South Pacific Commission Special Study:

The Epidemiology of Lung Cancer in New Caledonia

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South Pacific Commission

Noumea, New Caledonia

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I. Abstract

New Caledonia, a French territory in the South Pacific, has been mining and refining nickel, a known carcinogen, for more than a century. This report is a study of the epidemiology of lung cancer in N.C. and includes 1) the incidence rates for the 1970-74 period, 2) a case comparison study of the relation between nickel occupational exposures and lung cancer, and 3) a study of the distribution of the cases on the Island and in the city of Noumea where the smelter is.

The results show a moderately high incidence rate for the European male population and a high rate for the Melanesian female population. An association between nickel occupational exposure and lung cancer is found to be significant, as is the ordering in the distribution of the proportions of cases of lung cancer relative to the distance of their residence from the nickel smelter in Noumea.

II. Context of the problem

A. Statement of the problem and background

A review of cancer incidence and mortality data for eleven countries and territories of the South Pacific indicated that New Caledonia had lung cancer rates which were strikingly higher than all other areas except Guam (1). This finding stimulated an epidemiologic study of lung cancer in New Caledonia and its possible association with the refining of nickel which has been conducted there for more than a century.

New Caledonia is a French territory in the South Pacific located halfway between Fiji and Australia. The island is approximately 250 miles long and 30 miles wide and contains some 120,200 inhabitants as of July 1972. Of this number, 51,000 (42%) are native Melanesians, 48,000 (40%) are Europeans and 21,200 (18%) of other origins including Indonesian, Vietnamese and Polynesian.

Noumea, the largest city of the island had 52,000 inhabitants of which 58% were Europeans, 17% Melanesians and 25% other groups.

Nickel has been mined on New Caledonia since 1866 and smelted since 1885. Essentially all phases of mining, transporting, drying, leaching and smelting of serpentine ores are done there. Ore is transported from 4 open pit mines scattered around the island to Noumea for smelting. The final product, ferro nickel matte is exported. Approximately 4,000 to 5,000

persons are employed at any one time in the nickel industry whose product constitutes between 97 - 99% of the exports of the island.

B. Literature review

Experimental studies of the biological effects of nickel compounds have been carried out for many years. Some established their carcinogenic effects after intravenous, intramuscular, intrapleural or subcutaneous injections (2). Others like Sunderman (3 & 4) observed epidermoid, anaplastic and adeno-carcinomas of the lungs of rats after inhalation of gas carbonyl and Heuper (5) noticed the appearance of anaplastic and adeno-carcinomas of the lungs of guinea pigs and mice after inhalation of nickel dust. *

Nickel compounds were suspected of causing occupational diseases around 1932, in England where high prevalence of lung and nasal cancer among the workers at the Mond Nickel Works in Clydach, Wales first raised questions. Since then, there have been many other cases of lung and nasal cancer observed among nickel workers throughout the world. Studies by Doll (7,8) and Morgan (9) in England and Sutherland (10) and Mastromatteo (11) in Canada have demonstrated an enhanced prevalence of cancer of the

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* A complete review of the works on the biological effect of nickel compounds is presented by Sunderman (6).

respiratory tract relative to the prevalence in the general population among these workers. Furthermore, certain groups of nickel workers were identified as being still at higher risk by Doll among the Welsh workers employed directly on the nickel carbonyl process, by Mastromatteo among the Cuppola furnace workers and by Pedersen (12) among workers engaged in the roasting-smelting operation in electrolytic refining.

In all these epidemiologic studies of lung cancer among nickel workers, it has always been impossible to collect data on cigarette smoking and therefore there has been no study of a possible interaction between cigarette smoking and nickel. So when the prevalence rates and ratios were computed, because there were no data on the cigarette smoking habits of the nickel workers, one had to assume first that these workers' smoking habits were the same as those of the general population and secondly, that there was no interaction between nickel exposure and smoking.

C. Objectives of the study

New Caledonia offers a chance to look at these problems. There has never been any study of the effects of nickel exposure on the population of the island where, as cited above, nickel has been mined and refined for more than a century.

This study has three objectives. The first one is the determination of the incidence rate of lung cancer in New Caledonia

in order to evaluate the magnitude of the problem. The second one is to determine if nickel exposure is associated with lung cancer and the third one is to study the effects of the nickel smelter fumes on the population of the city of Noumea.

III. Methodology

A. Incidence of lung cancer in New Caledonia (1970-74)

1. The numerator

In order to ascertain the cases of lung cancer many sources had to be used since no single one contained the information. The most important one was the medical charts of the Pneumology Department of the Noumea Hospital where the charts were available only from 1970 and on even though the hospital is much older than that. The second most important source was an administrative form necessary for the transfer of cancer patients and others to Australia for diagnosis and treatment. Then the Hospital Death Registry and the Civil Death Registries of the native Melanesians and of the Europeans and others were consulted even though the medical diagnosis appeared only in the hospital one and only for the patients who died there. Finally the cancer registry of the Pathology laboratory was reviewed in order to find some cases or to confirm others. Other sources mostly administrative like the Social Services of N.C. and two Worker Compensation Organizations were consulted to find complementary demographic information like age, address, race, etc. (See annex I)

The cases of lung cancers found were divided into four (4) categories according to the following definitions. A Confirmed case is one for which a pathologic diagnosis of lung cancer had been established. A Strongly Suspected case is one for which

there was no pathological diagnosis but for which a bronchoscopy had been performed and a tumour seen and reported in the medical chart. A Possible case is a patient clinically and radiologically (chest x-ray and/or tomography) suspected of lung cancer. And finally, a Clinically Certain case is a possible case for which the final diagnosis was the one of lung cancer on the medical chart. The total number of cases in these four diagnostic categories constitute the numerator of the incidence rate.

2. The denominator

The denominators of the rates were computed by the "Service de la Statistique de la N.C." They are estimates of the population as of July 1, 1972, the mid-period of the study. These estimates are based on the 1969 and 1974 general census.

In order to have an idea of the magnitude of the problem of lung cancer in N.C., crude as well as specific and standardized rates were computed. In this latter case, the standard populations used are the ones of the International Union Against Cancer (13). The rates observed were then compared to the ones observed in other countries.

B. Case comparison study

1. Operationalization

Since it was not possible to obtain a list of all nickel workers during any past periods in order to form a cohort and since anyway it was impossible to ascertain the health outcome of the workers because the medical charts of the Hospital were not available before 1970, a prospective study could not be undertaken. The design is then the one of a case comparison study whose objective is to determine if nickel occupational exposure is associated with lung cancer in New Caledonia. The cases and the controls are then compared for their age, sex, smoking habits (i.e., cigarette smoker or not), and nickel occupational exposure (i.e., ever worked for the nickel company or not).

The case group: The cases are the ones who constitute the numerator in the incidence rate. The ascertainment method as well as the sources of information are also the same. In some cases however only partial information was available.

The comparison group is constituted by all patients 35 years old and over who attended the Hospital laboratory (Institut - Pasteur) or the Blood Bank on an ambulatory basis during the months of July and August, 1975. This group was interviewed by two technicians, one from each organization who had experience in the past with research and interviews. The purpose of these interviews was to gather information on the patient's

age, sex, race, address, smoking habits, and nickel occupational exposure. (See annexed questionnaire)

Ascertainment of exposures: The information on the smoking habits and nickel exposure was ascertained differently for the cases and for the comparison group. For this latter group, the information was gathered by interview as stated above. However for the cases, since they were almost all dead at the time of the study, the problem is more complex and needs to be looked at closely.

First, the smoking information comes from the medical charts of the Noumea Hospital and of the Royal Prince Alfred Hospital in Sydney, Australia where may cancer patients had been sent. Secondly, the nickel occupational exposure information was ascertained from many different sources. They are: either or both medical charts, the death certificates, the files of the agencies providing funds for travel and medical expenses and the Worker Compensation Organization where the work history of many cases were available. Finally a list of the cases of lung cancer was presented to the medical representatives of the nickel company who were asked to check if any of the patients on the list ever worked for them, and if yes, in which department and for how long. After this process, the cases of lung cancer for whom no information on their occupation had been found and had not been reported by the Company as one of their workers were classified as "not exposed to nickel."

2. Statistical problem

The objective of this case comparison study is to determine if nickel occupational exposure is associated with lung cancer in New Caledonia. For this purpose, males who suffered from lung cancer diagnosed in the 1970-74 period are compared with another male group without the disease on the basis of their age, smoking habits and nickel occupational exposure.

The statistical analysis of the data makes use of the "Log-linear model approach" as defined by Bishop, Fienberg and Holland (15) and of the "Stepwise procedure" based on a mixing of backward and forward steps as defined by L.A. Goodman (16). This method consists of searching for the simplest model which can explain the data.

C. Geographical distribution of the cases of lung cancer in New Caledonia

The last question this study is attempting to look at is the one of the potential health effects of air pollution caused in Noumea by the fumes and dust coming out of the nickel smelter chimneys. Even though the wind in Noumea is predominantly from the southeast and blows the nickel dust and fumes toward the sea and also that the nickel company had made some effort to decrease the amount of dust released in the air, there are still a fair amount of red clouds travelling across the city when the wind

blows in the other directions. Furthermore, there is still a thin layer of red dust visible on the cars and roofs some mornings in some neighborhoods.

Since the only measures of health hazards available are the incidence rates of lung cancer per 100,000 per neighborhood in Noumea, the only questions that are looked at are: (1) Were there in Noumea, during the 1970-74 period, more cases of lung cancer than one could expect on the basis of its population? (2) Are the proportion of cases of lung cancer diagnosed in Noumea distributed at random across the city?

Age standardized incidence rates in Noumea and outside Noumea are computed and compared to answer the first question using the modified X^2 for standardized incidence rates (17, 18) to determine the statistical significance of the difference, if any.

In order to answer the second question, the cases whose addresses are known were classified in one of the 23 neighborhoods of Noumea, which were then grouped to form three new zones.

A first one is far from the smelter and includes seven neighborhoods which are: Val Plaisance, Anse-Vata, Baie des Pecheurs, Vallon du Gaz, Magenta, Ouemo, Pointe aux Longs Cous, Riviere Salee (first and second sector), and Ducos. A second zone is near the smelter. Its seven neighborhoods are: Quartier Latin, Vallee du Genie, Centre Ville, Vallee des Colons, Vallee du Tir, Montravel, Montagne Coupee, and Nouville. Finally there

is a zone between the two first located at middle distance from the smelter and includes the following: Trianon, Mont Venus, Orphelinat, Mont Coffyn, Artillerie, Sainte Marie, Taragnat, Faubourg Blanchot, Port Despointes, Vallee Aubertin, Verteuil Musiciens, Haut Magenta, Porte de Fer, fifth KM (Lotissements), and seventh KM, Cite de Saint Quentin, Cite Yahoue, Normandie. (See annexed map of Noumea.)

The statistical analysis is done by the Bartholomew's test which permits to verify if there is any significant ordering in the distribution of the proportion of cases. The level of significance is also set here at 5%.

IV. Results

A. Incidence of lung cancer in New Caledonia

During the 1970-74 five year period, 92 cases of lung cancer were diagnosed in New Caledonia. This number includes 53 confirmed cases, 9 strongly suspected, 24 possible and 6 clinically certain cases. TABLE I shows the distribution of cases per year.

Table I Distribution of the number of new cases of lung cancer over the 1970-74 period in New Caledonia

Year	Male	Female	Total
1970	6	1	7
1971	10	2	12
1972	20	1	21
1973	21	5	26
1974	24	2	26
Total	81	11	92

This gives an annual average incidence rate of lung cancer of 15.31 per 100,000 population during this period and the sex-specific rates are 25.9 and 3.8 for males and females per

100,000 population per year. Table II shows the sex and race specific average annual rates.

Table II Sex and race specific average annual rates of lung cancer per 100,000 population (1970-74)

	Total No. Cases Over 5-year Period		Average Annual Incidence Rate per 100,000	
Race	Male	Female	Male	Female
European	44	3	34.8	2.6
Melanesian	24	8	17.9	6.3
Others	14	-	24.3	-

These rates show that the New Caledonian males of European origin have the highest rates followed by those of Other origin (i.e. Indonesian, Vietnamese, Polynesian, etc.) and by those of Melanesian origin. However when the rates are computed for the city of Noumea and compared with the ones outside Noumea (Table III) a different pattern appears. In Noumea the rates of the Melanesian males are now the highest followed by the European and the Others while in the rest of the island, the Europeans showing a consistently high rate are first. Throughout the two tables

however, the Melanesian females have the same higher rates than their European counterpart in the city as well as outside. However, this study did not provide any clue which could explain these findings.

Table III Age adjusted * average annual incidence rates of lung cancer per 100,000 population (1970-74)

	Noumea		Outside Noumea	
Ethnic group	Male	Female	Male	Female
Melanesian	64.2	5.5	23.5	10.3
	(42.1)	(4.1)	(15.3)	(6.8)
European	58.9	3.7	47.5	2.9
	(34.5)	(2.5)	(32.2)	(1.7)
Other	22.6	-	42.2	-
	(18.2)	-	(28.4)	-

* The standard population used here is the "world" one of the I.U.A.C. (The number in parenthesis are the age adjusted rates on the overall New Caledonian population.)

In order to have an idea of the importance of the problem of lung cancer in New Caledonia, incidence rates observed in the

Territory are compared with rates observed in other areas of the world. Of course, one has to be very careful when comparison of incidence rates are made between different parts of the world and even more when conclusions are drawn.

The problems encountered in making such comparison are numerous. It can be sufficient to mention the problems of comparability of the population themselves with their different biological backgrounds, their different attitudes and behavior toward disease, the problems of comparability of the different medical care systems and their accessibility and the problems of ascertainment of disease as well as the systems used to do so.

However, one problem: the distribution of the population per age group can somehow be handled by the techniques of age standardization. This method permits the comparison of rates in population with different age distribution by comparing all the different populations with standard ones with some arbitrary proportions of people in each age group (13). In Table IV the standard populations used are the World, European and African types as defined by the International Union Against Cancer. They serve to show how the incidence rates observed in New Caledonia after adjustment for age, do compare with the ones observed in specific areas throughout the world.

The objective of Table IV is not to give a specific rank to New Caledonia among the areas it is compared with but rather to present one way to evaluate the importance of the problem.

Table IV A

Bronchus and lung cancer (I.C. 162-3): Age standardized incidence rates per 100,000, annual average. (New Caledonia 1970-74, all others, 1960-64) Males *

Site of the Registry	Standard Population World	European	African
U.K., England and Wales, Liverpool	86.6	123.7	45.3
U.S.A., Hawaii, Hawaiians	70.3	99.6	38.1
New Zealand, Maori	70.1	103.0	34.6
Finland	70.0	99.7	36.0
U.K., Scotland	67.0	93.2	35.5
German Federal Republic	66.0	94.7	32.3
German Democratic Republic	48.8	68.6	24.9
New Caledonia, European	48.1	66.4	25.6
U.S.A., California, Alameda, White	47.8	68.2	24.3
Rhodesia, Bulawayo, African	47.1	67.0	25.1
New Zealand, European	45.1	64.6	23.3
U.S.A., Connecticut	44.0	62.9	23.0
U.S.A., California, Alameda, Black	43.8	61.1	25.3
New Caledonia, Others	35.1	50.9	22.5
Israel, Jews born in European America	29.6	43.3	15.3
New Caledonia, Melanesian	29.01	39.8	17.2
Canada, Quebec	28.7	40.3	15.1
Poland, Craiow City and District	27.9	38.9	15.0
Hungary, County Vas	22.8	32.6	11.4
Sweden	19.2	27.5	9.7
Colombia, Cali	17.5	25.7	9.0
Norway	16.5	23.1	8.6
Japan, Miyagi Prefecture	15.6	22.5	7.8

* Source: International Union Against Cancer

Table IV B

Bronchus and lung cancer (I.C. 162-3): Age standardized incidence rates: annual average per 100,000. (New Caledonia 1970-74, all others, 1960-64) Females *

Site of the Registry	Standard Population World	European	African
New Zealand, Maori	37.7	52.7	19.7
U.S.A., Hawaii, Hawaiians	22.3	31.6	12.7
U.K., England and Wales, Liverpool	11.8	16.7	6.9
New Caledonia, Melanesian	10.2	14.2	5.9
U.S.A., Hawaii, Caucasian	10.2	13.8	6.4
Germany Federal Republic	10.2	14.4	5.8
U.K., Scotland	9.9	13.5	6.0
Israel, Jews born in Europe or America	9.8	14.7	5.2
U.S.A., California, Alameda, Black	9.0	13.1	6.3
U.S.A., Connecticut	7.8	11.0	4.7
U.S.A., California, Alameda, White	7.4	10.5	4.4
New Zealand, European	6.1	8.5	3.4
Japan, Miyagi Prefecture	6.0	8.7	3.4
Hungary, County Vas	5.4	7.8	3.3
Rhodesia, Bulawayo, African	4.7	6.9	2.5
Finland	4.4	6.5	2.5
Sweden	4.4	6.5	2.4
German Democratic Republic	4.3	6.1	2.4
Canada, Quebec	4.3	5.9	2.7
Poland, Craiow City and District	3.9	5.5	2.2
Colombia, Cali	3.8	5.2	2.1
New Caledonia, European	3.6	4.8	1.7
Norway	3.1	4.5	1.7

* Source: International Union Against Cancer

The problem of lung cancer in New Caledonia is not as serious as it is in certain areas of the world. However, New Caledonia experiences an incidence rate for males which can be considered slightly above the median for the European and slightly under the median for the Melanesian and Others. As for the females, however, it is highly surprising once more to see the Europeans and Melanesians in two different directions.

IV. Results

B. Case comparison study

Of the 92 cases of lung cancer diagnosed during the period under study, complete information was available for only 68 or 74%. Their distribution per characteristic (i.e., smoking habit, nickel occupational exposure and age) as well as the ones of the 109 "controls" are presented in Tables V and VI.

Table V Distribution of the cases and the controls for age group, smoking habits and nickel occupational exposures.

Age Group	Smokers				Non Smokers				
	Ni Worker		Not Ni Workers		Ni Worker		Not Ni Worker		
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	
35-45	2	12	2	23	0	1	0	20	
46-55	13	7	14	14	0	1	1	12	
56 +	13	1	22	12	1	0	1	6	
Total	28	20	38	49	1	2	2	38	177

Table VI Proportions of cases and controls for characteristics

		Cases	Controls
Age Group	35-45	6%	51%
	46-55	41%	31%
	56 +	53%	17%
		Cases	Controls
Ni Worker	Yes	43%	20%
	No	57%	80%
		Cases	Controls
Smoker	Yes	97%	63%
	No	3%	37%

The purpose of this study is to look at the characteristics or factors involved: age, smoking, working for a nickel company and see if any of them alone or in interaction are associated with lung cancer.

Following the statistical methods cited above, the simplest model which fits the data is one in which:

1. Age is significantly associated with lung cancer *
   (likelihood ratio = G^2 = 45.45 with 2 d f).

See Annex 4.

* The α level of significance for all tests is 5%.

2. Cigarette smoking is significantly associated with lung cancer (G^2 = 25.26 with 1 d f).
3. Working at the nickel smelter is significantly associated with lung cancer (G^2 = 4.76 with 1 d f).
4. Finally, there is no significant interaction between cigarette smoking and nickel occupational exposure on lung cancer in this model. These findings are discussed in a further section.

C. Geographical distribution of lung cancer in New Caledonia

The age standardized incidence rates of lung cancer are 28.5 in Noumea and 20.2 on the rest of the Territory per 100,000 per year. A "Z" statistic (17, 18) used to test if these differences are statistically significant reveals a value (Z = .73) which clearly indicates that these differences in the rates are not significant and that there are not more cases in the city than on the rest of the Territory.

In order to test the second hypothesis, 42 cases out of the 46, known to have lived in Noumea, had an exact address. Table VII shows how the cases are distributed in Noumea relatively to the distance of their residence from the smelter as well as the proportion of cases per zones.

Table VII Distribution of the residences of the cases in Noumea per zone

Relative Distance from zone to smelter	Total Population per zone	Number of cases	5 year Proportion of cases in each zone
Far	20,993	7	.00033
Middle Distance	23,031	20	.00087
Near	13,071	15	.00115

Here the statistical analysis shows that there is an ordering in the proportion of cases per zone. The proportion of cases is significantly higher near the smelter than at middle distance and/or the proportion of cases who lived at middle distance is significantly greater than the proportion of cases who lived the farthest away from the smelter. These results are also discussed in the following section.

Discussion

Even though multiple sources were investigated for the ascertainment of the cases, the exact incidence rates of lung cancer in New Caledonia are not known as precisely as one would wish for any of the two major ethnic groups. Many Europeans are mostly transient in New Caledonia and the reasons for their departure, which can be, and are sometimes medical, as well as what happens to them once they are back in France in terms of diseases and causes of death, are not known.

The Melanesian population, though, is stable. However, its attitude toward disease and death which influences its utilization of the medical services, is not known, and therefore, the nature of their health problems is not completely known. Furthermore, Melanesians live mostly in the bush(es) where even though the medical services are available, the diagnostic means are less developed and accurate than in the city of Noumea.

For these reasons and because, as shown in Table I, few cases were found during 1970 and 1971 and also because there were already 11 new cases diagnosed during the first 6 months of 1975, the real incidence rates of lung cancer in New Caledonia are somewhat different and probably higher than those reported here.

The findings of the case comparison study are very much in accordance with what is already known or suspected on the subject.

Age and cigarette smoking have long been known to be associated with lung cancer. The association between nickel occupational exposure and lung cancer has also been demonstrated but no study had controlled for cigarette smoking, a major factor in the aetiology of lung cancer. However, even though the association of nickel occupational exposure and lung cancer looks strong in this study, extreme caution is advised in the interpretation of these results.

This word of caution comes about mostly because of the pitfalls of the study, many of which are explained by the extreme difficulties there were to obtain the necessary information and the time available to conduct the inquiry. These constraints forced dangerous trade-offs between the feasibility of the study and sound methodology. The choice of a comparison study instead of a cohort design is an example; the choice of the Hospital out-patient laboratory as the source of the control group is another one. Some consequences of this like a significant different mean age between the case group (58 years old) and the comparison group (46 years old) is of critical importance even though the statistical method employed permitted to control for age.

Caution is also advised because of the statistical method used to analyze the data. The model found is an empirical one developed after the fact. It is not a theoretical model undergoing testing. However, in this study where three factors were involved and also where interactions were possible between all of them, it is a more powerful test than the Mantel-Haenzel procedure (19).

Finally the findings of the last part of the study about the distribution of cases in the city of Noumea relative to the distance from the smelter are only interesting but not conclusive of anything. It is obvious here that many important factors like smoking, age and length of stay at current addresses were not controlled for and they may very well be and probably are confounding.

This study is by no means the final evidence that nickel dust is carcinogenic for human beings. It is only a step toward the understanding of the effect of nickel on man and his environment. And certainly that New Caledonia, because of its unique situation, will bring more light to the problem.

Conclusion

This report is an epidemiologic study of the problem of lung cancer in New Caledonia, a French Territory, in the South Pacific where nickel ore has been mined and smelted for more than a century.

This study had 3 objectives. It first determined the incidence of lung cancer in New Caledonia during the 1970-74 period. It observed a moderately high rate for New Caledonian males of European origin and a somewhat lower one for the New Caledonians of Melanesian origin. However, the Melanesian females experienced a surprisingly high incidence rate, finding not explained in this study.

Secondly, by fitting an empirical model to the data, it is demonstrated that age, smoking and being a nickel workers are significantly associated with lung cancer. However, no significant interaction between smoking and nickel exposure has been shown.

Finally, it is demonstrated that the age adjusted incidence rate observed in the city of Noumea where the smelter is located, is not significantly different from the rate observed outside the city. However, in the city itself, the proportion of cases of lung cancer follow a significant ordering pattern: these proportions being higher near the smelter than at middle distance and higher at middle distance than far from it.

However, because of the relatively small number of cases involved in the study and other methodologic problems, the authors

advise extreme caution in the interpretation of the results and present their findings as just one more step hopefully forward toward a more complete understanding of the biologic effect of nickel.

Acknowledgments

This study authorized by the Governor of the Territory of New Caledonia was partially supported by the South Pacific Commission, the Canadian High Commission in Canberra, Australia and by the authors themselves.

The authors wish to express their gratitude to all the people who in various ways assisted in this study. They are specially grateful to the late Dr. Guy Loison and Dr. Anne L. Bourre, respectively Director and Assistant Director of the Health Programme of the South Pacific Commission; to Mr. Jerry Michael, Dean, School of Public Health, University of Hawaii; to Dr. A. Chassary, Chief Physician at the Gaston Bourret Hospital in Noumea and to Dr. R. Baldenberger and J. Papillaud, heads of the Pneumology and Internal Medicine Departments; to Dr. G. Chanalet, Director of the Institut Pasteur in Noumea and his staff members, Mrs. F. Ferrer and C. Bourque; to the medical staff of the C.A.F.A.T. and Miss A. Fevre of the Social Service of New Caledonia; to the "Societe le Nickel" and Dr. R. Germain, Chief Physician of the Societe; to Miss Betty James and her staff at the Medical Record Department of the Royal Prince Alfred Hospital in Sydney, Australia, and Dr. Joyce Ford, of the Cancer Registry of the N.S.W. Australia; to Dr. Charles Metzner of the Medical Care Organization Department and Dr. G. Williams and Mr. Jean Lambert of the Biostatistics Department of the School of Public Health, University of Michigan.

Finally, the authors would like to thank very much Mrs. Therese Kikanoi, secretary of the Pneumology Department of the Gaston Bourret Hospital in Noumea for her investigative work and her tremendous patience and collaboration.

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414/75

Annex I

I.D. CARD

SOURCE

Chart Number _____ Service _____

Death Certificate from _____

Interview with _____

Other (specify) _____

TYPE OF CANCER

A) 1 = Lung 2 = Nasopharynx 3 = Oropharynx 4 = Other _____

5 = Control

B) 1 = confirmed 2 = strongly suspect 3 = possible .....

IDENTIFICATION

Surname _____ Name _____

Date of birth (write month and year) _____

Age (when diagnosis made) .....

Place of birth: 1 = Noumea 2 = Grande Terre 3 = Other islands of New Caledonia

4 = France 5 = Other _____

Sex: 1 = Male 2 = Female .....

Address: Street _____

City _____ Phone _____

1 = Noumea 2 = Other New Caledonia 3 = Other _____

Race: 1 = Melanesian 2 = European 3 = Other _____

Marital Status: 1 = Married 2 = Single 3 = Widowed 4 = Divorced/Seperated ...

Case referred by Dr. _____

ILLNESS (write month and code year)

Date of onset _____

Date of diagnosis _____

Date of death _____

Transferred to Australia, 1 = No 2 = Yes _____

DIAGNOSTIC PROCEDURES

1 = not done 2 = done/negative 3 = done/non-conclusive 4 = done/suggestive

5 = done/positive

X-Ray (specify) _____

Tomography (specify) _____

Broncoscopy .....

Histopathology .....

If done which specimen used: 1 = Biopsy _____

2 = Sputum 3 = Bronchial aspiration 4 = Autopsy 5 = Other _____

Specify diagnosis _____

THERAPEUTIC MEASURES: 1 = Radiotherapy 2 = Surgery 3 = Chemotherapy

4 = Other _____

COMMENTS: _____

EXPOSURES

1) Tobacco A) Ever smoked cigarettes 1 = No 2 = Yes.....

If Yes: Total number of years.....

Average number of cigarettes per day.....

Filtered cigarettes 1 = No 2 = Yes.....

B) Ever smoked pipe or cigars 1 = No 2 = Yes.....

If Yes: Total number of years.....

Smoking habit 1 = Heavy 2 = Moderate 3 = Occasional.....

2) Alcohol Ever drunk 1 = No 2 = Yes .....

If Yes: Beer 1 = No 2 = Yes .....

if yes, number of beers per week.....

Wine 1 = No 2 = Yes.....

if yes amount of consumption per week (litres) .....

Liqueurs & Spirits 1 = No 2 = Yes.....

if yes, average consumption per week (ounces).....

3) Occupational Exposures

Usual occupation _____

Ever worked in mines or smelters 1 = No 2 = Mines 3 = Smelters

4 = Mines & Smelters 5 = Other _____

If yes, total number of years in mines.....

in smelters.....

Date began _____ Date ended _____

Other exposures to chemical dust or fumes 1 = No 2 = Yes.....

If yes, specify _____ Date _____

4) Residence

Date of arrival in New Caledonia (year).....

Usual residence:

A) If Noumea, street _____

distance from smelter (km).....

direction from smelter _____

number of years in Noumea.....

B) If other New Caledonia

where _____

number of years.....

Annex 4

The simplest model which fits the data is the following one:

$$\ln p_{ijkl} = +\mu_{1(i)} +\mu_{2(j)} +\mu_{3(k)} +\mu_{4(l)} +\mu_{12(ij)} +\mu_{13(ik)} +\mu_{34(kl)} +\mu_{14(il)}$$

where 1 = cancer, 2 = age, 3 = smoking, 4 = nickel exposure and where $\ln p_{ijkl}$ is the natural logarithm of the probability that an observation will be in the cell defined by the i^{th} level of cancer (1 = cancer, 2 = no cancer), the j^{th} level of age (1 = 35-45 years old, 2 = 46-55, 3 = 56 + 1), the k^{th} level of smoking (1 = smoker, 2 = non-smoker) and the l^{th} level of nickel exposure (1 = nickel worker, 2 = not nickel worker).

The term μ represents the overall mean, the μ_t's (t = 1....4) represent the main effects and the μ_{pq}'s represent the interaction terms. The value of these terms are given in Table A.

Table A Estimated Factors for the Model $C_{12}C_{13}C_{34}C_{14}$

Effect	Factor	Std. Error	Stdzd. Factor
Grand Mean	1.32		
Cancer (1)	- 0.55	0.20	- 2.68
Age (1)	- 0.33	0.35	- 0.93
	0.24	0.25	0.95
	0.09	0.25	0.35
Smoking (1)	0.92	0.20	4.49
Nickel (1)	- 0.56	0.20	- 2.75
Cancer (1) X Age (1)	- 0.82	0.35	- 2.33
(2)	0.22	0.25	0.87
(3)	0.64	0.25	2.41
Cancer (1) X Smoking (1)	0.49	0.20	2.40
Smoking (1) X Nickel (1)	0.27	0.20	1.34
Cancer (1) X Nickel (1)	0.19	0.20	0.91

This model was obtained by the stepwise procedure based on a mixing of backward and forward steps as described by L.A. Goodman (16). Table B summarizes the main steps of that procedure.

Table B Analysis of association by forward selections and backward eliminations

Model	Sufficient Configurations	d.f.	Likelihood Ratio (G^2)	p.
1	$C_1C_2C_3C_4$	18	95.87	.000
2	$C_{12}C_{13}C_{14}C_{23}C_{24}C_{34}$	9	6.41	$>$.500
3	$C_{123}C_{124}C_{134}C_{234}$	2	0.40	$>$.500
4	$C_{12}C_3C_4$	16	50.42	.000
5	$C_{12}C_{13}C_4$	15	24.86	.052
6	$C_{12}C_{13}C_{34}$	14	14.15	.439
7	$C_{12}C_{13}C_{34}C_{14}$	13	9.39	$>$.500

In this table, model 1 which includes only the main effects and model 2 which includes the main effects plus the second order interaction leads to model 4 which gives the largest significant difference when compared with model 1 ($G^2_{(1)} - G^2_{(4)} = 95.87 - 50.42 = 45.45$ which is highly significant for 2 d.f.). So the first two factor interaction to be added is the cancer - age one: μ_{12}.

In a second step, the cancer - smoking interaction (μ_{13}) was added to model 4 in the same way to give model 5. Backward eliminations not yet necessary, knowing that the model $C_{13}C_2C_4$ which includes only the

main effects and the cancer - smoking interaction will not fit the data and knowing that model 4 does not fit either.

In a third forward selection, the smoking - nickel interaction (μ_{34}) is added: $G^2_{(5)} - G^2_{(6)} = 24.86 - 14.15 = 10.71$ with 1 d.f. At this point, deleting any of the previous two factor interaction (μ_{12}, μ_{13}) leads to models which do not fit the data. So μ_{12} and μ_{13} are kept in the model.

In a fourth step, we add the cancer - nickel interaction (μ_{14}): $G^2_{(6)} - G^2_{(7)} = 14.15 - 9.39 = 4.76$ which is significant ($p < 0.05$) with 1 d.f. Selecting any of the previous interaction leads to statistically different models and adding another two factor interaction in a fifth step does not bring any significant improvement.

So the procedure leads to model 7 as the simplest one to explain the data adequately and it is on this model that are based the results presented in this report.