Scand J Work Environ Health 1990;16(1):1-82
https://doi.org/10.5271/sjweh.1813
Issue date: 01 Feb 1990

Report of the International Committee on Nickel Carcinogenesis in Man.

The following article refers to this text: 2012;38(6):503-515

This article in PubMed: www.ncbi.nlm.nih.gov/pubmed/2185539

Print ISSN: 0355-3140 Electronic ISSN: 1795-990X

Scand J Work Environ Health 1990;16:1—82

Report of the International Committee on Nickel Carcinogenesis in Man

Funded and supported by

US Environmental Protection Agency
Commission of European Communities
Energy, Mines, and Resources Canada
National Health and Welfare Canada
Ontario Ministry of Labour
Nickel Producers Environmental Research Association

INTERNATIONAL COMMITTEE ON NICKEL CARCINOGENESIS IN MAN

Richard Doll (chairman)
Imperial Cancer Research Fund
Cancer Epidemiology and Clinical Trials Unit
Oxford, England

Aage Andersen
The Cancer Registry of Norway
Oslo, Norway

W Clark Cooper
Consultant in Occupational Health Lafayette, California,
USA

Irene Cosmatos[1]
Program Resources, Inc
Research Triangle Park, North Carolina, USA

Donna L Cragle
Oak Ridge Associated Universities
Oak Ridge, Tennessee, USA

Doug Easton
Institute of Cancer Research
Surrey, England

Philip Enterline
University of Pittsburgh
Pittsburgh, Pennsylvania, USA

Marcel Goldberg
Institut National de la Santé et la
Recherche Medicale
Paris, France

Len Metcalfe
INCO Europe Limited
Clydach, Wales

Tor Norseth
Statens Arbeitsmiljøinstitutt
Oslo, Norway

Julian Peto
Institute of Cancer Research
Surrey, England

Jean-Paul Rigaut
Institut National de la Santé et la
Recherche Medical
Paris, France

Robin Roberts
McMaster University
Hamilton, Ontario, Canada

Steven K Seilkop[2]
Program Resources, Inc
Research Triangle Park, North Carolina, USA

Harry Shannon
McMaster University
Hamilton, Ontario, Canada

Frank Speizer
Harvard Medical School
Cambridge, Massachusetts, USA

F William Sunderman, Jr
University of Connecticut
Farmington, Connecticut, USA

Philip Thornhill
Falconbridge Limited
Sudbury, Ontario, Canada

J Stuart Warner
INCO Limited
Toronto, Ontario, Canada

John Weglo
Falconbridge Limited
Sudbury, Ontario, Canada

Michael Wright
United Steel Workers of America
Pittsburgh, Pennsylvania, USA

Report prepared by Program Resources Inc, Science and Technology Center, Po Box 12794, Research Triangle Park, NC 27709, USA

---

[1] Current affiliation: University of Pennsylvania, Philadelphia, Pennsylvania, United States.

[2] Current affiliation: Analytical Sciences, Inc, Research Triangle Park, North Carolina, United States.

PREFACE

When, in the autumn of 1984, the sponsors of this report sought the assistance of epidemiologists in an attempt to clarify the nature and extent of the risk of cancer that nickel and its compounds might cause, the response was enthusiastic. All but one of the epidemiologists who had studied groups of nickel workers agreed to cooperate, and a meeting at which a collaborative investigation was planned was held in Oxford in January 1985.

It was realized from the start that, if any clear picture was to emerge, much more information would be needed about the amount of nickel and its compounds to which individual workers had been exposed and about the workers' subsequent mortality. The latter was relatively simple to obtain. But the former presented immense difficulties, and the committee is greatly indebted to the industrial staff who spent many months delving into old records, constructing an informative account of the environment in which the major hazards of the past had occurred, and codifying the occupational histories of individual workers in such a way that their modality could be related to the environmental conditions to which they had been exposed. It was realized, too, that the integration and analysis of the mass of epidemiologic data would be more than any one of the academic groups would be able to undertake, if it was to be done as quickly as was planned, and it was agreed that each of the participating epidemiologists would send their data in a standard form to an American research group on a contractual basis. This proved to be a good decision, and the two scientific representatives of the group that was commissioned to undertake the work rapidly became valued members of the team.

The research program was developed at the first Oxford meeting and was modified in the light of experience at two further meetings, one in Toronto in January and another in Oxford in June of the following year. Finally the report was planned in outline at a meeting at Hilton Head in South Carolina in September 1987.

A first draft of the report was prepared by Mr Seilkop in consultation with an editorial subcommittee, consisting of Dr Anderson, Dr Enterline, Professor Peto, Dr Roberts, Professor Speizer (consultant in epidemiology to the contracting research group), and Mr Thornhill, and was circulated to the whole committee for comments in January 1989. The revised draft, which took account of the many comments received, was then prepared by Mr Seilkop and edited by the Chairman. A report prepared in this way, which attempts to synthesize the views of many individuals with different interests and different skills, is inevitably a compromise, and no one member of the committee can be expected necessarily to agree with every statement in it. It was, therefore, decided that footnotes to the report should be included whenever in the Chairman's judgment disagreements were sufficiently serious to warrant them. It is an indication of the spirit of cooperation that has imbued the whole project that it has not, in fact, been found necessary to include any footnotes of this sort. This should not, however, be taken to mean that all the statements have been unanimously agreed upon. Individual members of the committee have reserved the right to qualify any of the specific conclusions in the edited version of the report, if they disagree with the way the results have been presented or interpreted.

The report was originally intended to be published by the end of 1987; but the difficulty in obtaining worthwhile estimates of the concentration of various nickel species in the air in the past in the major refineries delayed the identification of all the occupational groups that were worthy of individual study. If, in addition, we had waited until the last bit of information had been obtained and statistical analyses had been carried out based on refined modeling, publication could have been held up for five years.

It was therefore decided not to undertake any major reanalyses after the spring of 1989, with the result that some late information relating to the environmental estimates in the Kristiansand refinery could not be taken into account. This information revealed, first, that some nickel species (namely, nickel carbonate and nickel hydroxide) were classified as soluble, but would have been regarded as insoluble in the INCO refineries. The amounts were not large, but their inclusion resulted in an exaggeration of the differences in exposure to soluble nickel between the electrolysis departments in Kristiansand and elsewhere. Second, it was reported that samples of flue dust in the Port Colborne refinery and from part of the gas handling system in the roasting, smelting, and calcining department in Kristiansand may have contained 20—30 % nickel sulfate (possibly in an anhydrous and relatively insoluble form). This information was late only in the sense that it came to the attention of Mr Seilkop and myself after the main text had been approved, but it had previously been taken into account by the hygienists responsible for describing the environment in the refineries. It caused me, however, to misunderstand the position, and footnotes relating to it were consequently inserted in tables 6 and 11. On further investigation, it is clear that the information does not affect the conclusions of the report. The footnotes were, however, present in a prepublication copy that was sent for information to the International Agency for Research on Cancer, and I have thought it advisable to retain them and to explain the position in detail in an addendum to this preface, in the hope of avoiding further misunderstanding.

Two deficiencies, of which all members of the committee were aware, were the inability to differentiate more precisely between nickel species and the lack of information about the smoking habits of the employees. The former could be of particular importance if it proved that there was a specific hazard from nickel-copper oxide, while the latter complicates the interpretation of standardized mortality ratios for lung cancer that are above average when the lower confidence limits are less than about 150. This is a particular problem in Norway, where smoking habits used to vary so greatly from one part of the country to another and industrial workers may have had materially different habits from those of the neighboring fishermen and farmers. In this situation, the relationship of moderately raised modality ratios to the duration of employment and time from first exposure may carry much more weight than their numerical size.

It will be obvious from these prefatory remarks that our report does not provide a final answer to all the questions with which the committee was faced. It does nevertheless provide qualitatively new information, which should make it easier to control the carcinogenic hazards of nickel compounds in a rational way. It also demonstrates that much can be learned in a relatively short period when government, industry, and independent research workers are given the opportunity of working together to tackle a problem of international interest. The diverse character and extent of the collaboration achieved in the planning and conduct of the work is, I suspect, unique. That it was achieved so successfully is due principally to the personality of those who represented the sponsoring organizations, namely, Dr Hayes and (until October 1988) Ms Sivulka of the United States Environmental Protection Agency; Dr Warner of the Nickel Producers Environmental Research Association; Dr Robinson of the Ontario Ministry of Labour; Mr Telewiak of Energy, Mines, and Resources, Canada; Dr Toft of Health and Welfare, Canada; and Dr Berlin of the Commission of the European Communities. All who were involved in the study are greatly indebted to them.

Richard Doll

Addendum

A communication to the Committee on 15 December 1986 reported that water-soluble nickel was present in the environment of the roasting, smelting and calcining department in Kristiansand in concentrations of less than 1 % of the concentration of nickel oxide. This figure, which was derived from the existing statistical records of the refinery, was for all the sulfate formed in the roasting systems, including that recovered in the periodic removal of caked material from roaster heads and flues. Such removal was an occasional job that could fall to any member of an unspecified labor pool and the "average" worker's exposure to sulfate was thought to be too low to warrant classification in the "L" category. Smelter mechanics were, however, frequently called on to make repairs in an environment of flue dusts and group 3e workers in table 6 (mechanics) were classed as having category "L" exposure to soluble nickel. A new process started in 1978 resulted in the findings for Kristiansand reported in the preface. The process caused some highly sulfated products to be formed in a closed system, these products being eventually combined with the main roaster product and fed to a leaching tank in a mixture containing 0.5 % nickel sulfate and 18 % nickel oxide. The only men thought to come into contact with sulfate to a sufficient extent to justify describing them as having exposure to soluble nickel were (as before) the smelter mechanics required to make repairs to the dust collecting system.

CONTENTS

INTRODUCTION

Nickel (Ni) is used extensively in a variety of economically important industries, including stainless steel and nickel alloy production, electroplating, battery and coinage manufacturing, and catalyst use, production and reclamation. People engaged in manufacturing industries which use nickel, as well as those involved with the primary production of nickel, are exposed to a variety of nickel compounds in the air that they breathe. The general populace is also exposed to nickel compounds in the air primarily from the combustion of oil and coal and to a lesser extent from emissions from industries in which nickel is produced or used.

Clear evidence of increased risks from lung and nasal sinus cancer among some nickel refinery workers in the past has prompted governmental regulatory bodies to attempt to protect both nickel-exposed workers and the general populace through regulations which limit nickel exposure. Given the importance of nickel to industrialized societies, it would be difficult to eliminate it totally from our manufacturing processes and the environment. It is therefore important to understand the human health risks associated with exposure to different chemical forms of nickel (including metallic nickel). To date, the epidemiologic and animal data have not provided this understanding. The mechanisms of nickel carcinogenesis are not understood, good animal studies with relevant routes of exposure (inhalation) are scarce, and most of the epidemiologic studies have suffered from a lack of exposure data that could be used to provide an understanding of the forms and amounts of nickel that are related to increased cancer risks.

The purpose of this report is to summarize the results of a large-scale epidemiologic investigation designed to improve the understanding of human health risks associated with nickel exposure. The primary objective of the study was to determine the specific forms of nickel (ie, metallic nickel, oxidic nickel, soluble nickel salts, and sulfidic nickel) which are associated with an increased risk of cancers of the lung and nasal sinuses. A secondary objective was to ascertain whether exposure to nickel or nickel compounds gives rise to other forms of cancer. Implicit in both objectives was the desire to use the effects of occupational nickel exposure to provide useful dose-specific estimates of risk.

The investigation was a collaborative effort sponsored by both government and industry, and it involved epidemiologists, engineers, industrial hygienists, and other scientists. The main approach of the study was to collect, update, and jointly analyze data from 10 previously studied cohorts of men whose occupations were associated with the production and use of nickel. An essential part of the effort was the estimation of the types and levels of nickel exposure in individual workplaces. These estimates were made with the use of knowledge of chemical processes in the workplaces and historical records of plant operations and, where available, environmental measurements. Through linkage of these estimates to work history data in the epidemiologic data bases, cancer mortality was studied in relation to exposure to different forms of nickel.

REVIEW OF PAST EPIDEMIOLOGIC STUDIES OF NICKEL-EXPOSED POPULATIONS

The first indication that some form of nickel can give rise to lung and nasal sinus cancer was obtained from refinery workers at Clydach, Wales, over 50 years ago (1). Firm evidence that some hazard in the refinery caused these cancers was published 25 years later (2, 3). Cohorts of Clydach's nickel-exposed workers have continued to be studied in efforts to determine the parts of the refining process which produced these risks (4—8). Large excess risks of lung and nasal cancer have also been revealed for other refinery workers in Ontario, Canada, in unpublished ("Summary of Report on Respiratory Cancer Mortality 1930—1957" prepared by RB Sutherland for the International Nickel Company of Canada, Ltd, Port Colborne, Ontario, Canada, in 1959) and published (9, 10) reports, and at Kristiansand, Norway (11, 12). Increased respiratory tract cancer has also been reported for nickel workers in the German Democratic Republic, Japan, and the Soviet Union (13).

Cancers in sites other than the lung and nasal sinuses have also been found in excess of expected numbers in isolated groups of workers exposed to nickel. It is unclear whether these are chance findings or genuine indicators of increased risk caused by nickel exposure. An excess of laryngeal cancer was found both in refinery workers at the Kristiansand refinery in Norway (12) and in nickel miners in Canada (14). The excess among the miners was not associated with duration of exposure, and no excess was found at the Clydach (Wales) and the International Nickel Company (INCO) (Ontario) refineries. Increased stomach cancer risks reported for workers from four nickel refineries in the Soviet Union (15, 16) have not been replicated among other refinery workers. Other reports of isolated excess deaths from other types of cancer in nickel-exposed populations include excess kidney cancer in workers outside of the high-risk groups identified in the Ontario refinery (10), prostate cancer in smelter workers (14), and cancer of the buccal cavity and pharynx in the barrier plant workers at the Oak Ridge Gaseous Diffusion Plant (17).

The epidemiologic data indicated that, to a large extent, lung and nasal cancer risks among refinery workers were associated with exposure to roasting, sintering, and calcining processes which converted impure nickel-copper matte to an oxide. In particular, men involved in these dusty operations in Clydach, Kristiansand, and Ontario had large (three- to tenfold) increased risks of lung cancer and large numbers of nasal cancers. Because of the mixture of oxidic and sulfidic nickel forms in these processes, it has been unclear which of the compounds was responsible for the risks. Animal studies have provided little insight into the question since there has been little experimentation in which inhalation has been used as the route of exposure. (A review is under preparation by the International Agency for Research on Cancer.) There is some evidence that nickel subsulfide is a respiratory carcinogen (18), but the testing of oxidic nickel compounds by inhalation has been very limited. The situation has been far from clear since all calcining operations did not seem to produce similar risks. For instance, men exposed to a calcining operation in the state of West Virginia in the United States (19) gave little if any evidence of excess lung cancer risk, although there was an excess of nasal cancer.

There has been evidence to implicate soluble forms of nickel, inferred primarily from the excess lung and nasal cancer risks reported among electrolysis workers at the Kristiansand refinery (11, 12). In these studies, however, men were classified by the department in which they had worked the longest. This categorization has cast doubt on the role of soluble nickel in inducing these cancers since workers associated with the electrolysis process could have also worked in the roasting, smelting, and calcining areas of the refinery, where they would have been exposed to oxidic and sulfidic forms of nickel. In addition, the evidence concerning soluble nickel seemed to be contradictory since electrolysis workers at the INCO refinery in Ontario showed no evidence of increased lung cancer risk (10).

Workers involved in nickel mining and smelting have not exhibited the same levels of lung and nasal cancer risk as men in refineries. For example, men working in the Falconbridge smelting operations in Ontario (14), had a twofold lung cancer risk, but no nasal cancers. Among Falconbridge miners, lung cancer risks were increased by approximately 50 %, but again with no nasal cancers. Other studies of mining and smelting workers have given little if any evidence of increased respiratory cancer risk. A study of workers in the Hanna mining and smelting operation in the state of Oregon in the United States (unpublished paper, "A Study of Mortality in a Population of Nickel Miners and Smelter Workers" prepared for the Hanna Nickel Smelting Company, Riddle, Oregon, by Cooper & Wong in 1982), for example, showed no pattern of association between exposure to nickel and lung cancer, and these workers had no nasal cancers. In a case-referent study of workers in the nickel mining, smelting, and refining industry in New Caledonia (20, 21) there was also no evidence of an association between level of nickel exposure and respiratory cancer incidence.

Other studies of people whose occupations required the use of nickel in metallic or oxidic forms to manufacture other products have also given no indication of excess risk of lung or nasal cancer. For example, the lung cancer mortality rate of workers exposed to metallic nickel powder in the production of "barrier" material at the Oak Ridge Gaseous Diffusion Plant in the state of Tennessee in the United States was similar to those with no exposure to nickel (17, 22). Neither was there an excess of lung cancer nor any nasal cancers among men producing nickel alloys in England (23). In a study of 28 000 workers in high nickel alloy production in the United States (24), there was also no evidence of increased risk of either lung or nasal cancer.