Occupational lung cancer and smoking: a review in the light of current theories of carcinogenesis

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This paper considers modern theories of carcinogenesis as they apply to the induction of lung cancer by tobacco smoking and occupational exposure to carcinogens. Some of the known and postulated factors affecting carcinogenesis are discussed, with particular reference to syncarcinogenesis and thresholds. Factors affecting the intensity of smoking exposure are reviewed, and the generally accepted occupational lung carcinogens are listed. Relative risks for the various carcinogens according to smoking status (where known) are presented. The carcinogens are considered individually, and known or postulated interactions with smoking are discussed. It is concluded that the effects of lung carcinogens can be explained on the basis of current theories that support a rational definition of priorities for the prevention of occupational lung cancer.

Cette étude s'intéresse aux théories modernes de la carcinogénèse telles qu'elles s'appliquent à l'induction du cancer du poumon par le tabac et par les risques du métier relié aux carcinogènes. Quelques facteurs connus ou postulés relatifs à la carcinogénèse sont discutés, avec un intérêt particulier pour la syncarcinogénèse et les seuils de tolérance. Les facteurs qui influencent l'intensité de l'exposition au tabac sont revus et on fait l'inventaire des carcinogènes pulmonaires reliés au métier. On présente les risques relatifs (lorsqu'ils sont connus) des différents carcinogènes chez les fumeurs. Les carcinogènes sont considérés individuellement, et les interactions connues ou postulées avec l'usage du tabac sont discutées. On conclut que les effets des carcinogènes pulmonaires peuvent s'expliquer à partir des théories courantes qui soutiennent une définition rationnelle des priorités visant à prévenir le cancer professionnel du poumon.

Most people now accept that smoking plays a major part in the genesis of lung cancer[1] and that in the general population it is probably the most important factor. The evidence is largely epidemiologic and, while strong, is still questioned.[2] It is also generally accepted that several types of industrial exposure are capable of causing lung cancer.[3] The role that smoking plays in association with industrial hazards is less clear. There is a tendency for some of those associated with industry to play down the occupational risks and emphasize smoking.[4] The tobacco industry and cigarette addicts tend to do the opposite. This paper will briefly review the current theories of carcinogenesis and explore the possible mechanisms of interaction between smoking and occupational hazards.

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Factors in carcinogenesis

Genetic mutation

Research has failed to show an association of viruses with most cancers that occur in humans. Currently the favourite theory is that most cancers arise as a result of genetic mutations, which may be induced by chemicals, ultraviolet or ionizing radiation, or the interaction of viral deoxyribonucleic acid (DNA) and cellular DNA, or may be congenital.[5] Carcinogenic chemicals react with DNA because they are usually strongly electrophilic or alkylating. A number of known carcinogens require conversion to an active form in the organism. An example is benzo[*a*]pyrene, one of the earliest carcinogens to be isolated. This substance is converted by a complex enzyme, aryl hydrocarbon hydroxylase, which is present in various tissues.[6] The active carcinogen is one of a number of products of the normal metabolic degradation of this type of polycyclic compound. Hereditary variations in the inducibility of aryl hydrocarbon hydroxylase may play some part in the cancer susceptibility of individuals. Experiments have shown that lung cancers in animals may occur from the absorption and systemic spread of ingested carcinogens that may be activated in the lung or other tissues, such as liver, but in humans all the known causes of lung cancer are inhaled and appear to act locally.[7]

It is thought that several sequential mutations are required for malignant transformation. Some chemicals, while capable of inducing the complete process alone, have a massively enhanced effect in animals if a promoter chemical is administered subsequently.[8] The mechanisms of promotion are only partly understood, and the processes involved in the often prolonged latent period between exposure and tumour development remain obscure. Promotion may involve enzyme induction, derepression of suppressed genetic traits, or simple chemical or physical facilitation. Latency may be a function of host response, cumulated dose, age, carcinogenic potency or target tissue type.

Known and postulated variables

Some of the known and postulated variables are shown in simplistic form in Table I. There is some confusion in terminology between authors, but it seems best to limit the use of the term syncarcinogenesis to the additive effect of two or more carcinogens independently acting on the same target tissue.

Threshold concentrations

There has been a vigorous debate on whether there are threshold concentrations of carcinogens below

which there is no risk of cancer among exposed persons. Most authors seem to accept that there is no absolutely safe threshold concentration for a carcinogen and that, therefore, one must be concerned with establishing practical levels. Kotin[10] and Mantel and Schneiderman[16] favoured establishing "virtually safe levels", recognizing that at low exposures effects may be delayed beyond the normal life-span. Flowers[17] developed the concept of "radioequivalent level" — the dose of a carcinogen that results in a cancer risk equal to that produced by normal background radiation — and suggested this as a practical level. These authors ignored the problems of cocarcinogenesis and syncarcinogenesis.

Preussman,[18] Brown,[19] Bingham, Niemeier and Reid,[8] and Truhaut[20] seem to have concluded that neither "safe" nor "virtually safe" levels are practical because of syncarcinogenesis.

Nutrition

There is evidence that vitamin A deficiency renders some epithelial tissues more prone to carcinogenic effects.[14] There are suggestions that this may be reversible, and the use of vitamin A analogues in the prophylaxis of lung cancer in high-risk groups is currently under investigation.

Smoking

The prevalence of smoking in industrial situations is very poorly documented, as often are the data on exposure to other carcinogens, particularly if exposure occurred many years previously. Some employers permit smoking at any time, some at "breaks" only and some never. Cigarette smoking is a powerful addiction and there is likely a self-selection by addicts away from jobs where smoking is banned or restricted. This may partly account for the low incidence of lung cancer in coal miners.[21] Whether the reverse is true, with smokers tolerating fumes or smells better than non-smokers and possibly being subject to higher risks, is a matter of speculation. It certainly cannot be assumed that the prevalence of smoking in any occupational subgroup reflects that of the general working population.

Cigarette smoke contains a number of carcinogenic substances. The group of polycyclic aromatic hydrocarbons, including benzo[*a*]pyrene, is usually thought of as prominently involved.[22] Although their carcinogenic potency is low, the intensity and duration of exposure produced by the inhalation of cigarette smoke are thought to account for their strong effect in humans. Cigarette smoking may enhance the effect of other carcinogens in at least two ways. First, cigarette smoke is directly toxic to ciliated epithelium.[23] Smoking soon leads to a loss of ciliary function and resultant difficulty in clearing sputum, which may contain a variety of inhaled carcinogens. Later, smoking induces metaplasia of the bronchoepithelium to a squamous type. It is also postulated that the particles in cigarette smoke are of such a size that they can adsorb other carcinogens and carry them to the epithelium of the lower bronchial tree.[24]

Occupational carcinogens

Table II lists the industrial hazards for which there is substantial epidemiologic evidence of a causal relation to lung cancer. Only bronchogenic carcinoma will be considered, although several of the substances pose other risks to health. Tumour types vary considerably, and there may be some relation between the degree of differentiation of the cells in a tumour and the activity of the causal agent, but this is too indefinite to be of use in assigning responsibility to a given agent.[25,26]

The degree of occupational hazard depends partly on exposure and partly on the carcinogenic potency of the substance. A review of

Table I—Known and postulated variables in carcinogenesis

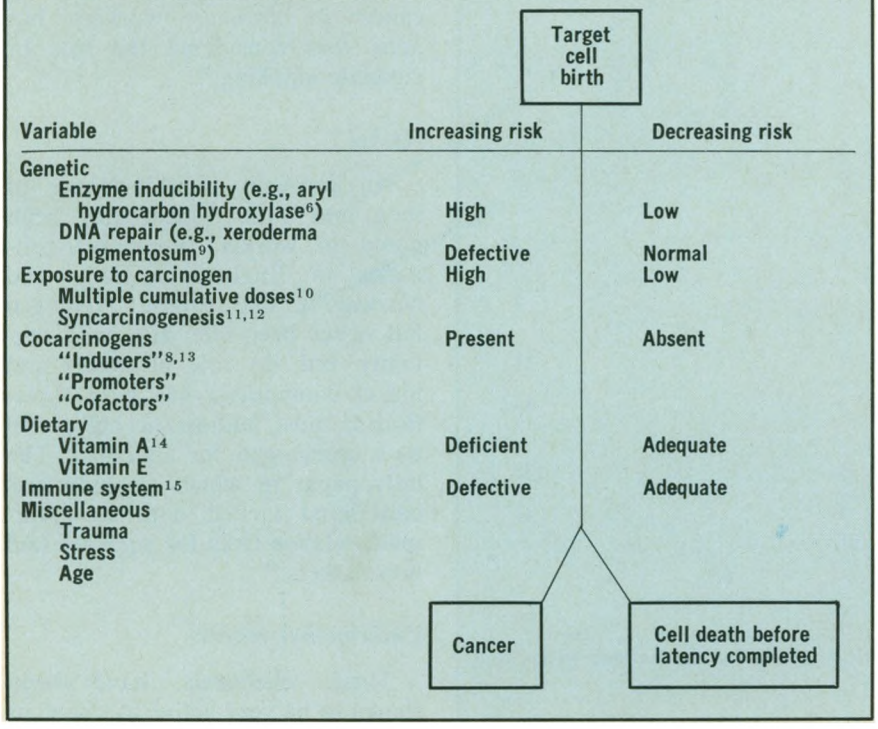

Table II—Occupational lung carcinogens

Carcinogen	Occupation
Asbestos	Mining, refining, insulation work, manufacturing and construction
Arsenic	Mining, metal refining, work involving agricultural chemicals
Chlormethyl ethers	Work involving these chemicals
Chromates	Refining and manufacturing
Coal tar distillates	Coke oven operation, work with coal gas and tar
Mustard gas	Manufacturing
Radiation	Uranium mining and processing, fluorspar and hematite mining
Nickel	Refining

the relative risks has been attempted in Table III within the very marked limitations imposed by difficulties in relating the statistical conclusions of various studies to each other when they are based on different designs, have used different population controls and have involved large variations in the degree of exposure. The conclusions of studies lacking smoking data in which the risk of cancer was low are particularly vulnerable to criticism. Unfortunately, fairly solid relative risks for smokers and nonsmokers have been established only for asbestos workers and uranium miners.

Not shown in Table III are the wide differences in latent periods and in the relative doses required to induce an effect. Mustard gas and the chlormethyl ethers are apparently intensively reactive, with lung cancer occurring after a relatively short latent period (8 to 16 years).[41] The latent period associated with radiation exposure in mines is similar.[42] Asbestos,[30] nickel,[34] coal tar distillates[36,37] and mustard gas[38] all seem to involve latent periods of at least 20 years, while the latent period for arsenic may be 35 to 40 years.[31]

Asbestos

The relative risks of bronchogenic carcinoma for smokers and nonsmokers exposed to asbestos are well documented from a variety of sources.[43] The evidence suggests that the risk for a nonsmoker is relatively low but that the risk for a smoker is high.[30] Asbestos is nonreactive in the Ames mutagenic testing system and therefore may not be a true carcinogen but instead may act as a foreign body implanted in the vulnerable tissues, where it can adsorb and then slowly release active carcinogens derived from the air, the diet or metabolic sources.[44] There is some evidence of covalent binding of benzo[*a*]pyrene by the trace metals associated with asbestos. As well, exposure to asbestos may interfere with the immune system and thereby increase the risk of cancer.[45]

Arsenic

There has been much debate on whether arsenic is a carcinogen. The authors of the National Academy of Science report "'Arsenic' 1977" reviewed published and unpublished data and concluded that there was strong evidence of pulmonary carcinogenesis with a dose–response relation, particularly when exposure was associated with sulfur dioxide, and an astonishingly long latent period — up to 40 years.[46] They noted the absence of an animal model for the carcinogenicity of arsenic. It is well known that orally administered arsenic produces skin changes that ultimately progress to cancer in humans, but it is possible that arsenic's role is that of an initiator only and that this substance may be inactive in the absence of some promoter (or vice versa). Most of the reported cases of lung cancer associated with exposure to arsenic have been in smelter workers, and the reports have lacked both smoking data and environmental analyses for polycyclic aromatic hydrocarbons, although one would expect significant levels of these compounds in the environment of such operations. There have been, however, a few cases of lung cancer reported in agricultural workers exposed to arsenical sprays or dusts.

Chromates

There have been several reports of an increased incidence of lung cancer in chromate workers, but none that considered the role of cigarette smoking.[33]

Nickel

An unusually high incidence of lung and sinus cancer has been noted in workers in nickel refineries in England, Canada and Norway.[33,34] The specific carcinogen has never been identified with certainty, but the role of nickel and nickel compounds has been questioned; most authors accept nickel as a carcinogen for animals.[47] The only paper in which smoking was considered lacked data to determine relative risks for smokers and nonsmokers.[48]

Chlormethyl ethers

These chemicals have been shown to be very active carcinogens

Table III—Relative risks of lung cancer due to smoking and occupational hazards

	Relative risk*					
	Occupationally unexposed			Occupationally exposed		
Hazard and study	Nonsmoker	Smoker	Unknown	Nonsmoker	Smoker	Unknown
Smoking						
Hammond[27]	1	14.7	–	–	–	–
Minerals						
Asbestos						
Meurman et al[28]	1	12	–	1.4	17	–
Berry et al[29]	1	–	–	4	32	–
Selikoff[30]	1	–	–	3	92	–
Arsenic						
Ott et al[31]	–	–	1	–	–	7
Lee et al[32]	–	–	1	–	–	8
Chromates						
International Agency for Research on Cancer[33]	–	–	1	–	–	15.6
Nickel						
Mastromatteo[34]	–	–	1	–	–	3
Chemicals						
Chlormethyl ethers						
Figueroa et al[35]	–	–	1	–	–	30
Coal tar distillates						
Redmond et al[36]	–	–	1	–	–	10.8
Environmental Protection Agency[37]	1	26	–	–	–	132
Mustard gas						
Wada et al[38]	–	–	1	–	–	33
Radiation						
Uranium mines						
Archer et al[39]	1	4	–	6.5	76	–
Fluorspar mines						
Wright et al[40]	–	–	1	–	–	29

*Estimated ratios of the incidence in those exposed to a hazard to the incidence in those not exposed.

for animals, and the observed exposure and latent period in humans with lung cancer induced by these substances have been relatively brief.[35] The numbers of cases were small and the distribution of smokers and nonsmokers was similar to that of the general work force. One paper, however, suggested that the irritant action of these substances was so great that it discouraged smoking, so that the greatest exposure to chlormethyl ethers was recorded in nonsmokers.[49]

Coal tar distillates

The active agents in coal tar distillates include polycyclic aromatic hydrocarbons. Industrial exposure is principally in coke oven and gas and coal tar workers.[36,37] Unfortunately, none of the published studies considered smoking histories. The authors of the US Environmental Protection Agency report used a formula to derive a relative risk for nonsmoking steelworkers to show that all the risk could not be attributed to smoking. It is probably reasonable to as-

Occupational exposure to carcinogens can occur anywhere, from greenhouses to nuclear power plants. Exposure is reduced by the appropriate clothing. (Photographs from the National Film Board–Photothèque).

sume that the carcinogens in tobacco tars and coal tars are similar and that there is a simple additive effect.

Polycyclic aromatic hydrocarbons are widespread, occurring with almost all forms of combustion.[50] They have been detected in kitchens, barbecued steaks and, at low levels, ambient air. Exposure is universal and not limited to smokers or certain occupations, although it is obviously greater in some occupations.

Mustard gas

Mustard gas is a highly reactive alkylating agent that is, one hopes, of historical interest only. Cases of lung cancer in humans resulted from its manufacture as "war gas" in Japan.[38] Derivatives of this agent are used in the treatment of cancer and are suspected of being capable of causing cancer.

Ionizing radiation

Lung disease was described in the Schneeberg miners in Europe long before cigarettes were invented, and was shown to be cancerous in 1879. As early as the 1920s this problem was attributed to radiation exposure in the mines. Uranium miners in Colorado and Ontario have been shown to have an excessive incidence of lung cancer.[39,49] It is theorized that radon daughters can adsorb onto aerosol particulates, so that damage from α-radiation is localized to the areas of the respiratory tract where such particles tend to deposit.[51] There is evidence from Colorado of only a slightly increased risk of lung cancer for miners who are nonsmokers. There smoking seems to have been permitted underground (it was banned in Ontario in 1973); hence, it is possible that the cigarette smoke aerosol was a factor and that α-emitters were deposited on already damaged bronchial epithelium with reduced natural defences.

A tragic epidemic of lung cancer in fluorspar miners in Newfoundland has also been attributed to radiation exposure from radon daughters.[40] The exposure was comparable to that in Colorado for which Archer and Lundin[52] showed a relative risk of 7.9. A report of the Newfoundland tragedy indicated that the prevalence and intensity of smoking in the fluorspar miners was unusually high.[40] The tumours were epidermoid rather than the oat-cell variety encountered with uranium exposure in Colorado. This epidemic occurred in a relatively isolated and possibly inbred community, so that one might suspect that genetic factors were involved. However, the exposure–response relation was strong,[53] and radiation exposure *per se* was probably the most important risk factor.

Conclusions

In cases in which smoking and occupational carcinogens interact, the combined effects may be accounted for by an additive mechanism of syncarcinogenesis that includes delayed clearance of carcinogens from mucosa already damaged by cigarette smoke. The result for smokers exposed to airborne asbestos or radiation is a greatly increased risk of lung cancer. Data are either absent or extremely scanty, however, for exposure to all occupational carcinogens except asbestos and radiation, and the mechanism of carcinogenesis by asbestos is still obscure. As most cases of lung cancer associated with exposure to arsenic, chromates and nickel have occurred in situations in which polycyclic aromatic hydrocarbons would have been present, one can speculate that the metals may have acted as promoters rather than initiators. Careful epidemiologic evaluation of smoking as a factor in these cases is desirable but may be impossible since conditions of poor industrial hygiene in these industries are now generally a thing of the past.

Considering the dual role of smoking in the induction of lung cancer, one would expect smokers to be the first to show an increased incidence of lung cancer when exposed to relatively weak additional lung carcinogens. As a corollary, while one must not ignore the known occupational carcinogens, the most effective immediate step to reduce the incidence of occupational lung cancer would be to concentrate on reducing smoking. It will probably be impossible to eliminate all respiratory carcinogens from the environment. Therefore, thought could be given to restricting employment in possibly hazardous jobs to nonsmokers, although this might be considered discrimination by some and could be difficult to implement. Ultimately, in view of the large number of mutagens and potential carcinogens, both natural and man-made,[54] techniques to improve host defences may prove to be the most practical way to reduce the risk of lung cancer to negligible levels, but this is still only a distant possibility.

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References

1. *Smoking and Health. Report to the Surgeon General,* US Dept of Health, Education, and Welfare, Public Health Service, Washington, 1964
2. STERLING TD: A critical reassessment of the evidence bearing on smoking as the cause of lung cancer. *Am J Public Health* 65: 939, 1975
3. KEY MM (ed): *Occupational Diseases: a Guide to Their Recognition,* DHEW (NIOSH) publ 77-181, US Dept of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, Washington, 1977, p 443
4. KOTIN P: quoted in *Occup Health Saf Lett* 7 (10): 7, 1977
5. GOLDSTEIN A, ARONOW L, KALMAN S: Mechanism of action of chemical carcinogens, in *Principles of Drug Action: The Basis of Pharmacology,* 2nd ed, Wiley, New York, 1974, p 673
6. KELLERMAN G: Hereditary factors in human cancer, in *Origins of Human Cancer. Book B,* HIATT HH, WATSON JD, WINSTEIN JA (eds), Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, 1977, p 837
7. CROSBY NT, SAWYOR R: N-nitrosamines: a review of chemical and biological properties and their estimation in foodstuffs. *Adv Food Res* 22: 1, 1976
8. BINGHAM E, NIEMEIER RW, REID JB: Multiple factors in carcinogenesis. *Ann NY Acad Sci* 271: 14, 1976
9. SETLOW RB, AHMED FE, GRIST E: Xeroderma pigmentosum: damage to DNA is involved, in *Origins of Human Cancer. Book B,* op cit, p 889
10. KOTIN P: Dose–response relationship and threshold concepts. *Ann NY Acad Sci* 271: 22, 1976
11. FALK HL: Possible mechanisms of combination effects in chemical carcinogenesis. *Oncology* 33: 77, 1976

12. SCHAMHL D: Combination effects in chemical carcinogenesis (experimental results). Ibid, p 73
13. SIVAK A: Mechanisms of tumor promotion. Cocarcinogenesis: a summary from one point of view, in *Carcinogenesis, a Comprehensive Survey*, vol 2: *Mechanisms of Tumor Promotion and Cocarcinogenesis*, SLAGA TJ, SIVAK A, BOUTWELL RK (eds), Raven, New York, 1978, p 553
14. SPORN MB: Prevention of epithelial cancer by vitamin A and its synthetic analogues (retinoids), in *Origins of Human Cancer, Book B*, op cit, p 801
15. KERSEY J, SPECTOR B: Immune deficiency diseases, in *Persons at High Risk of Cancer: an Approach to Cancer Etiology and Control: Proceedings of a Conference, Key Biscayne, Florida, Dec. 10–12, 1974*, FRAUMENI JF JR (ed), Acad Pr, New York, 1975, p 55
16. MANTEL N, SCHNEIDERMAN MA: Estimating "safe" levels: a hazardous undertaking. *Cancer Res* 35: 1379, 1975
17. FLOWERS ES: Proposal: a non-zero approach to environmental limits for carcinogens. *Occup Health Saf* 46: 35, 1977
18. PREUSSMAN R: Chemical carcinogens in the human environment — problems and quantitative aspects. *Oncology* 33: 51, 1976
19. BROWN CC: Mathematical aspects of dose–response studies in carcinogenesis — the concept of threshold. Ibid, p 62
20. TRUHAUT R: Can permissible levels of carcinogenic compounds in the environment be established? in *Proceedings, XI International Cancer Congress, Florence, 20–26 October 1974* (Excerpta Medica International Congress Series 351), BUCALOSSI P, VERONESI U, CASCINELLI N (eds), vol 3: *Cancer Epidemiology*, Excerpta Medica, New York, 1975, p 50
21. COSTELLO J, ORTMEYER CE, MORGAN WKC: Mortality from lung cancer in U.S. coal miners. *Am J Public Health* 64: 222, 1974
22. SEVERSON RF, SNOOK ME, HIGMAN HC, et al: Isolation, identification, quantitative analysis of the polynuclear aromatic hydrocarbons in tobacco smokers, in *Carcinogenesis, a Comprehensive Survey*, vol 1: *Polynuclear Aromatic Hydrocarbons: Chemistry, Metabolism and Carcinogenesis*, FREUDENTHAL R, JONES PW (eds), Raven, New York, 1976, p 253
23. IDE G, SUNTSEFF V, COWDRY EV: A comparison of the histopathology of tracheal and bronchial epithelium of smokers and nonsmokers. *Cancer* 12: 473, 1959
24. PALMER HE, PERKINS RW, STUART BO: The distribution and deposition of radon daughters attached to dust particles in the respiratory system of humans exposed to uranium mine atmospheres. *Health Phys* 10: 1129, 1964
25. HARRIS CC: The epidemiology of different histologic types of bronchogenic carcinoma. *Cancer Treat Rep* 4 (suppl): 59, 1973
26. ARCHER VE, SACCOMANNO G, JONES JH: Frequency of different histologic types of bronchogenic carcinoma as related to radiation exposure. *Cancer* 34: 2056, 1974
27. HAMMOND EC: Tobacco, in *Persons at High Risk of Cancer: an Approach to Cancer Etiology and Control: Proceedings of a Conference, Key Biscayne, Florida, Dec. 10–12, 1974*, op cit, p 131
28. MEURMAN LO, KIVILUOTO R, HAKAMA M: Mortality and morbidity among the working population of anthophyllite asbestos miners in Finland. *Br J Ind Med* 31: 105, 1974
29. BERRY G, NEWHOUSE ML, TUROK M: Combined effect of asbestos exposure and smoking on mortality from lung cancer in factory workers. *Lancet* 2: 476, 1972
30. SELIKOFF IJ: Cancer risk of asbestos exposure, in *Origins of Human Cancer, Book C*, HIATT HH, WATSON JD, WINSTEN JA (eds), Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, 1977, p 1765
31. OTT MG, HOLDER BB, GORDON HL: Respiratory cancer and occupational exposure to arsenicals. *Arch Environ Health* 29: 250, 1974
32. LEE AM, FRAUMENI JF JR: Arsenic and respiratory cancer in man: an occupational study. *J Natl Cancer Inst* 42: 1045, 1969
33. IARC Working Group on the Evaluation of the Carcinogenic Risk of Chemicals to Man: *Some Inorganic and Organometallic Compounds*, International Agency for Research on Cancer, Lyons, 1973, p 102
34. MASTROMATTEO E: Nickel: a review of its occupational health aspects. *J Occup Med* 9: 129, 1967
35. FIGUEROA WG, RASZKOWSKI R, WEISS W: Lung cancer in chloromethyl methyl ether workers. *N Engl J Med* 288: 1096, 1973
36. REDMOND CK, STROBINO BR, CYPESS RH: Cancer experience among coke by-product workers. *Ann NY Acad Sci* 271: 102, 1976
37. *An Assessment of the Health Effects of Coke Oven Emissions*, US Environmental Protection Agency, office of research and development, Washington, 1978
38. WADA S, MIYANISHI M, NISHIMOTO Y: Mustard gas as a cause of respiratory neoplasia in man. *Lancet* 1: 1161, 1968
39. ARCHER VEW, WAGONER JK, LUNDIN FE JR: Uranium mining and cigarette smoking effects on man. *J Occup Med* 15: 204, 1973
40. WRIGHT ES, COUVES CM: Radiation-induced carcinoma of the lung — the St. Lawrence tragedy. *J Thorac Cardiovasc Surg* 74: 495, 1977
41. IARC Working Group on the Evaluation of the Carcinogenic Risk of Chemicals to Man: *Some Aromatic Amines, Hydrazine and Related Substances, N-Nitroso Compounds and Miscellaneous Alkylating Agents*, International Agency for Research on Cancer, Lyons, 1974, p 237
42. HEWITT D: Radiographic lung cancer in Ontario uranium mines 1955–1974, in *Report of the Royal Commission on the Health and Safety of Workers in Mines*, Ontario Ministry of the Attorney General, Toronto, 1976, p 319
43. IARC Working Group on the Evaluation of the Carcinogenic Risk of Chemicals to Man: *Asbestos*, International Agency for Research on Cancer, Lyons, 1977, p 62
44. THOMSON R, KILROE-SMITH TA, WEBSTER I: The effect of asbestos-associated metal ions on the binding of benzo(*a*)pyrene to macromolecules *in vitro*. *Environ Res* 15: 309, 1978
45. KAJAN E, SOLOMON A, COCHRANE JC, et al: Immunologic studies of patients with asbestosis (two parts). *Clin Exp Immunol* 28: 261, 268; 1977
46. *"Arsenic" 1977*, committee on medical and biologic effects of environmental pollutants, National Research Council, National Academy of Sciences, Springfield, Va, 1977, p 222
47. FURST A: Inorganic agents as carcinogens, in *Environmental Cancer*, KRAYBILL HF, MEHLMAN MA (eds), Wiley, New York, 1977, p 209
48. KREYBERG L: Lung cancer in workers in a nickel refinery. *Br J Ind Med* 35: 109, 1978
49. WEISS W: Chlormethyl ethers, cigarettes, cough and cancer. *J Occup Med* 18: 194, 1976
50. BRIDBORD K, FINKLEA JF, WAGONER JK, et al: Human exposure to polynuclear aromatic hydrocarbons, in *Carcinogenesis, a Comprehensive Survey*, vol 1: *Polynuclear Aromatic Hydrocarbons: Chemistry, Metabolism and Carcinogenesis*, op cit, p 319
51. ARCHER VE, WAGONER JK: Lung cancer among uranium miners in the United States. *Health Physics* 25: 351, 1973
52. ARCHER VE, LUNDIN FE: Radiogenic lung cancer in man: exposure–effect relationships. *Environ Res* 1: 370, 1967
53. DE VILLIERS AJ, WINDISH JP, BRENT F DE N, et al: Mortality experience of the community and of the fluorspar mining employees at St. Lawrence, Newfoundland. *Occup Health Rev* 22: 1, 1971
54. AMES BN: Environmental chemicals causing cancer, birth defects: developing a strategy for minimizing human exposure. California Policy Seminars, Berkeley, Dec 1977