electrolysis department [43]. Cases of nasal cancer have been reported in other plants that refine nickel electrolytically [41,48]; some of these workers had no known additional exposure to nickel from work in other parts of the refinery (see Table XV-3) [41].

At least six cases of kidney cancer have been recorded in nickel refinery workers; three of these cases were observed in a group of 225 electrolysis workers in Canada [44] and the other three occurred in workers at a nickel refinery in Norway (E Pederson, written communication, November 1976). Animal studies [138,150] have shown that nickel may accumulate in the kidneys. Nickel subsulfide administered to rats by intrarenal injection produced carcinomas; nickel metal and nickel monosulfide did not [103]. No information was found for other nickel salts or for routes of administration more analogous to human exposure. This limited information

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is the first to suggest that nickel may contribute to the development of cancer of the kidney.

Epidemiologic studies of other industries that use nickel are limited. Preliminary studies [41,47] of workers at a nickel alloy plant showed a slight excess (O/E ratio of 1.57) of cancer of the respiratory organs in retired hourly workers [47], but not in the plant population as a whole (O/E ratio of 0.97) [41]. Three deaths from nasal cancer occurred in workers from this plant; at least two of these workers had been involved in calcination of nickel sulfide ore, a process not normally used in an alloy plant. A mortality study [46] of nickel miners and of refinery workers employed in the mill and separation areas and as converter furnace workers did not show a statistically significant increase in deaths from cancer of the respiratory organs (7 observed, 6.81 expected). The number of deaths from these cancers was too small to determine conclusively whether or not there was a carcinogenic risk for nickel workers in these occupations.

Although dust from a Canadian nickel refinery flue was found to contain nickel subsulfide, nickel oxide, and nickel sulfate [87], no additional information has been found on individual compounds to which nickel workers were exposed. Based on process information [10,23,36,41] it seems likely that calciner, sinter, and converter furnace workers were exposed mainly to dusts and fumes of nickel sulfides and nickel oxide. After 1933, exposures at the refinery in Clydach, Wales, probably differed from Canadian operations since the sulfur contents of the feed materials at Clydach were reduced [23]. After 1945, the feed material in Clydach was nickel oxide [36]. In Canada, cupola furnace workers may have been exposed to nickel sulfides; anode furnace workers were exposed to nickel oxide,

although some exposure to elemental nickel may have been possible. In electrolytic refining, the tanks contain nickel salts, such as nickel sulfate and nickel chloride, in an acid solution [10]. Worker exposure varies with operating conditions, such as the current density and the temperature of the contents of the tank. Auxiliary operations in electrolytic refining could involve exposures to additional nickel compounds, such as nickel metal and nickel carbonate; the relevance of these exposures cannot be resolved without more detailed occupational histories. Nickel miners and at least some mill and separation workers were probably exposed to the mineral pentlandite [10]. Workers who developed cancer of the respiratory organs were generally exposed to mixtures of several nickel compounds and only rarely to a single compound. In addition, some of the groups of workers who had only a slight increase in incidence of cancer were exposed to the same compounds as those groups of workers that did have an increased risk of cancer.

The limited area-monitoring data available [41] are not sufficient to determine the exposures of workers who developed lung or nasal cancer. However, the amount of nickel dusts and fumes present in the immediate area can be classified into high, moderate, and low exposure categories. More than four orders of magnitude separate the highest (about 150 mg/cu m) and the lowest (0.006 mg/cu m) estimated values [41]. High nickel dust and fume concentrations occurred in the Clydach calciner buildings from 1902 to 1925 and at the Port Colborne and Copper Cliff sinter plants in Ontario, Canada. Moderate exposures were more likely around the Clydach calciners after 1925 and in the nickel alloy plant. Lower exposures would be expected near converter furnaces, and the lowest exposures should have

occurred in mill and separation areas and in nickel mining [41]. It is not possible, in retrospect, to determine if some workers employed in areas with high dust levels were able to avoid these exposures over at least part of the work shift; however, this exposure classification parallels the lung and nasal cancer incidences observed in these groups.

Animal studies [81-83] do not clearly indicate that exposure to airborne nickel metal increases the risk of developing cancer of the respiratory organs; metaplastic changes were noted in the lungs of rats [82,83] and guinea pigs [82], but hamsters showed almost no effects attributable to exposure to nickel [83]. However, the inhalation of nickel subsulfide at 1 mg/cu m for about 80 weeks produced benign and malignant pulmonary tumors in rats [78]. Inhalation of nickel oxide by hamsters did not produce an excess incidence of pulmonary tumors over that seen in controls [80]. Questions regarding the suitability of some animal species for nickel carcinogenicity testing, the latent period necessary for the production of the effect, and the failure to produce any nasal cancers make the results of animal studies equivocal.

Nevertheless, nickel refinery workers have had an increased mortality rate from lung cancer and nasal cancer. Although lung cancer might be accounted for by factors in the refinery environment other than nickel, the high incidence of nasal cancer cannot. It must therefore be concluded that exposure to airborne nickel was a major contributing factor in a substantial portion of the excess deaths from lung and nasal cancer in nickel refinery workers. Based on this conclusion and supporting animal data, NIOSH considers that nickel subsulfide is a respiratory system carcinogen. Since many workers who developed nasal cancer were probably

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exposed to nickel oxide as well, and since others developed nasal cancers after using nickel salts, such as nickel chloride and nickel sulfate, these compounds are probably also carcinogenic. Although the evidence implicating metallic nickel is not as strong, metaplastic changes have been noted in animals exposed to nickel metal [82], and the air-oxidation of fine dusts of nickel metal probably results in inhalation of nickel oxide by workers exposed to airborne nickel metal. Metallic nickel, therefore, must be considered a suspect carcinogen. Despite a lack of adequate experimental animal studies that might confirm the carcinogenicity of all nickel compounds, the chemical properties of those that can be implicated in the development of cancer are diverse, and many other nickel compounds would be expected to have similar toxicologic properties. There is no evidence to suggest that inorganic nickel is carcinogenic when ingested. NIOSH therefore concludes that, in the absence of evidence to the contrary, nickel metal and all inorganic nickel compounds, when airborne, should be considered carcinogens.

The full significance of data showing that nickel and its compounds cause injection-site sarcomas is not clear, and these data have not been used in judging occupational tumorigenic potential. However, they suggest that nickel and its compounds should not become imbedded in skin, for example from entrainment in healing wounds.

Nickel is a common contact allergen; in a study of contact dermatitis patients it was determined that in approximately 7% of all cases, both occupational and nonoccupational in origin, the patients were sensitive to nickel [32]. In the workplace, appreciable skin contact with nickel solutions has produced dermatitis [28,29], although heat has been

implicated as an additional factor [18,27], possibly because sweating enhances the dissolution of nickel salts. Cuts and abrasions from plated items [28,29] and the use of degreasers in electroplating [29] have been mentioned as contributing factors in the development of nickel dermatitis. Once a worker has been sensitized, that sensitivity has been retained [29,30], so that the worker may develop recurring dermatitis upon additional contact with nickel. Work practices, including appropriate clothing, and protective equipment should be used to minimize the chance of becoming sensitized to nickel. Because the measures needed to ensure that a worker will never come into contact with nickel in any form in the workplace are too severe to be practical, the standard will not adequately protect already sensitized workers in all situations.

The worker must be protected to minimize the risks of sensitization resulting from contact with nickel and of cancer resulting from exposure to airborne nickel. For these reasons, occupational exposure to nickel is defined as working with compounds, solutions, or metals containing nickel that can become airborne or spill or splash on the skin or in the eyes. If there is occupational exposure to nickel in a workroom, all employees assigned to that area, even temporarily, for any purpose including maintenance or repair, should be regarded as occupationally exposed. This definition does not include the wearing or use of nickel-containing products, such as pens, watches, typewriters, or stainless steel sinks that may be encountered in the workplace. The handling of solid products, eg, ingots, bars, or stainless-steel tools, by workers is also excluded provided that particle-generating operations such as grinding, cutting, or welding are not performed on these solid products.

There is overwhelming evidence that nickel refinery workers have had an excess of deaths from cancer of the respiratory organs. Evaluation of this evidence has led NIOSH to conclude that many of these cancers were nickel-induced, and that inorganic nickel should be regulated as a carcinogen. In the absence of adequate information on the amount of inorganic nickel that can be inhaled over a working lifetime without an excess risk of cancer, it is proposed to recommend a permissible limit based on the lowest TWA concentration of nickel reliably detectable over a single work shift.

Nickel is ubiquitous in the environment, and this factor must be considered in establishing a permissible exposure limit. Nickel concentrations in ambient air in urban locations averaged 0.017 μg/cu m [225], although some higher concentrations have been reported. The Huntington, West Virginia, area, for example, has had nickel concentrations in ambient air averaging 1.2 μg/cu m [223]. Since 10 μg of nickel must be collected to be measured reliably by the recommended analytical method, interferences from nickel in ambient air would be minimal for the 700-liter volume of air specified for sampling collection. NIOSH therefore recommends that exposure to inorganic nickel be controlled so that no worker is exposed to airborne nickel in excess of 15 μg/cu m, measured as nickel, in a 10-hour period.

(b)   Sampling and Analysis

Measurement of total airborne nickel is considered essential since the development of nasal cancers in nickel workers suggests that the respirable fraction alone is not a good indicator of the worker's exposure to nickel. On the other hand, very large fragments, not breathable by the

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worker, may be cast into the air by operations such as grinding or welding. Thus, the sampling method should provide the best possible estimate of the nickel actually available to the worker in the breathing-zone air. For this reason, closed-faced sampling is recommended. A cellulose mixed-ester filter is recommended because it has a low nickel content and is easily digested in acids, so that this filter will provide minimal interference in subsequent nickel analysis. The recommended sampling method is described in Appendix I.

The analytical method used should be capable of measuring the amount of nickel present in the breathing-zone air of a worker when a sample is collected over a period of time approaching the length of the workshift. The error of measurement at the limit of detection should not exceed a 10% relative standard deviation under normal working conditions, and the amount of nickel in the blank should be minimized. For flame AAS, these conditions can be met by collection of a 700-liter air sample, use of a filter with a low nickel content, and digestion in a minimum amount of acid. Flame AAS has been shown to be accurate and precise, has been thoroughly tested, and provides quick and simple analyses [206]. Flame AAS is recommended for the analysis of nickel samples, as described in Appendix II. Other methods, such as polarography and emission spectroscopy, may be more suitable in specific applications and can also be reliable.

With chemical analysis, there is no practical means of distinguishing only those nickel compounds identified in the standard, since some, but not all, organometallic compounds containing nickel exist also in a solid form. Therefore, in rare instances, the total particulate nickel measured could include both inorganic nickel and compounds specifically exempted from the

recommended standard. In those situations where mixed exposures to both types of nickel may occur, the total airborne particulate nickel must be considered inorganic nickel.

(c)   Medical Surveillance

It is proposed that mandatory medical surveillance include preplacement and periodic examinations of the lungs, the upper respiratory tract, and the skin. Pulmonary function tests and chest X-rays should be performed to aid in the detection of any adverse effects of nickel on the lungs. Examinations of the upper respiratory tract should identify any evidence of nasal erosions or perforations and should be directed to the detection of possible adverse effects, including hyperplastic or premalignant changes. Examinations of the skin should be directed to identification of any evidence of nickel sensitivity; patch tests should not be performed routinely because of the possibility that they may, themselves, sensitize the worker. Preplacement and interim medical histories should supplement the information obtained from the medical tests. Periodic examinations should be given annually to workers frequently exposed to nickel to permit early detection of adverse effects on the respiratory organs and of sensitization to nickel. Medical records should be retained for 40 years after the last occupational exposure to nickel because cancer of the respiratory organs has been observed as long as 40 years after employment in a nickel refinery. Many of the cases of cancer listed in Tables XV-3 and XV-4 occurred from 30-40 years after cessation of employment.

Smokers should be counseled on their possible increased risk of developing lung cancer from exposure to airborne nickel.

Specific tests to detect cancer, to measure kidney function, or to determine the extent of exposure to airborne nickel are recommended. Although the benefits of sputum cytology for the early detection of cancer are controversial and there are only a limited number of adequately trained personnel to perform these examinations, the results of an ongoing sputum cytology screening program for former nickel workers have been encouraging [56,57]. Cytologic examination of sputum to supplement chest X-rays is therefore recommended, particularly for nickel workers whose medical or work histories may indicate a high risk of developing lung cancer. A questionnaire designed to assess chronic respiratory symptoms is suggested to supplement medical and work histories. The concentration of nickel in the urine has not been adequately correlated with the individual's health status to warrant a requirement for biologic monitoring [222], but urinary nickel has been used as an index of exposure for groups of workers [221,222]. Although there is evidence that ip injection of nickel chloride in rats can result in proteinuria [148], the possibility of kidney damage in humans exposed to inorganic nickel has not been adequately studied. In addition, kidney damage may be unlikely at exposure concentrations near the recommended TWA concentration limit. However, general kidney function screening tests, such as the measurement of protein or albumin in the urine, are not difficult to perform. Therefore, kidney function tests are recommended for workers exposed to inorganic nickel.

(d)   Personal Protective Equipment and Clothing

Protective clothing is recommended in order to minimize the risk of dermatitis in unsensitized workers likely to have appreciable skin contact with solutions of nickel. This equipment should include, where

appropriate, face shields, shoe covers, aprons, gloves, and arm shields or coats. Fire-retardant work clothing should be worn where there is a chance of skin burns from molten nickel. Only self-contained or air-supplied respirators are recommended for working in areas where airborne nickel is present, since inorganic nickel is considered a carcinogen.

All foreseeable events that could result in the necessity of escape from a hazardous area should be evaluated to establish evacuation procedures and to determine the equipment needed. Escape equipment should be kept in readily accessible locations. A self-contained breathing apparatus with positive pressure in the facepiece should be provided for escape except for those situations in which the time required to put on the respirator exceeds the time otherwise needed to escape from the area or in which an immediate life-threatening situation does not exist.

(e)   Informing Employees of Hazards

Continuing education is an important part of a preventive hygiene program for employees exposed to inorganic nickel. Workers should be instructed periodically by properly trained persons about possible sources of exposure, adverse health effects associated with exposure to nickel, engineering and work practice controls in use or being planned to limit exposure, and environmental and medical monitoring procedures used to check control procedures. The function of monitoring equipment, such as personal samplers, should be explained, so that employees understand their part in environmental monitoring. Medical monitoring procedures, especially the use of chest X-rays and pulmonary function tests, and their importance in detecting possible adverse health effects should be explained.

(f)   Work Practices

Inorganic nickel, when airborne, can cause cancer in the respiratory system, and it can produce dermatitis, especially if there is appreciable skin contact with nickel-containing materials. Thus, procedures used for the cleanup of spills, waste disposal, general housekeeping, and storage of inorganic nickel should minimize dispersion of nickel and the worker's contact with nickel. Personal hygienic measures should be adopted to eliminate wound contamination and accidental intake of nickel and to further reduce the probability of sensitization to nickel. Because of the severe adverse effects associated with exposure to inorganic nickel, entry into areas where there is occupational exposure to nickel should be restricted to those persons needed to perform the job. Records of persons entering restricted areas should be maintained to provide documentation of those workers who are occupationally exposed to nickel. In order to prevent the spread of nickel contamination beyond the workplace, work clothing should be removed and the worker should shower at the end of the work shift. Soiled clothing should be stored and laundered in a manner not harmful to persons who handle or launder them.

(g)   Monitoring and Recordkeeping Requirements

Industrial hygiene surveys should be made as soon as possible after the promulgation of a standard based on these recommendations and within 30 days of any process change. Where there is occupational exposure to nickel, the TWA concentration limit for each employee should be determined and the workplace air around every operation should be sampled and analyzed quarterly in order to provide the protection necessary to minimize the risk of respiratory cancer.

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Records of environmental measurements should be retained for 40 years after the last occupational exposure to nickel to permit correlation with any chronic health effects which may ensue.

VII. COMPATIBILITY WITH OTHER STANDARDS

Ambient air quality standards for nickel have not been established. Other standards and guidelines which have been published are described below. Since these are not air standards, they appear to be compatible with the recommended TWA environmental concentration.

The Environmental Protection Agency (EPA) has issued effluent guidelines and standards for electroplating. For existing establishments, using the best available technology to reduce effluents, the maximum discharge allowed for any 1 day is 160 mg/sq m/operation (32.7 pounds/million square feet/operation), and the average value for 30 consecutive days must not exceed 80 mg/sq m/operation. For new sources, the daily maximum has been reduced to 80 mg/sq m/operation and the 30-day average limit to 40 mg/sq m/operation. These effluent limitations apply to discharges of nickel and other pollutants resulting from the process in which a ferrous or nonferrous base material is rack or barrel electroplated with nickel, copper, chromium, zinc, or any combination thereof. These standards were published in 40 CFR 413 (39 Federal Register 11510, March 28, 1974; amended by 39 Federal Register 26642, July 22, 1974).

EPA has not established a primary drinking water standard for nickel. EPA is preparing Quality Criteria for Water [249] which will not have direct regulatory force but will form the basis for judgment in several EPA and state water programs. The nickel criterion, not based on human toxicity, is 1% of the 96-hour LC50 for fresh and marine aquatic life. Values given for the 96-hour LC50 ranged from 4.6 to 9.8 mg/liter in soft

water and from 39.2 to 42.4 mg/liter in hard water.

The Food and Drug Administration has not established a tolerance for nickel in food or food products.

VIII. RESEARCH NEEDS

In the development of this document, information was found on a limited number of nickel compounds. Before the hazards to the work population from exposure to metallic nickel and inorganic nickel compounds can be thoroughly evaluated, extensive epidemiologic and toxicologic research is required. Epidemiologic studies are needed to assess the risk of cancer associated with exposure to airborne nickel in operations other than those already studied. These studies should include nickel alloy workers, nickel catalyst makers, nickel salt producers, nickel-cadmium battery makers, nickel platers without concurrent exposure to chromium, and workers engaged in the roasting and smelting of sulfur-free nickel ores.

For all nickel workers, including those exposed to nickel sulfides, the risk of developing cancer in sites other than the respiratory organs, such as the kidneys, needs to be studied. The effects of smoking, dermatitis, and chronic respiratory disease on nickel toxicity need to be examined to determine if some worker groups have an increased risk of developing cancer. Determinations of the concentrations of nickel and of other substances present in the air, eg, sulfur dioxide, arsenic, and other metals, should be included in epidemiologic studies to determine whether any toxicologic interaction is additive, potentiating, independent, or antagonistic.

Studies are also needed to determine whether adverse effects other than cancer, which have been observed in animals exposed to inorganic nickel by various routes of administration, are applicable to human

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exposure. Effects on the lungs and kidneys and on glucose metabolism need to be examined. Information is needed on both humans and animals to clarify whether there is an effect of nickel on the functioning of the thyroid and pituitary glands and on the developing fetus.

Toxicologic studies in animals are needed to establish both acute and chronic effects of the many nickel compounds that have not been studied. In addition, long-term inhalation studies in a suitable animal species are needed to better assess the carcinogenicity of such nickel compounds as nickel chloride, nickel sulfate, nickelous and nickelic oxide, and metallic nickel.

Limiting worker exposure to inorganic nickel to the maximum extent possible should be an immediate goal. Improved control technology, particularly in furnace operations, and the development of a flameless atomic absorption method for analysis of airborne nickel are needed. Should additional studies indicate that all inorganic nickel compounds need not be controlled to the same exposure limit, analytical methods that can identify individual compounds will be necessary.

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X. APPENDIX I

METHOD FOR SAMPLING NICKEL IN AIR

The following sampling method is adapted from that described in Method No. 173 of the NIOSH Manual of Analytical Methods [187].

General Requirements

Collect breathing-zone samples representative of the individual employee's exposure. At the time of sample collection, record a description of sampling location and conditions, equipment used, date, time and rate of sampling, and any other pertinent information.

Equipment

The sampling train consists of a filter in a filter cassette, a suitable length of tubing, and a vacuum pump.

(a) Filters and cassettes: a 2- or 3-piece filter cassette containing a 37-mm cellulose mixed-ester membrane filter with a 0.8-μm pore size.

(b) Pump: A battery-operated vacuum pump, complete with clip for attachment to the employee's belt, capable of operating at 2.0 liters/minute for up to 8 hours.

Calibration

Accurate calibration of a sampling pump is essential to obtain a correct value for the volume of air sampled. The frequency of calibration depends on the use, care, and handling to which the pump is subjected. If the pump receives hard use, more frequent calibration may be necessary. Pumps should be recalibrated if they have been subjected to misuse or if they have just been repaired or received from a manufacturer. Maintenance and calibration should be performed and recorded on a regular schedule, for example, after every 40 hours of use or once a month regardless of use.

Ordinarily, pumps should be calibrated in the laboratory both before they are used in the field and at intervals after they have been used to collect a large number of field samples. The accuracy of calibration depends on the type of instrument used as a reference. The choice of calibration instrument will depend largely upon where the calibration is to be performed. For laboratory testing, a 1-liter soapbubble meter is recommended, although other standard calibrating instruments, such as the wet-test meter, can be used.

Instructions for calibration with the soapbubble meter follow. If another calibration device is used, equivalent procedures should be used. The calibration setup for a personal sampling pump with a filter is shown in Figure XV-2. Since the flow rate obtained with a pump depends on the pressure drop across the sampling device, in this case a cellulose mixed-ester membrane filter, the pump must be calibrated while operating with a representative filter in line.

(a) Check the voltage of the pump battery with a voltmeter to assure adequate voltage for calibration. Charge the battery if necessary.

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(b)   Place a membrane filter in the holder.

(c)   Assemble the sampling train as shown in Figure XV-2.

(d)   Turn the pump on and moisten the inside of the soapbubble meter by immersing the buret in the soap solution. Draw bubbles up the inside until they are able to travel the entire buret length without bursting.

(e)   Adjust the pump rotameter to provide the desired flowrate.

(f)   Check the water manometer to insure that the pressure drop across the sampling train does not exceed 12 inches of water (approximately 1 inch of mercury) at 2.0 liters/minute.

(g)   Start a soapbubble up the buret and measure with a stopwatch the time it takes for the bubble to move from one calibration mark to another. If, for the pump being calibrated, the number of strokes is used to determine volume, count the number of strokes required to move the bubble from one marker to another.

(h)   Repeat the procedure in (g) at least three times, average the results, and calculate the flowrate by dividing the volume between the preselected marks by the time required for the soapbubble to traverse the distance.

(i)   Record calibration data, including the volume measured, elapsed time, pressure drop, air temperature, atmospheric pressure, serial number of the pump, date, and name of the person performing the calibration.

(j)   Use graph paper to record the airflow as the ordinate and the rotameter readings as the abscissa.

Sampling Procedure

(a)   Open a filter cassette and connect the back of the cassette to the pump with tubing. The filter cassette is supported or clipped in a vertical position, facing down, in the employee's breathing zone.

(b)   Sample a minimum of 700 liters of air. For example, 2.0 liters/minute for about 6 hours.

(c)   Measure and record the temperature and pressure of the atmosphere being sampled.

(d)   Treat at least one filter in the same manner as sample filters (break open, reseal, and ship), but draw no air through it. This filter serves as a blank.

(e)   Immediately after the samples are collected, recap the filter cassette, label, and ship for analysis. Include a blank filter with each batch of filters sent to be analyzed.

XI. APPENDIX II

ANALYTICAL METHOD FOR AIRBORNE NICKEL

The recommended atomic absorption spectrophotometric method is based on Method No. 173, described in the NIOSH Manual of Analytical Methods [187].

Principle of the Method

Particles are collected on a cellulose mixed-ester membrane filter. The filter is ashed in nitric acid, and the residue is dissolved in dilute nitric acid. The absorbance of nickel at 232 nm is determined by atomic absorption spectrophotometry in an oxidizing flame and compared to the absorbance of standards.

Range and Sensitivity

The working range of the method is 1.0-20 μg nickel/ml of the redissolved ash solution. This range is somewhat instrument dependent and can be extended to higher concentrations by dilution of the sample or measurement of a less sensitive line.

The sensitivity of the method has been determined to be 0.2 μg nickel/ml of the redissolved ash solution. This value will vary somewhat depending on individual instrumentation.

Interferences

No interferences are listed in the NIOSH Manual of Analytical Methods [187], although another report [209] has indicated that a hundredfold excess of iron, manganese, chromium, copper, cobalt, or zinc may decrease the absorbance recorded for nickel by as much as 12%. However, it also was noted [209] that this effect can be minimized by proper burner elevation and by the use of an oxidizing flame. In addition, a high solids content in the aspirated solution will cause increased nonspecific absorbance if the 232-nm line is used [250].

Precision and Accuracy

The coefficient of variation for analysis by atomic absorption is approximately 2% for absorbances greater than 1%. An absorbance of less than 1% increases the coefficient of variation. At the lowest end of the working range, a reading error of as much as 3% can occur with an instrument equipped with a digital readout.

No data on accuracy are available at this time.

Apparatus

(a)   Atomic absorption spectrophotometer with nickel hollow-cathode lamp and a burner head for an air-acetylene flame.

(b)   Hotplate.

(c)   Volumetric flasks.

(d)   Pipets.

(e)   Oxidant: air   which   has   been   filtered   to   remove   oil,   water,
and other foreign materials.

(f)   Fuel: commercially available acetylene.

(g)   Pressure-reducing valves.

(h)   Beakers.

(i)   Watchglasses.

Reagents

All reagents used must be ACS certified reagent grade or better.

(a)   Doubly distilled or deionized water.

(b)   Redistilled concentrated nitric acid.

(c)   Distilled 1:1 hydrochloric acid.

(d)   Commercially   prepared   aqueous   stock   standard   (1,000 μg of
nickel/ml):   serially dilute commercial standards   in   5%   nitric   acid   to
cover   a   range   of   nickel concentrations from 1.0 μg/ml to 20 μg/ml.   The
diluted standards should be stored in polyethylene bottles which have been
soaked in 5% nitric acid and should be stored for no more than 1 week.

Procedure

(a)   Clean glassware if it has never been used by soaking it for 24
hours in 5% nitric acid.   Rinse throughly with warm tap water and then with
doubly   distilled   water.   After glassware has been used, wash it first in
detergent and rinse with tap water.   Then soak it in 5% nitric acid   for   1
hour, rinse it thoroughly with doubly distilled water, and allow it to dry.
Use plastic containers for washing and do not handle the glassware   without

gloves which are impervious to sweat.

(b)   Transfer the sample and the blank filter to 125-ml beakers and add 5 ml of concentrated nitric acid to each. Cover each beaker with a watchglass and heat it on a hotplate in a ventilation hood until only a few drops of solution remain in the beaker. Several additions of nitric acid may be needed for complete ashing.

(c)   Dissolve the ash in 5% nitric acid with heating. If solids are present in the solution, repeat the ashing procedure with an additional 5 ml of a 1:4 mixture of hydrochloric and nitric acids. Quantitatively transfer the solution to a volumetric flask. Increase the total volume to 10 ml with 5% nitric acid. Dilution may be necessary if the amount of nickel in the sample exceeds the upper limit of the range of detection.

(d)   Aspirate the sample solutions and the standard solutions into an oxidizing flame. Measure and record the absorbance of each sample at 232 nm. It is advisable to run the set of standards before, during, and after a sample run to ensure that conditions have not changed. Correction for nonspecific absorption can be made for measurements at 232.0 nm by the use of a hydrogen or deuterium lamp, or by subtracting the absorbance at the 231.7-nm nonabsorbing line of nickel.

Calculations

Prepare a calibration curve by plotting the absorbance of the standards versus the concentration (μg/ml) of each standard on linear graph paper. Subtract the absorbance of the filter blank from the absorbance of each sample. Read the nickel concentration corresponding to this

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absorbance value from the corrected calibration curve. The concentration
of nickel in air is calculated as:

$$\mu g \text{ nickel/cu m} = \frac{\mu g \text{ nickel/ml (from graph) x total ml of solution}}{\text{cu m of air sampled}}$$

XII. APPENDIX III

ANALYSIS OF URINARY NICKEL

The atomic absorption spectrophotometric method of Nomoto and Sunderman [155], with some simplification of the wet ashing procedure, is recommended.

Principle

Preshift and postshift urine samples are collected. The urine sample is wet ashed, the ash is dissolved in water, the pH of the solution is adjusted, and nickel is reacted with ammonium pyrrolidine dithiocarbamate. The complex is extracted into methyl isobutyl ketone. The absorbance of the solution at 232 nm is determined and compared to the absorbance of the standards.

Range and Sensitivity

For a 50-ml sample of urine, the detection limit is approximately 0.02 μg nickel/100 ml of urine, which corresponds to a recorder signal equivalent to twice the baseline noise level. This sensitivity is achieved with a three-slot burner, and it is 1.5 times that attained with a single-slot burner.

The useful range for this method is 0.1-2 μg nickel/100 ml for a 50-ml sample. The lower limit is determined by the absorbance of the reagent blank. The upper range may be extended, but the relationship of absorbance

to nickel concentration is no longer linear. However, the working range may be extended to higher concentrations by sample dilution.

The sensitivity of the method and the useful range will vary somewhat depending on the instrument used, the type of burner, height of the aspirator above the flame, and the acetylene-air ratio of the fuel.

Interferences

The addition of at least a 100-fold excess of arsenic, calcium, chromium, cobalt, copper, iron, lead, magnesium, manganese, potassium, silver, sodium, zinc, ammonium, carbonate, chloride, citrate, nitrate, oxalate, persulfate, phosphate, or sulfate did not change the absorbance of solutions containing nickel. Solutions containing 0.5 μg of cadmium or 2.5 μg of gold caused a 5% inhibition in nickel absorbance, and 10 mg of cadmium caused a 25% inhibition of absorbance of 0.5 μg of nickel. Concentrations of iron in excess of 100 times the nickel concentration may also cause interference.

Precision and Accuracy

The coefficient of variation for duplicate analyses of nickel in 50 urine specimens was 10.3%. An average recovery of 100% with a range from 98-102% was obtained when nickel (2.5 μg/100 ml) was added to five urine samples.

Apparatus

(a)   Atomic absorption spectrophotometer with nickel hollow-cathode lamp, air, and acetylene fuel.

(b)   Low-speed centrifuge with head capable of holding 50-ml tubes.

(c)   pH meter with a combination glass-calomel electrode.

(d)   Hotplate.

(e)   Borosilicate or polyethylene bottles.

(f)   Ehrlenmeyer flasks.

(g)   Calibrated centrifuge tubes.

(h)   Stoppered vials.

(i)   Volumetric flasks, pipets, graduated cylinders.

Reagents

All reagents must be ACS certified reagent grade, unless specified othewise.

(a)   Doubly distilled or deionized water.

(b)   Redistilled concentrated nitric acid.

(c)   Ultrapure sulfuric acid.

(d)   Commercially prepared aqueous stock standard, 1,000 μg Ni/ml. Working standards are prepared by dilution of the stock solution with 5% nitric acid. Working standards should not be stored longer than 1 week.

(e)   Ammonium pyrrolidine dithiocarbamate (APDC), 2 g/100 ml: One gram of APDC is dissolved in 50 ml of water, and the solution is extracted twice with 5 ml of methyl isobutyl ketone (MIBK). This solution is prepared each day.

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(f)   Phthalate buffer, pH 2.5: 10.2 g of potassium acid phthalate and 39 ml of 1.0 N hydrochloric acid/liter; 10 ml of APDC is added and the solution is extracted 5 times with 25 ml of MIBK.

(g)   Methyl isobutyl ketone (MIBK), water saturated.

(h)   Ammonium hydroxide, concentrated.

Procedure

(a)   Cleaning of Equipment

Clean glassware, prior to first use, by soaking it for 24 hours in 5% nitric acid, rinsing with tap water, and finally rinsing with doubly distilled water. After glassware has been used, wash first with detergent, rinse with tap water, soak in 5% nitric acid for 1 hour, and rinse thoroughly with doubly distilled water. Allow to dry. Use plastic containers for cleaning and do not handle the cleaned glassware with bare hands, as sweating may cause nickel contamination.

(b)   Collection of Samples

Urine samples of about 100 ml are collected in borosilicate or polyethylene containers. About 1 ml of concentrated hydrochloric acid is added to the specimen upon receipt in the laboratory.

(c)   Analysis of Samples

(1)   Transfer the unknown samples (50 ml of urine) and 50 ml of at least three standards of different concentrations covering the range of interest to separate 125-ml Erhlenmeyer flasks, and add 10 ml of a 1:5 mixture of sulfuric:nitric acids to each flask. Heat the flasks on a hotplate in a fume hood, adding additional 1:5 sulfuric and nitric acid in 2-ml increments to each flask until digestion is complete, a white residue

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is obtained, and the final volume is less than 2 ml. If low recovery yields are obtained, addition of 1 part of perchloric acid to the digestion mix may overcome this difficulty. Routine use of perchloric acid is not recommended because of its explosive properties.

(2)   Allow the flasks to cool, transfer the contents of each flask quantitatively to a 50-ml centrifuge tube, and adjust the volume of each tube to 20 ml with distilled water.

(3)   Add 2 ml of phthalate buffer to each sample, and adjust the pH to 2.5 by addition of ammonium hydroxide drop by drop.

(4)   Add 2 ml of APDC solution and mix the contents. Then add 3 ml of MIBK and shake for 1 minute.

(5)   Centrifuge the tubes at approximately 900 G for 5 minutes.

(6)   Transfer the organic phase to a 5-ml stoppered vial.

(7)   Aspirate into the atomic absorption unit and read the absorbance at 232 nm. Stabilize the baseline of the atomic absorption unit by aspiration of water-saturated MIBK for 20-30 minutes prior to reading of the samples. Adjust the flame to obtain optimum sensitivity with minimum baseline noise.

Calculations

A calibration curve is prepared by plotting the absorbance versus the concentration of each standard on linear graph paper. The concentration of nickel that corresponds to the absorbance for the sample is read from the graph.

XIII. APPENDIX IV

MATERIAL SAFETY DATA SHEET

The following items of information which are applicable to a specific product or material shall be provided in the appropriate block of the Material Safety Data Sheet (MSDS).

The product designation is inserted in the block in the upper left corner of the first page to facilitate filing and retrieval. Print in upper case letters as large as possible. It should be printed to read upright with the sheet turned sideways. The product designation is that name or code designation which appears on the label, or by which the product is sold or known by employees. The relative numerical hazard ratings and key statements are those determined by the rules in Chapter V, Part B, of the NIOSH publication, <u>An Identification System for Occupationally Hazardous Materials</u>. The company identification may be printed in the upper right corner if desired.

(a)   Section I. Product Identification

The manufacturer's name, address, and regular and emergency telephone numbers (including area code) are inserted in the appropriate blocks of Section I. The company listed should be a source of detailed backup information on the hazards of the material(s) covered by the MSDS. The listing of suppliers or wholesale distributors is discouraged. The trade name should be the product designation or common name associated with the material. The synonyms are those commonly used for the product, especially formal chemical nomenclature. Every known chemical designation or

competitor's trade name need not be listed.

(b)   Section II. Hazardous Ingredients

The "materials" listed in Section II shall be those substances which are part of the hazardous product covered by the MSDS and individually meet any of the criteria defining a hazardous material. Thus, one component of a multicomponent product might be listed because of its toxicity, another component because of its flammability, while a third component could be included both for its toxicity and its reactivity. Note that a MSDS for a single component product must have the name of the material repeated in this section to avoid giving the impression that there are no hazardous ingredients.

Chemical substances should be listed according to their complete name derived from a recognized system of nomenclature. Where possible, avoid using common names and general class names such as "aromatic amine," "safety solvent," or "aliphatic hydrocarbon" when the specific name is known.

The "%" may be the approximate percentage by weight or volume (indicate basis) which each hazardous ingredient of the mixture bears to the whole mixture. This may be indicated as a range or maximum amount, ie, "10-40% vol" or "10% max wt" to avoid disclosure of trade secrets.

Toxic hazard data shall be stated in terms of concentration, mode of exposure or test, and animal used, eg, "100 ppm LC50-rat," "25 mg/kg LD50-skin-rabbit," "75 ppm LC man," or "permissible exposure from 29 CFR 1910.1000," or, if not available, from other sources of publications such as the American Conference of Governmental Industrial Hygienists or the American National Standards Institute Inc. Flashpoint, shock sensitivity,

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or similar descriptive data may be used to indicate flammability, reactivity, or similar hazardous properties of the material.

(c)   Section III. Physical Data

The data in Section III should be for the total mixture and should include the boiling point and melting point in degrees Fahrenheit (Celsius in parentheses); vapor pressure, in conventional millimeters of mercury (mmHg); vapor density of gas or vapor (air = 1); solubility in water, in parts/hundred parts of water by weight; specific gravity (water = 1); percent volatiles (indicated if by weight or volume) at 70 degrees Fahrenheit (21.1 degrees Celsius); evaporation rate for liquids or sublimable solids, relative to butyl acetate; and appearance and odor. These data are useful for the control of toxic substances. Boiling point, vapor density, percent volatiles, vapor pressure, and evaporation are useful for designing proper ventilation equipment. This information is also useful for design and deployment of adequate fire and spill containment equipment. The appearance and odor may facilitate identification of substances stored in improperly marked containers, or when spilled.

(d)   Section IV. Fire and Explosion Data

Section IV should contain complete fire and explosion data for the product, including flashpoint and autoignition temperature in degrees Fahrenheit (Celsius in parentheses); flammable limits, in percent by volume in air; suitable extinguishing media or materials; special firefighting procedures; and unusual fire and explosion hazard information. If the product presents no fire hazard, insert "NO FIRE HAZARD" on the line labeled "Extinguishing Media."

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(e)   Section V. Health Hazard Information

The "Health Hazard Data" should be a combined estimate of the hazard
of the total product. This can be expressed as a TWA concentration, as a
permissible exposure, or by some other indication of an acceptable
standard. Other data are acceptable, such as lowest LD50 if multiple
components are involved.

Under "Routes of Exposure," comments in each category should reflect
the potential hazard from absorption by the route in question.   Comments
should indicate the severity of the effect and the basis for the statement
if possible. The basis might be animal studies, analogy with similar
products, or human experiences. Comments such as "yes" or "possible" are
not helpful. Typical comments might be:

> Skin Contact--single short contact, no adverse effects likely;
> prolonged or repeated contact, possibly mild irritation.

> Eye Contact--some pain and mild transient irritation; no corneal ,
> scarring.

"Emergency and First Aid Procedures" should be written in lay
language and should primarily represent first-aid treatment that could be
provided by paramedical personnel or individuals trained in first aid.

Information in the "Notes to Physician" section should include any
special medical information which would be of assistance to an attending
physician including required or recommended preplacement and periodic
medical examinations, diagnostic procedures, and medical management of
overexposed employees.

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(f)   Section VI. Reactivity Data

The comments in Section VI relate to safe storage and handling of hazardous, unstable substances. It is particularly important to highlight instability or incompatibility to common substances or circumstances, such as water, direct sunlight, steel or copper piping, acids, alkalies, etc. "Hazardous Decomposition Products" shall include those products released under fire conditions. It must also include dangerous products produced by aging, such as peroxides in the case of some ethers. Where applicable, shelf life should also be indicated.

(g)   Section VII. Spill or Leak Procedures

Detailed procedures for cleanup and disposal should be listed with emphasis on precautions to be taken to protect employees assigned to cleanup detail. Specific neutralizing chemicals or procedures should be described in detail. Disposal methods should be explicit including proper labeling of containers holding residues and ultimate disposal methods such as "sanitary landfill" or "incineration." Warnings such as "comply with local, state, and federal antipollution ordinances" are proper but not sufficient. Specific procedures shall be identified.

(h)   Section VIII. Special Protection Information

Section VIII requires specific information. Statements such as "Yes," "No," or "If necessary" are not informative. Ventilation requirements should be specific as to type and preferred methods. Respirators shall be specified as to type and NIOSH or US Bureau of Mines approval class, ie, "Supplied air," "Organic vapor canister," etc. Protective equipment must be specified as to type and materials of construction.

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(i)   Section IX. Special Precautions

"Precautionary Statements" shall consist of the label statements selected for use on the container or placard. Additional information on any aspect of safety or health not covered in other sections should be inserted in Section IX. The lower block can contain references to published guides or in-house procedures for handling and storage. Department of Transportation markings and classifications and other freight, handling, or storage requirements and environmental controls can be noted.

(j)   Signature and Filing

Finally, the name and address of the responsible person who completed the MSDS and the date of completion are entered. This will facilitate correction of errors and identify a source of additional information.

The MSDS shall be filed in a location readily accessible to employees exposed to the hazardous substance. The MSDS can be used as a training aid and basis for discussion during safety meetings and training of new employees. It should assist management by directing attention to the need for specific control engineering, work practices, and protective measures to ensure safe handling and use of the material. It will aid the safety and health staff in planning a safe and healthful work environment and in suggesting appropriate emergency procedures and sources of help in the event of harmful exposure of employees.

MATERIAL SAFETY DATA SHEET

I PRODUCT IDENTIFICATION	
MANUFACTURER'S NAME	REGULAR TELEPHONE NO EMERGENCY TELEPHONE NO.
ADDRESS	

TRADE NAME

SYNONYMS

II HAZARDOUS INGREDIENTS

MATERIAL OR COMPONENT	%	HAZARD DATA

III PHYSICAL DATA

BOILING POINT, 760 MM HG		MELTING POINT	
SPECIFIC GRAVITY (H_2O=1)		VAPOR PRESSURE	
VAPOR DENSITY (AIR=1)		SOLUBILITY IN H_2O, % BY WT	
% VOLATILES BY VOL		EVAPORATION RATE (BUTYL ACETATE=1)	
APPEARANCE AND ODOR			

IV FIRE AND EXPLOSION DATA

FLASH POINT (TEST METHOD)		AUTOIGNITION TEMPERATURE	

FLAMMABLE LIMITS IN AIR, % BY VOL	LOWER		UPPER	

EXTINGUISHING MEDIA	
SPECIAL FIRE FIGHTING PROCEDURES	
UNUSUAL FIRE AND EXPLOSION HAZARD	

V HEALTH HAZARD INFORMATION

HEALTH HAZARD DATA

ROUTES OF EXPOSURE

INHALATION

SKIN CONTACT

SKIN ABSORPTION

EYE CONTACT

INGESTION

EFFECTS OF OVEREXPOSURE
ACUTE OVEREXPOSURE

CHRONIC OVEREXPOSURE

EMERGENCY AND FIRST AID PROCEDURES

EYES

SKIN

INHALATION.

INGESTION

NOTES TO PHYSICIAN

VI REACTIVITY DATA

CONDITIONS CONTRIBUTING TO INSTABILITY

INCOMPATIBILITY

HAZARDOUS DECOMPOSITION PRODUCTS

CONDITIONS CONTRIBUTING TO HAZARDOUS POLYMERIZATION

VII SPILL OR LEAK PROCEDURES

STEPS TO BE TAKEN IF MATERIAL IS RELEASED OR SPILLED

NEUTRALIZING CHEMICALS

WASTE DISPOSAL METHOD

VIII SPECIAL PROTECTION INFORMATION

VENTILATION REQUIREMENTS

SPECIFIC PERSONAL PROTECTIVE EQUIPMENT

   RESPIRATORY (SPECIFY IN DETAIL)

   EYE

   GLOVES

   OTHER CLOTHING AND EQUIPMENT

IX SPECIAL PRECAUTIONS

**PRECAUTIONARY
STATEMENTS**

**OTHER HANDLING AND
STORAGE REQUIREMENTS**

PREPARED BY

ADDRESS

DATE

XIV. APPENDIX V

GLOSSARY

Calcining—A process in which nickel sulfide is heated and oxidized to form nickel oxide. The sulfur is driven off the feed material but agglomeration of fine particles does not occur.

Cementation—The purification of electrolyte by precipitation with metallic copper.

Converting—The process in which iron is removed by oxidation and concentration in slag. The amount of sulfur required for subsequent operations is also controlled; excess sulfur is driven off as sulfur dioxide.

Cupola furnaces—Used in the "Orford process" (see below) to make copper tops and nickel bottoms after iron was removed. The charge was matte, coke, and sodium sulfide.

Electrowinning—A method of electrolysis which has a net cell reaction and is used to refine soluble anodes of nickel sulfide.

Matte—An impure metallic sulfide mixture produced by smelting of sulfide ores.

Nickel monosulfide—In this document, nickel monosulfide refers to NiS.

Nickel subsulfide—In this document, nickel subsulfide refers to Ni3S2.

Nickel sulfides—Nickel sulfides refer to nickel-sulfur compounds in nickel matte.

Orford process—Obsolete method for separation of nickel and copper. Copper sulfide is more soluble in sodium sulfide than is nickel sulfide. The copper, therefore, tends to float because sodium sulfide has a specific gravity of 1.9, whereas nickel sulfide, with a specific gravity of 5.7, settles out.

Pentlandite—A nickel-bearing mineral with an ideal formula of (Ni,Fe)9S8 and a nickel content of 34.22%.

Reduction—Conversion of nickel oxide to nickel metal.

Roasting—Oxidizing process in which nickel sulfide ores are heated to oxidize iron and to drive off sulfur as sulfur dioxide. Fluid-bed roasters, multihearth roasters, and sintering machines have been used.

Sintering—A process in which nickel sulfide is heated and oxidized to form nickel oxide. Sulfur is driven off the feed material and agglomeration of fine particles occurs.

Slimes—Anode impurities that do not go into solution in electrolytic tanks.

Smelting--Thermal treatment of nickeliferous sulfide ores or ore concentrates to bring about physical and chemical changes leading to the recovery of nickel and valuable metals.

TABLE XV-1

PROPERTIES AND USES OF NICKEL AND COMMERCIAL NICKEL COMPOUNDS

| Compound | Formula | Solubility | | Uses | | | | |
		Water	Other Solvents	Alloy	Cata-lyst	Nickel Plating	Pigment, Fixative	Other*
Nickel	Ni	Insol	HNO3,HCl, H2SO4	X	X	X	X	1
Nickel acetate	Ni(C2H3O2)2	Sol	Alcohol		X		X	
Nickel ammonium chloride	NiCl2 .NH4Cl .6H2O	"				X	X	
Nickel ammonium sulfate	NiSO4 .(NH4)2SO4 .6H2O	"	Alcohol			X		
Nickel arsenate	Ni3(AsO4)2	Insol	Acid		X			
Nickel boride	NiB	**	HNO3,aqua regia					2
Nickel bromate	Ni(BrO3)2 .6H2O	Sol						
Nickel bromide	NiBr2	"	NH4OH, ether					
Nickel carbonate	NiCO3	"	Acid		X	X	X	
Nickel carbonate hydroxide	NiCO3 .2Ni(OH)2 .4H2O	Insol	HCl, NH4OH		X	X	X	

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TABLE XV-1 (CONTINUED)

PROPERTIES AND USES OF NICKEL AND COMMERCIAL NICKEL COMPOUNDS

Compound	Formula	Solubility		Uses				
		Water	Other Solvents	Alloy	Cata- lyst	Nickel Plating	Pigment, Fixative	Other*
Nickel chloride	NiC12	Sol	Alcohol, NH4OH			X	X	4
Nickel chromate	NiCrO4					X		
Nickel cyanide	Ni(CN)2	Insol	KCN	X		X		
Nickel fluo- borate	Ni(BF4)2					X		
Nickel fluoride	NiF2	Sol	NH3,acid, ether					
Nickel hydroxide	Ni(OH)2	"	NH4OH, acid					3,5
Nickel nitrate hexa- hydrate	Ni(NO3)2 .6H2O	"	Alcohol, NH4OH		X	X	X	
Nickel nitrate tetra- amine	Ni(NO3)2 .4NH3 .2H2O	"				X		
Nickel ortho- phosphate	Ni3(PO4)2 .8H2O	Insol	Alcohol, acid,NH4 salts			X	X	
Nickel oxide	NiO	"	Acid, NH4OH	X			X	1
Nickel peroxide	Ni2O3	"	Acid					3

TABLE XV-1 (CONTINUED)

PROPERTIES AND USES OF NICKEL AND COMMERCIAL NICKEL COMPOUNDS

Compound	Formula	Solubility		Uses				
		Water	Other Solvents	Alloy	Cata-lyst	Nickel Plating	Pigment, Fixative	Other*
Nickel phosphate hepta- hydrate	Ni3(PO4)2 7H2O	"	Acid, NH4OH			X	X	
Nickel potassium chromate	NiK2(CrO4)2							
Nickel potassium sulfate	NiSO4K2SO4 .6H2O	Sol						
Nickel stannate	NiSnO3.2H2O						X	
Nickel sub- sulfide***	Ni3S2	Insol	HNO3					
Nickel sulfamate	N2O6S2NiH4					X		
Nickel sulfate	NiSO4	Sol	Methanol	X	X	X	6,7	
Nickel sulfate hepta- hydrate	NiSO4.7H2O	"	Alcohol	X			X	6
Nickel sulfate hexa- hydrate	NiSO4.6H2O	"	Alcohol, NH4OH	X	X	X		
Nickel sulfide	NiS	"	HNO3, KHS					

TABLE XV-1 (CONTINUED)

PROPERTIES AND USES OF NICKEL AND COMMERCIAL NICKEL COMPOUNDS

Compound	Formula	Solubility		Uses				
		Water	Other Solvents	Alloy	Cata- lyst	Nickel Plating	Pigment, Fixative	Other*
Nickel titanate	NiTiO4						X	
Nickel zirconate	NiZrO5							3
Nickelic hydroxide	Ni(OH)3							5

*Other uses: 1--fuel-cell electrodes, 2--prisms, 3--batteries, 4--gas-mask absorbant, 5--nickel salts, 6--food additive, 7--blackener for zinc and brass
**Decomposes
***Not produced or used, but may form during refining of nickel matte

Adapted from references 4-9

TABLE XV-2

OCCUPATIONS WITH POTENTIAL EXPOSURE TO NICKEL

Battery makers, storage	Nickel miners
Catalyst workers	Nickel refiners
Cemented-carbide makers	Nickel smelters
Ceramic makers	Nickel workers
Disinfectant makers	Oil hydrogenators
Dyers	Organic-chemical synthesizers
Electroplaters	Paint makers
Enamelers	Penpoint makers
Gas-mask makers	Petroleum-refinery workers
Inkmakers	Spark-plug makers
Jewelers	Stainless-steel makers
Magnet makers	Textile dyers
Metallizers	Vacuum-tube makers
Mond-process workers	Varnish makers
Nickel-alloy makers	Welders

Adapted from reference 14

TABLE XV-3

OCCUPATIONAL HISTORIES OF WORKERS AT A NICKEL REFINERY IN PORT COLBORNE, ONTARIO,
WHO DEVELOPED NASAL CANCER BETWEEN 1930 AND JUNE 1976

Case No.	Year of First Employment	Year of Death (or Diagnosis)	Number of years		Years of Employment in Each Exposure Group							Classification with longest Exposure
			Employed	From First Employment to Death (Diagnosis)	Furnace				Electrolysis	Other Dust	Not Dusty	
					Cupola	Calciner	Sinter	Anode				
1*	1920	1955	31.0	35	0	8.5	22.5	0	0	0	0	Sinter
2	1922	1962	41.9	40	21.5	0	0	0	20.4	0	0	Cupola
3*	1923	1953	29.0	30	9.0	0.3	0.2	19.2	0	0	0.3	Anode
4*	1923	1953	29.0	30	0	7.2	21.3	0	0	0	0.5	Sinter
5	1923	1963	22.2	40	0.9	0	0	0	7.3	0	14.0	Not dusty
6	1923	1969	31.3	46	0.3	23.0	0	0	0	0	8.0	Calciner
7*	1924	1955	28.5	31	7.5	0.5	17.0	3.5	0	0	0	Sinter
8	1924	1973	33.3	49	0	8.7	17.0	0	0	0	7.6	"
9*	1925**	1948	23.4	23	0	4.3	18.6	0	0	0	0.5	"
10	1926	1973	37.2	47	0	0	0	37.2	0	0	0	Anode
11*	1928	1946	15.3	18	0	0	0	0	14.8	0	0.5	Electrolysis
12*	1928	1957	24.2	29	0.9	0	0	0.2	6.3	15.8	1.0	Other dust
13*	1928	1957	24.5	29	0	0	18.5	0	0	0.3	5.7	Sinter
14*	1928	1959	11.2	31	2.8	0	1.5	0.7	0	6.2	0	Other dust
15	1928	1960	31.4	32	0	2.3	26.2	0	2.9	0	0	Sinter
16	1928	1960	25.9	32	1.1	22.2	0	0	0	0	2.6	Calciner
17*	1928	1965	22.3	37	0.3	16.9	1.2	0.7	3.1	0	0.1	"
18	1928	(1973)	33.3	(45)	0	11.0	1.0	0	21.3	0	0	Electrolysis
19	1928	(1973)	38.3	(45)	0	0	0.3	0	38.0	0	0	"
20*	1930	1954	18.6	24	1.7	0	0	0	16.8	0.1	0	"
21	1930	1975	41.0	45	0	0	0	0	39.4	0	1.6	"
22	1931	1969	36.6	38	0	0	0	0	36.6	0	0	"
23*	1933	1959	20.8	26	0	0	16.7	4.1	0	0	0	Sinter
24	1934	1959	7.4	25	0	3.0	4.4	0	0	0	0	"
25	1935	(1971)	13.6	(36)	0	5.0	7.6	0	0	0	1.0	"
26	1935	1972	9.7	37	0	5.0	0	0	4.7	0	0	Calciner
27	1936	(1966)	30.5	(30)	0	29.5	1.0	0	0	0	0	"
28	1936	1972	28.0	36	0	7.3	0.2	0	0	0	20.5	Not dusty
29	1936	(1973)	6.9	(37)	0	0	0	1.1	1.0	0	4.8	"
30	1940	1971	30.0	31	0	0	4.5	0	25.5	0	0	Electrolysis
31	1941	1964	22.0	23	0	2.6	4.7	0	13.7	0	1.0	"
32	1941	(1973)	30.1	(32)	0	4.8	3.3	0	0	0	22.0	Not dusty
33	1942	1972	28.1	30	0	0	0	0	0	0	21.8(a)	"
34	1944	1964	25.7	20	0	0	11.0	0	0	0	14.7	"
35	1944	1967	22.7	23	0	0.2	0	0	21.0	0	1.5	Electrolysis
36	1956	(1973)	13.6	(17)	0	8.0	0	0	0	5.1	0.5	Calciner

Mean=25.5 Mean=32.8
SD= 9.1 SD= 8.4

*In the study by Sutherland [44] and Inco [41]; all others in the Inco report only
**Cancer of the nasopharynx
(a)Carpenter

Adapted from Sutherland [44] and Inco [41]

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TABLE XV-4

OCCUPATIONAL HISTORIES OF WORKERS AT A NICKEL REFINERY IN PORT COLBORNE, ONTARIO,
WHO DEVELOPED LUNG CANCER BETWEEN 1930 AND JUNE 1976

Case No.	Year of First Employment	Year of Death (or Diagnosis)	Number of Years Employed	From First Employment to Death (Diagnosis)	Furnace Cupola	Calciner	Sinter	Anode	Electrolysis	Other Dust	Not Dusty	Classification with Longest Exposure
1	1919	1968	37.7	49	0	33.1	0	0.1	0	4.1	0.4	Calciner
2*	1922	1956	32.2	34	0	0	0	0	0	0	32.2	Not dusty
3	1922	1961	20.5	39	0	12.2	0	0	8.3	0	0	Calciner
4	1922	1963	23.1	41	0	0	0	0	0	0	23.1	Not Dusty
5	1922	1963	21.3	41	0.5	20.8	0	0	0	0	0	Calciner
6	1922	1968	18.0	46	5.8	0	0.4	0.1	0.3	0.1	11.3	Not dusty
7	1922	1970	35.4	48	0	0	0	0	35.3	0	0.1	Electrolysis
8	1923	1966	14.7	43	3.3	10.4	0	0.1	0	0	0.9	Calciner
9	1923	1966	31.5	43	0	0	(b)	0	0	31.5	0	Other dust
10	1923	1967	18.2	44	0.2	15.0	0	0	0	0	3.0	Calciner
11	1923	1968	8.5	45	0	3.3	2.0	1.1	1.8	0	0.3	"
12	1923	1969	16.4	46	0	0	0	0	4.3	0	12.1	Not dusty
13	1923	1974	10.3	51	0	0	0	0	0	10.3	0	Other dust
14*	1924	1954	26.0	30	0	0	0	0	0	26.0	0	"
15*	1924	1955	28.5	31	7.5	0.5	17.0	3.5	0	0	0	Sinter
16	1925	1951	13.8	26	0.7	2.6	3.4	0.2	3.8	3.1	0	Electrolysis
17*	1925	1953	27.8	28	2.9	0.4	24.0	0.5(c)	0	0	0	Sinter
18	1925	(1961)	19.4	(36)	0	(b)	(b)	0	0	19.4	0	Other dust
19	1925	(1961)	23.6	(36)	0	2.9	20.7	0	0	0	0	Sinter
20	1925	1967	34.5	42	0.1	0.1	0	0	0.1	34.2(d)	0	Other dust
21	1925	(1972)	32.1	(47)	3.8	0.1	0	0.1	0	0.1	28.0	Not dusty
22	1925	1975	31.8	50	3.8	0.1	0	0	0	0	27.9	"
23*	1926	1949	22.9	23	0.8	0	0	0	21.8	0.3	0	Electrolysis
24*	1926	1957	30.0	31	0	0	0	0	0	0	30.0	Not dusty
25	1926	1967	6.2	41	0.2	1.1	3.0	0	0	1.8	0.1	Sinter
26*	1927	1953	11.6	26	0.6	8.3	0.2	0	0	0	2.5	Calciner
27	1927	(1972)	36.0	(45)	0.2	3.9	0.3	0.2	31.3	0	0.1	Electrolysis
28*	1928	1946	13.6	18	3.5	0.3	0	9.8	0	0	0	Anode
29*	1928	1954	24.1	26	0.1	0	3.5	0	6.8	13.7	0	Other dust
30*	1928	1954	24.8	26	0.2	0	9.6	0	0.3	0	14.7	Not dusty
31*	1928	1955	24.8	27	1.6	1.9	0	0	21.3	0	0	Electrolysis
32*	1928	1956	25.8	28	3.2	1.8	16.2	0	4.6	0	0	Sinter
33*	1928	1956	25.2	28	0	3.0	21.4	0	0	0.8	0	"
34*	1928	1959	27.1	31	0.5	0	17.8	1.7	0.8	0	6.3	"
35	1928	1963	23.1	35	0	6.4	4.6	0	0	10.4	1.7	Other dust
36	1928	1964	5.9	36	0	0	0.1	0.5	3.1	1.6	0.6	Electrolysis
37	1928	1964	16.6	36	0	0	0	0	0.2	13.3	3.1	Other dust
38	1928	1965	27.6	37	3.0	0.2	0	0.1	0	24.3	0	"
39	1928	1967	32.8	39	0	0	0	19.2	0	0.1	14.5	Anode
40	1928	1969	32.7	41	0	0	17.3	0	3.5	0.7	11.2	Sinter
41	1928	1971	31.9	43	0.5	0.1	0	0	31.0	0.1	0.2	Electrolysis
42	1928	1972	30.8	44	0	12.8	3.7	0.1	2.9	11.3	2.0	Calciner
43	1928	1973	15.5	45	0	0	0	0	0	0	15.5	Not dusty
44*	1929	1954	24.7	25	4.2	0	17.5	0	0	3.0	0	Sinter
45	1929	1956	11.9	27	0	0	11.9	0	0	0	0	"
46*	1929	1956	19.9	27	0	0	0	0	18.8	0	1.1	Electrolysis
47*	1929	1959	33.0	30	1.0	----17.0----		0	0	15.0	0	Calciner/sinter
48	1929	1960	9.2	31	1.0	0	0	0	7.8	0.1	0.3	Electrolysis
49	1929	1960	30.7	31	0	5.9	0.7	0	23.2	0	0.9	"
50	1929	(1962)	20.3	(33)	0	0.3	0.1	17.0	2.8	0.1	0	Anode
51	1929	1963	12.0	34	2.1	0.4	9.3	0	0	0.2	0	Sinter
52	1929	1964	16.1	35	0.7	14.5	0	0	0	0.9	0	Calciner
53	1929	1965	3.7	36	1.8	1.9	0	0	0	0	0	"
54	1929	(1968)	29.2	(39)	0	0	17.4	0	0	0	11.8	Sinter
55	1929	1973	36.1	44	0	0	0	0	0	31.3	4.8	Other dust

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TABLE XV-4 (CONTINUED)

OCCUPATIONAL HISTORIES OF WORKERS AT A NICKEL REFINERY IN PORT COLBORNE, ONTARIO,
WHO DEVELOPED LUNG CANCER BETWEEN 1930 AND JUNE 1976

Case No.	Year of First Employment	Year of Death (or Diagnosis)	Number of Years		Years of Employment in Each Exposure Group							Classification with Longest Exposure
			Employed	From First Employment to Death (Diagnosis)	Furnace				Electrolysis	Other Dust	Not Dusty	
					Cupola	Calciner	Sinter	Anode				
56	1929	1973	9.7	44	2.5	0	1.2	0	0	1.0	5.0	Not dusty
57*	1930	1955	21.8	25	1.9	0.8	0	0	18.8	0	0.3	Electrolysis
58	1931	1965	34.2	34	0	13.7	13.3	0.1	0.1	4.5	2.5	Calciner
59*	1933	1953	19.6	20	0	0	0	18.8	0	0.3	0.5	Anode
60*	1933	1955	22.9	22	0.5	0	0	21.9(c)	0	0	0.5	"
61*	1933	1958	22.5	25	0	0	0	0	0	0	22.5	Not dusty
62	1933	1963	28.6	30	0	4.8	23.8	0	0	0	0	Sinter
63	1933	1967	27.8	34	0	0	0	0	2.0	25.8	0	Other dust
64	1933	1972	29.0	39	0	0	0.5	0	27.4	0	1.1	Electrolysis
65	1934	1964	29.1	30	1.6	0	0	0	25.8	0.8	0.9	"
66	1935	1962	12.2	27	0	0.2	10.2	0	1.8	0	0	Sinter
67	1935	1965	29.5	30	0	0	0	0.1	0	29.3	0.1	Other dust
68	1935	1971	31.6	36	0	0.2	0	0.1	1.9	29.3	0.1	"
69	1935	1971	10.2	36	0	0	0	0	9.8	0	0.4	Electrolysis
70*	1936	1957	20.8	21	0	5.5	13.8	0	0	0	1.5	Sinter
71	1937	1961	19.4	24	0	0	0	0.1	17.2	0.2	1.9	Electrolysis
72	1937	1967	24.4	30	0	0	0	0.1	9.9	0	14.4	Not dusty
73	1937	1970	28.0	33	0	0	0	0.1	10.5	0	17.4	"
74	1937	1971	26.1	34	0	0	6.4	0	0	19.7	0	Other dust
75	1939	1970	12.8	31	0.3	12.1	0	0	0	0.3	0.1	Calciner
76	1939	1971	27.7	32	0	0.2	3.3	0	0	2.9	19.3	Not dusty
77	1940	(1973)	26.6	(33)	0	0	0	0	0.1	0.2	26.3	"
78	1941	1965	10.2	24	0	0	0	0	9.5	0	0.7	Electrolysis
79	1942	1963	24.8	21	0	2.6	0.2	0	11.0	0	11.0	Electrolysis/not dusty
80	1942	1966	22.9	24	0	0	0	0	22.7	0	0.2	Electrolysis
81	1942	1970	26.7	28	0	1.4	0	0.1	23.5	0	1.7	"
82	1942	1972	27.2	30	0	0.3	3.2	0	22.8	0.1	0.8	"
83	1942	1973	28.3	31	0	0.3	0	0	17.7	10.3	0	"
84	1944	1964	20.0	20	0	4.3	3.5	0	1.4	0	10.8	Not dusty
85	1947	1962	9.8	15	0	0	0	2.8	0	0.3	6.7	"
86	1948	1970	14.7	22	0	0	0	0.6	5.8	0.5	7.8	"
87	1948	1974	5.4	26	0	0	0	0	0	5.1	0.3	Other dust
88	1950	(1973)	22.8	(23)	0	0	0	0	0	22.8	0	"
89	1951	1972	20.9	21	0	----9.2----		0.1	0.1	11.4	0.1	"
90	1953	1973	17.2	20	0	0.3	0	0	9.5	0	7.4	Electrolysis

Mean=22.5 Mean=33.0
SD=8.3   SD=8.4

*Included in the study by Sutherland [44] and Inco [41]; all others the Inco report only
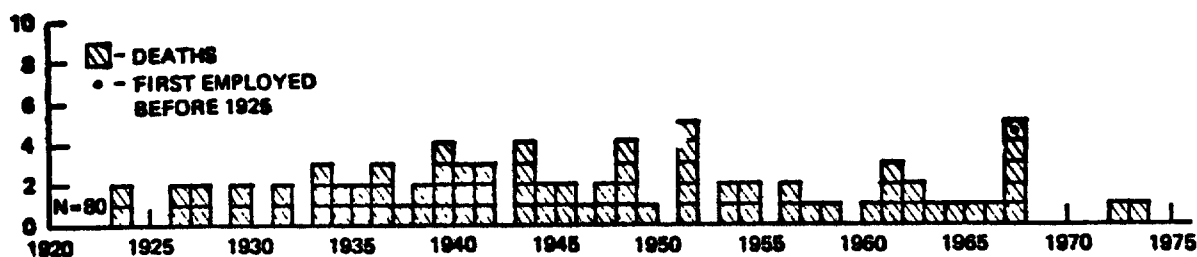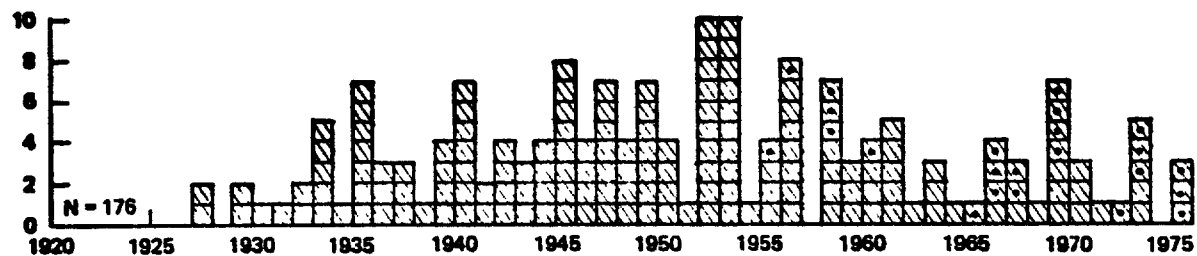(a)Management
(b)Worked occasionally in maintenance
(c)Molder, not exposed
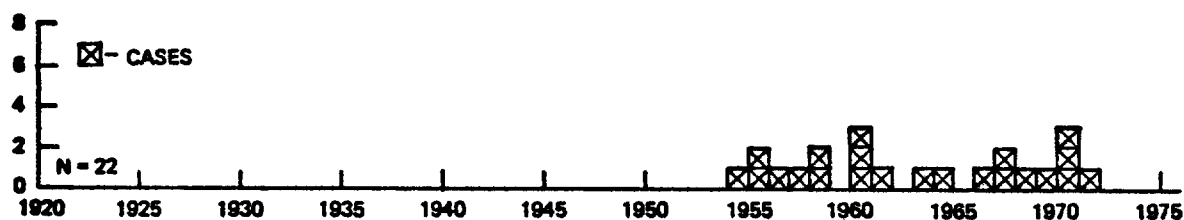(d)Sinter conveyorman
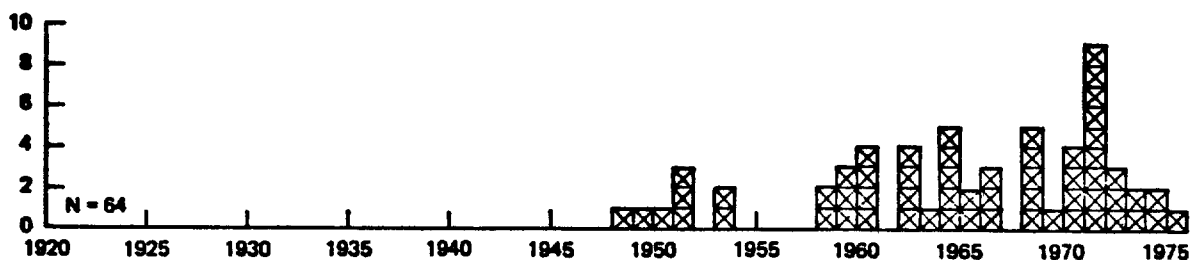
Adapted from Sutherland [44] and Inco [41]

a. NASAL CANCER BY YEAR OF DEATH IN WORKERS
AT A NICKEL REFINERY IN CLYDACH. WALES [41]

b. LUNG CANCER BY YEAR OF DEATH IN WORKERS
AT A NICKEL REFINERY IN CLYDACH, WALES [41]

c. NASAL CANCER BY YEAR OF DIAGNOSIS IN
WORKERS AT A NICKEL REFINERY IN KRISTIANSAND, NORWAY
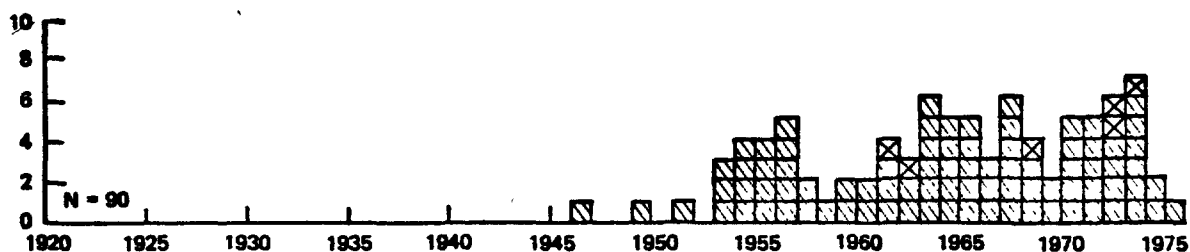(B Roy. written communication, October 1976)

d. LUNG CANCER BY YEAR OF DIAGNOSIS IN
WORKERS AT A NICKEL REFINERY IN KRISTIANSAND, NORWAY
(B Roy, written communication, October 1976)

FIGURE XV-1

LUNG AND NASAL CANCERS IN NICKEL REFINERY WORKERS

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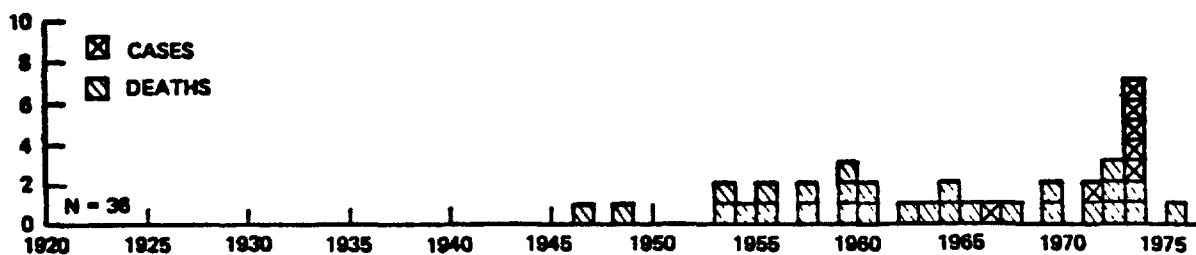
e. NASAL CANCER BY YEAR OF DIAGNOSIS OR DEATH IN
WORKERS AT A NICKEL REFINERY IN PORT COLBORNE, ONTARIO [41]

f. LUNG CANCER BY YEAR OF DIAGNOSIS OR DEATH IN
WORKERS AT A NICKEL REFINERY IN PORT COLBORNE, ONTARIO [41]
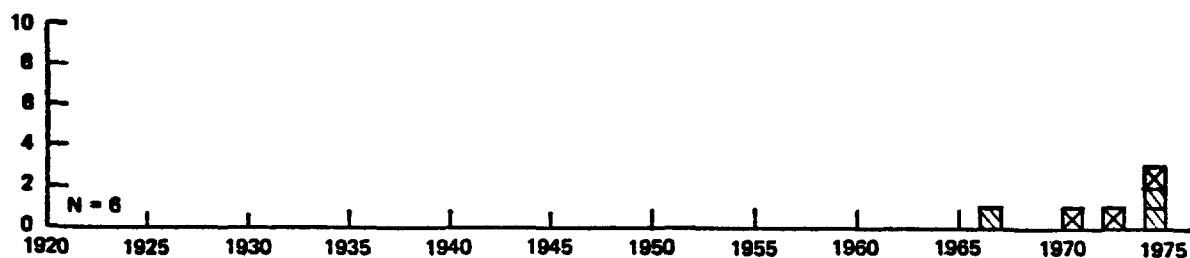
g. NASAL CANCER BY YEAR OF DIAGNOSIS OR DEATH IN
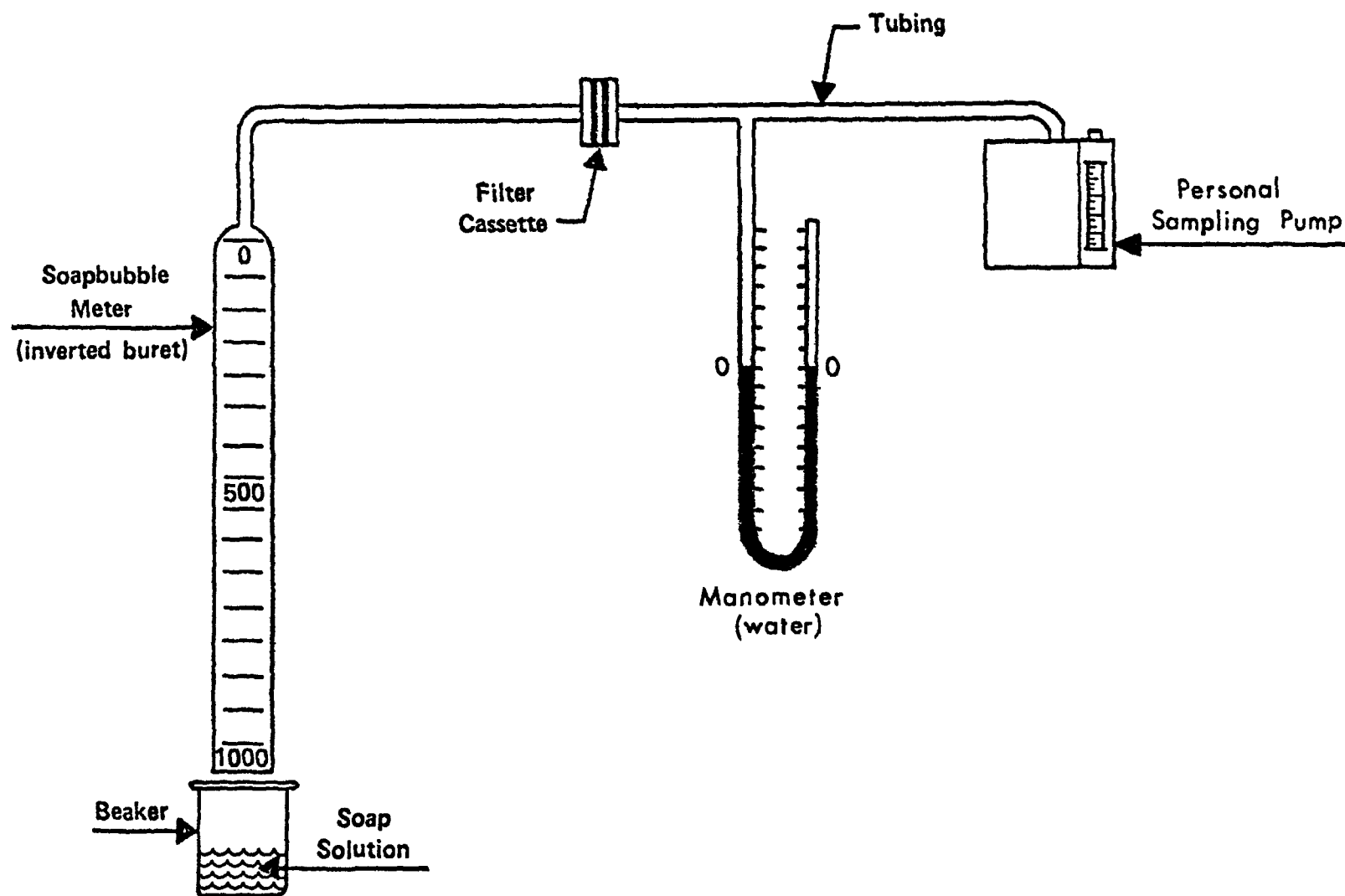WORKERS AT A SINTER PLANT AT A NICKEL REFINERY IN COPPER CLIFF, ONTARIO [41
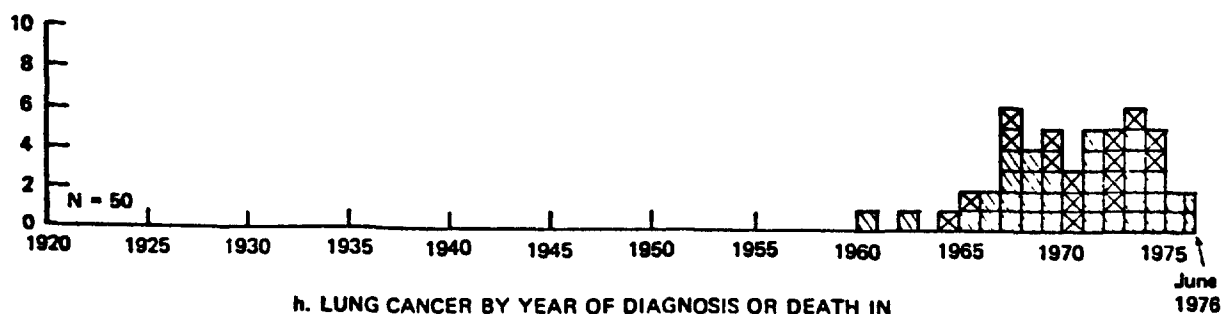
h. LUNG CANCER BY YEAR OF DIAGNOSIS OR DEATH IN
WORKERS AT A SINTER PLANT AT A NICKEL REFINERY IN COPPER CLIFF, ONTARIO [41]

FIGURE XV-1 (CONTINUED)

LUNG AND NASAL CANCERS IN NICKEL REFINERY WORKERS

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FIGURE XV-2 CALIBRATION SETUP FOR PERSONAL SAMPLING PUMP WITH FILTER CASSETTE

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