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Cancer and the environment: Ten topics in environmental cancer epidemiology in Canada

Shirley A. Huchcroft, Yang Mao and Robert Semenciw, Editors

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Executive Summary

This *Chronic Diseases in Canada* supplement is a compilation of literature reviews by scientific experts. It was initiated as follow-up to the Green Plan, the federal government's environmental agenda in the 1990s. In recognizing that Canadians are concerned about the environment and its relationship to their health, this document attempts to address some of these concerns in relation to cancer by reviewing and summarizing the epidemiological literature for ten environmental exposures, and highlighting future research needs. The topics include three types of radiation exposure (ultraviolet, radon and electromagnetic (powerfrequency electromagnetic fields)), three classes of chemical exposure (organochlorines, disinfection by-products, and pesticides), two types of air pollution (environmental tobacco smoke and outdoor air pollution), and two industrial sources (pulp and paper milling, and metal mining and processing).

This publication is intended to provide a base of information for researchers interested in environmental cancer epidemiology and to assist with the formulation of research priorities. The ten topics reviewed here were selected because concern about them has been expressed or because they involve known animal carcinogens. Complete elimination of exposures to carcinogens in the environment, synthetic or natural, is not technically feasible if cancer can potentially occur at any level of exposure (i.e., the linear non-threshold theory). Consequently, it is important to have an operational concept of safety which is more practical than that of zero risk. Such an approach uses the concept of acceptable or essentially negligible risk to determine the exposure

levels at which carcinogens are regulated.¹ Acceptable risk has been defined as one that is "so small, whose consequences are so slight, or whose associated benefits (perceived or real) are so great that persons or groups in society are willing to take or be subjected to that risk". The level of risk where remedial action is recommended will vary according to the "agent or process being regulated, the economic and social costs and benefits and technology factors".¹⁻³

In accordance with the system used by the International Agency for Research on Cancer (IARC) to assess the strength of the evidence for human carcinogenicity,⁴ the ten exposures reviewed here can be grouped into three broad categories, with some exposures occupying more than one and the first category—human carcinogens—should be subdivided. Tables 1-4 refer to these categories. For many of the exposures discussed here, ongoing etiological research awaits methods development, particularly in exposure assessment.

I Human carcinogens

a) Exposures for which estimated attributable numbers of cancers are cause for concern

The epidemiological evidence is adequate to conclude that ultraviolet radiation, environmental tobacco smoke and radon are human carcinogens, and to estimate the number of cancer cases and deaths attributable to them at typical exposure levels (Table 1).

Ultraviolet radiation

Approximately 69,000 Canadians are diagnosed with non-melanoma skin cancer each year, making it the most common form of cancer, and about 350 are diagnosed with lip cancer.⁵ Approximately 94% percent of all new cases of skin cancer are basal or squamous cell, with malignant melanoma accounting for the remaining 6 percent. Exposure to solar ultraviolet

radiation is likely responsible for over 90 percent of skin cancer in Canada and for more than half of lip cancer.^{6,7} Malignant melanoma is the most serious of the skin cancers and accounts for approximately 4,600 cases and 900 deaths in Canada each year.⁵ Death from non-melanoma skin cancer and lip cancer is rare. It is estimated that approximately 450 UVR-related cancer deaths yearly (one half the total UVR-related deaths) are preventable by reducing sun exposure.

Environmental tobacco smoke

Tobacco smoke is the major component of indoor air pollution. Recent research suggests that each year about 250 non-smoking Canadians die of lung cancer caused by prolonged exposure to other people's tobacco smoke.⁸ A recent meta-analysis (i.e., systematic summary of studies) estimated the risk of lung cancer among non-smoking women as 24 percent higher for those living with a smoker than for those not, and 39 percent higher for those exposed to ETS in the workplace. Because of the large number of Canadians who have never smoked but have been exposed to second-hand smoke regularly over a number of years as a child, as a spouse and/or in the workplace, the risk associated with exposure has significant public health implications.

Radon

Radiation from radon gas is carcinogenic to humans.⁹ Most of the evidence for carcinogenicity has been obtained from studies of miners exposed to high concentrations; however, radon exposure at levels to which many Canadians are routinely exposed have also been found to increase the risk of lung cancer. Radon has been estimated to be responsible for over fifteen hundred cases of lung cancer a year in Canada (about 8% of lung cancer cases).¹⁰ A number of techniques are available to homeowners to reduce radon concentrations in their homes.

b) Exposure levels that result in small increases in risk

For three exposures—selected organochlorine insecticides, outdoor air pollution and some nickel species—the accumulated evidence suggests that typical Canadian

exposure levels result in small increases in risk (Table 2). To estimate the number of cases of cancer that can be attributed to an exposure, it is necessary to know the prevalence of the exposure and the magnitude of the risk. There is only limited evidence regarding the prevalence of exposure to these agents in the Canadian population. As well, much evidence of their carcinogenicity comes from occupational studies, where exposures are much higher than those experienced by the general Canadian population. The nature of the exposure-response relationships at low exposure levels is unclear, making it inappropriate to attempt to quantify the cancer burden in the Canadian population which can be attributed to their exposures. In addition, it has been difficult to control for potential confounding factors.

Organochlorine insecticides

The limited epidemiological evidence regarding a number of organochlorine insecticides and several cancers generally supports the toxicological evidence of an association with cancer. Because of these concerns and others, and with the exception of lindane, which is permitted for the treatment of head lice as a pharmaceutical, organochlorine insecticides are no longer marketed in Canada.

Air pollution

The most commonly measured outdoor air pollutants in Canada include particulates, ground-level ozone, carbon monoxide, sulphur dioxide and oxides of nitrogen. These substances are the principal ingredients of precursors of smog and acid rain.² Some particulates are small enough to be inhaled and deposited in the lungs. Some studies suggest that long-term, regular exposure to particulate matter is associated with increased risk of lung cancer.¹¹ In Western industrialized countries that have pollution regulations, air pollution poses only a small risk for developing cancer. Further research is a priority to better control residual confounding from cigarette smoking (active and passive), and more accurately assign air pollution exposures.

Nickel mining and processing

IARC has concluded that there is sufficient evidence in humans for the carcinogenicity

of nickel sulphate and the combinations of nickel sulphides and oxides encountered in the nickel refining industry. Furthermore, there is sufficient evidence in experimental animals to conclude that metallic nickel is possibly carcinogenic to humans.¹² Some early studies of nickel workers in the early half of the 20th century revealed higher-than-expected rates of various cancers of the respiratory tract. Since then, exposure levels to workers have been reduced to the point where there is little or no detectable risk in most sectors of the nickel industry. The general population risk from the extremely small concentrations of nickel compounds detectable in ambient air is negligible.

II Exposures for which the epidemiological evidence of carcinogenesis in humans is limited

According to the IARC classification, limited evidence of carcinogenicity in humans means that a positive association has been observed between exposure and cancer for which a causal interpretation is credible, but chance, bias or confounding cannot be ruled out with reasonable confidence.⁴ Limited evidence exists for three of the ten exposures reviewed here (Table 3).

Dioxins

Polychlorinated dibenzo-*para*-dioxins (PCDDs)—a class of organochlorines—are formed as inadvertent by-products during the production of chlorophenols and chlorophenoxy herbicides and have been detected as contaminants of these products. Dioxins may also be produced in thermal processes such as incineration and metal-processing, and the bleaching of paper pulp with free chlorine. Dioxins have been related sufficiently to specific cancers such as soft-tissue sarcoma, non-Hodgkin's lymphoma and Hodgkin's disease, to warrant further research. This judgement is based on consistency of findings across studies, the magnitude of the risk estimates and absence of major sources of bias. Toxicological studies have demonstrated the carcinogenicity of 2,3,7,8-tetrachlorodibenzo-*para*-dioxin, but other dioxins are not classifiable as to their carcinogenicity.¹³

Phenoxy herbicides

Pesticides encompass many classes of chemicals that share the ability to kill or otherwise control pests. Many are rated as possible or probable human carcinogens. Epidemiological studies suggest that phenoxy herbicides may be associated with non-Hodgkin's lymphoma and soft-tissue sarcomas; however, this finding is not supported by the toxicological evidence. IARC has concluded that there is limited evidence that phenoxy acid herbicides as a group are carcinogenic in humans, with inadequate evidence of carcinogenicity in animals.¹⁴

This position was based on the class of chemicals which included the more highly contaminated 2,4,5-T and "may not apply to individual chemicals within the group". The United States Environmental Protection Agency (US EPA) considers 2,4-D is not classifiable as to human carcinogenicity.¹⁵ However, both the US EPA and the Canadian Pest Management Regulatory Agency have recently concluded that the domestic use of one of the most commonly used phenoxy herbicides, 2,4-D, does not entail an unacceptable risk of harm to human health.

Electromagnetic fields

Electric and magnetic fields, both of which are forms of non-ionizing radiation, are ubiquitous in Canada. Sources include electrical equipment, power lines and household appliances. IARC rates extremely low-frequency magnetic fields as possibly carcinogenic to humans and extremely low-frequency electric fields as not classifiable as to their carcinogenicity to humans. There is limited evidence in humans for the carcinogenicity of extremely low-frequency magnetic fields in relation to childhood leukemia.¹⁶

TABLE 1
Estimated numbers of cancer cases and deaths annually attributable to environmental carcinogens to which Canadians are commonly exposed

Exposure	Most likely cancer sites	Estimated attributable annually ^a		Comment
		Cases	Deaths	
Ultraviolet radiation	Skin and lip	70,000 ^b	450	Solar UVR is the major environmental risk factor for skin and lip cancers. Phenotype and exposure factors, such as age, intensity and duration, affect risk.
Environmental tobacco smoke	Lung	280 ^c	252	Environmental tobacco smoke is considered a causal agent in lung cancer. The estimated numbers are for non-smoking Canadians exposed to environmental tobacco smoke.
Radon	Lung	1,589	1,430 ^c	Radon is a cause of lung cancer.

^a Except where indicated, estimates are taken from the individual topic chapters.

^b Estimated at approximately 90% of estimated skin and lip cancers.⁵

^c Estimated on the basis of 90% case fatality rate.⁵

TABLE 2
Exposure levels that result in very small increases in cancer risk in the Canadian population

Exposure	Most likely cancer sites	Comment
Organochlorine insecticides	Sarcoma, lymphoma, leukemia	Many of the organochlorine insecticides used in Canada in the past are now considered to be known or suspected animal carcinogens. The limited epidemiological evidence regarding a number of organochlorine insecticides generally supports the toxicological evidence of an association with cancer.
Air pollution	Lung	Slightly increased risks of lung cancer are associated with exposure to highly polluted air. In general, air pollution in Canada is not severe enough to pose a significant cancer threat.
Nickel mining and processing	Respiratory	Risks are related primarily to high levels of exposure to certain nickel compounds encountered in the work environment in the past. The general population risk from the extremely small concentrations detectable in ambient air is negligible.

III Exposures for which the epidemiological evidence is inadequate for assessing carcinogenicity in humans

In IARC's classification, inadequate epidemiological evidence means that the available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of a causal association between exposure and cancer, or no data on cancer in humans are available (Table 4).⁴

Disinfection by-products

To prevent water-borne diseases, most municipal Canadian water supplies are disinfected with chlorine. During water disinfection, chlorine reacts with organic material in the water, producing a number of by-products, including trihalomethanes (THMs). Several studies of cancer incidence in human populations have reported associations between long-term exposure to high levels of disinfection by-products and increased risk of bladder and possibly colon cancer. However, toxicological studies do not support the magnitude of risk observed in the epidemiological studies. A recent summation of the toxicological and epidemiological evidence can be accessed via the Web site of the WHO International Programme on Chemical Safety (IPCS).¹⁷ IARC rates chlorinated drinking water as not classifiable as to its carcinogenicity to humans because the evidence for carcinogenicity in both humans and experimental animals is considered inadequate.¹⁸

TABLE 3
Exposures for which the epidemiological evidence of human carcinogenicity is limited

Exposure	Most likely cancer sites	Comment
Dioxins	Soft-tissue sarcoma, non-Hodgkin's lymphoma, Hodgkin's disease	For specific groups of organochlorines, the epidemiological evidence of an association with specific cancers is sufficient to warrant concern, such as dioxins and soft-tissue sarcoma, non-Hodgkin's lymphoma and Hodgkin's disease. Toxicological studies have demonstrated that 2,3,7,8-Tetrachlorodibenzo- <i>para</i> -dioxin (TCDD) is carcinogenic.
Electromagnetic fields	Leukemia	Some studies of high exposures suggest an association with leukemia; however, others show no such association. There is inadequate evidence that residential exposures to electric or magnetic fields are associated with increased cancer risks for adults. In particular, evidence is inconclusive as to whether living close to a source of EMF (e.g., power lines) increases one's risk of developing cancer.
Phenoxy herbicides	Non-Hodgkin's lymphoma and soft-tissue sarcoma	Epidemiological studies suggest associations with phenoxy herbicides; however, this finding is not supported by the toxicological evidence obtained using animal studies.

TABLE 4
Exposures for which the epidemiological evidence is inadequate for assessing human carcinogenicity

Exposure	Most likely cancer sites	Comment
Disinfection by-products	Bladder	The sum of evidence, especially from studies with the most detailed exposure assessments, supports a modest increase in risk of bladder cancer after many years of exposure. However, toxicological data do not support the magnitude of risk observed in epidemiological studies.
Pulp and paper milling	Various	Several compounds found in bleached pulp mill effluent are mutagenic and have been identified as mammalian carcinogens in laboratory studies. Studies of both workers and communities nearby pulp and paper mills have failed to produce conclusive results.
Gold and copper mining and processing	Lung and stomach	Some associations between lung and stomach cancer and gold and copper mining were found primarily in early studies of workers before the introduction of methods to reduce dust exposure. Conclusions linking cancer to exposures in gold and copper mining and processing are not possible.

The pulp and paper industry

Although several chlorinated organic compounds found in bleached pulp mill effluent are mutagenic and proven carcinogens in mammals, epidemiological studies of pulp and paper mill workers and nearby communities have failed to produce conclusive results. IARC rates exposures from pulp and paper manufacture as not classifiable as to their carcinogenicity to humans.¹⁹

Gold and copper mining

Conclusions linking cancer to exposures generated by gold and copper mining and processing are not yet possible.

General considerations

No single epidemiological study should be expected to provide the definitive answer regarding the carcinogenic potential of an environmental exposure. Thus, despite the often large number of studies reviewed, the need for further research is a recurring theme for most of the topics examined here. However, the types of research required differ across exposures. For ultraviolet radiation and environmental tobacco smoke, risk-reduction research as well as etiological research into other cancer sites is called for. For the three exposures that result in small increases in risk at typical exposure levels for Canadians (organochlorine insecticides, air pollution and nickel mining and processing), ongoing monitoring of exposure levels is important. For those exposures where the potential to cause cancer in humans is still in question, etiological research is a priority. For many of these exposures, further etiological research awaits methods-development research, particularly in relation to exposure assessment.

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- compile and disseminate results of cancer-related work funded under the Government of Canada Green Plan program. Initiated in December 1991, the Green Plan program was the federal government's environmental agenda in the 1990s. In addition, the Federal-Provincial-Territorial Advisory Committee on Environmental and Occupational Health recommended improving the identification and assessment of factors in the environment that influence health.
- Researchers with expertise in specific subject areas were asked to provide material for a supplement that would review the epidemiological literature on the risk of cancer, if any, associated with some Canadian exposures. The text was received, reviewed for scientific accuracy and edited over the next few years. Each section retained its own style and can stand alone as an essay on its topic. Introductory and summary sections were written to present important concepts and to tie the document together, and a glossary was added. However, the views expressed remain those of the authors rather than the Public Health Agency of Canada. This supplement to *Chronic Diseases in Canada* is the result of the process.
- This is a technical document most suited to the information needs of the many parties interested in environmental health and members of the cancer control community, especially health professionals, policy makers and researchers. In particular, students and teachers in the health sciences may find this a useful introduction to the area of environmental cancer epidemiology.
- Finally, a work of this magnitude and complexity takes a long time to produce.

Preface

The Public Health Agency of Canada's Canada's Centre for Chronic Disease Prevention and Control produces and communicates cancer surveillance findings and their implications for cancer control policies and programs. In 1998, a review committee recommended that the Centre (then housed within Health Canada)

Introduction

This supplement assesses the epidemiological evidence relating ten environmental exposures to cancer causation. Environmental exposures are defined broadly as those that are not a lifestyle choice (such as diet and smoking), are ubiquitous (e.g., ultraviolet radiation and air pollution) and/or involve involuntary

exposure (e.g., occupational exposures, industrial pollution and environmental tobacco smoke). Although biological agents (e.g., bacteria, protozoa, viruses, fungi, algae, dust mites, and allergens, such as pollen) are a class of environmental exposures/hazards, they are not dealt with here.

The material in this supplement is organized into four main sections: radiation, chemicals, air pollution and industry. The radiation section includes chapters on radon, ultraviolet radiation and electromagnetic fields. The chemicals section includes organochlorines, disinfection by-products and pesticides. The air section includes environmental tobacco smoke and air pollution. The industry section includes chapters on pulp and paper mills and gold, nickel and copper mining and processing. Occupational exposures are included for three reasons: First, the pulp and paper and metal mining industries are prominent in Canada. Second, occupational epidemiology is closely related to environmental epidemiology in that the exposure and disease experiences of workers can be extrapolated to give an estimate of the degree of risk associated with non-occupational exposures to the same substances. Third, occupational studies are particularly valuable in instances where too few community studies are available to provide an estimate of the degree of risk to the general population. For example, most of the information on the hazards of radiation from exposure to radon gas derives from occupational studies.

The exposures discussed arise from both the “natural” and “built” (i.e., constructed or human-made) environments.³ Ultraviolet radiation and radon are examples of the former, whereas by-products of the disinfection of water, electromagnetic fields, pesticides, air pollution and environmental tobacco smoke arise primarily from the built environment. However, it is acknowledged that exposures are often the interaction of factors in both environments.

Also, several of the topics are not mutually exclusive. For example, the disinfection of water as well as the pulp and paper industry both produce organochlorines, and several pesticides are organochlorines. As well, workers in metal mining are not infrequently

exposed to radiation from radon decay products and environmental tobacco smoke is a component of air pollution.

Estimating cancer risk from the environment in Canada

Incidence, contaminant sources and exposure variation

Excluding non-melanoma skin cancer, approximately 160,000 Canadians are diagnosed with cancer each year and half that many die from it.¹ Cancers of the lung, breast, prostate, colon and rectum account for over half of all cancers diagnosed in Canada. Lung cancer is the most common cancer cause of death in either sex, accounting for over a quarter of cancer deaths. The most common cancer among women is breast cancer, accounting for 30 percent of new cases, while the most common cancer among men is prostate cancer, accounting for one quarter of new cases. Although cancer is primarily a disease of older Canadians (with 69 percent of new cancer cases and 82 percent of deaths occurring among those who are at least 60 years old), it attacks all ages, including infants.²

Public opinion polling conducted at the outset of this publication showed that a major concern of Canadians in relation to their health in general—and to cancer in particular—is environmental pollution. Although most Canadians believe that air is the primary route by which environmental contaminants reach us, Canadians are exposed to environmental contaminants primarily through food. Food accounts for 80 to 95 percent of our total daily intake of persistent organic pollutants, air for between 10 and 15 percent and, for most persistent substances, soil and drinking water contribute less than five percent.³

The nature and degree of exposures to environmental hazards vary significantly from region to region across Canada and by many factors such as age, sex, occupation and eating habits. Also, the potential of a specific exposure to cause harm depends on a variety of factors, including exposure levels (duration and concentration), inherent toxicity, the route by which individuals take in the contaminant (e.g.,

ingestion versus inhalation) and the susceptibility of different groups. The very young, the elderly, people with weakened immune systems and native populations are particularly susceptible.³ Children can be more vulnerable to environmental contaminants because of their rapid growth and metabolic immaturity, as well as their greater food, air and fluid intake relative to body weight.⁴ Native populations are particularly susceptible because of the tendency of many organic pollutants to concentrate in colder northern climates and contaminate fish and other wildlife on which these populations depend for sustenance.

Risk investigations

Estimates of the degree of risk associated with exposure to environmental contaminants depend upon various types of investigation. Since environmental exposures are low for both radiological and chemical hazards, risk levels are rarely detectable from direct observational studies of human populations.⁵ For effects such as cancer, it is often difficult to estimate exposure or demonstrate cause and effect in the general population because cancer takes a long time to develop and multiple factors may be involved in its onset. Sources of variability in epidemiological studies include physiological parameters (such as body weight, respiratory rate and cardiac output, which can vary among individuals), routes of exposure, uncertainties in exposure estimates, errors in disease diagnosis and the effects of confounding factors.

Toxicology experiments, typically performed in laboratories on non-human models, are used widely to identify possible human health hazards (especially for chemicals) and to determine, for specific substances, the levels of exposure that present little or no risk to humans. Highly sensitive tests are available to examine a variety of deleterious effects, including tests of acute and chronic toxicity in animals, metabolism of chemicals, reproductive and developmental effects, and long-term carcinogenic effects.⁵

Biological markers are useful in the study of chemical hazards. These are biochemical changes that indicate that an exposure has occurred, but that are not necessarily linked

to a clinically harmful effect. These markers may be studied to evaluate exposure, health effects or susceptibility, to assess intra- and inter-subject variability, to clarify mechanisms, or to identify dose-response relationships. Their ultimate usefulness is the extent to which they can predict disease occurrence.⁵

Structure/activity relationship studies use the chemical structure of a compound to predict toxic or carcinogenic effects. Predictions are often based on the known behaviour of similar compounds, considering specific properties and attributes. However, while such classification rules are useful, they are not perfect predictors of health effects.⁵

Extrapolations are used to relate the results of tests involving high doses of substances in different species to relatively low doses of substances in humans. Similar models for quantitative risk assessment are used for both radiation and chemicals.⁵ For genotoxic carcinogens, such as ionizing radiation and certain types of chemicals that cause cancer by damaging DNA, it is assumed that there is a probability of harm at any level of exposure (in other words, it is assumed that there is no threshold for effects). Although dose-response curves may be non-linear at high doses, it is generally assumed that the dose-response curve for ionizing radiation and genotoxic chemicals is linear at low doses. Risks at low doses are therefore predicted from effects observed at high doses using what is known as the linear, non-threshold hypothesis (LNTH). This assumption has been widely used in cancer risk assessment in the absence of convincing evidence to the contrary. For other substances, including chemicals that cause cancer but do not damage DNA (non-genotoxic carcinogens), it is assumed that there is a threshold dose below which adverse effects are unlikely to occur.

Although epidemiology and toxicology are useful for estimating risk, both have limitations that can result in considerable uncertainty. For example, when human risks are estimated using animal toxicology, some uncertainty is introduced from the

extrapolation of effects seen at the high doses used in laboratory studies to potential effects at the lower exposure levels experienced by humans in everyday life.³ Results from studies of people exposed to particular contaminants in the workplace may not apply to people exposed in other settings because the health effects observed at high levels of exposure may not occur at lower levels. Thus, when performing risk assessments, a range of possible risks is considered, as indicated by a careful analysis of all sources of uncertainty in the data, and conclusions are generally based on appropriately conservative interpretations. Such uncertainties are believed to be smaller for ionizing radiation than for genotoxic chemical hazards.

Information sources

It should be noted that the data cited in this supplement, including the toxicology data, were obtained from the published literature only. It is acknowledged that extensive additional databases for the chemicals cited exist within regulatory agencies, including Health Canada, and that their data may not support the conclusions in this supplement. However, current legislation restricts access to these databases as they contain proprietary data supplied by manufacturers.

Three sources that were relied upon heavily as background material for this introduction are recommended for further reading. The first is *Health and Environment: Partners for Life*,³ a Health Canada publication that describes our current understanding of the relationship between human health and the Canadian environment. It focuses on contaminants that are of particular concern to the health of Canadians, notes the progress made in reducing levels of environmental contamination and describes the impact that either the human-made or built environments can have on our health. The report also provides practical suggestions for things that individuals can do to protect and enhance their own health, and notes some emerging issues and future challenges related to health and the environment.

A second major resource is *Assessment and Management of Cancer Risks from*

Radiological and Chemical Hazards,⁵ produced jointly by Health Canada and the Atomic Energy Control Board of Canada (now the Canadian Nuclear Safety Commission). This publication describes the risk assessment and management processes used to protect the public from radiation, chemicals and microbiological hazards.

Thirdly, *It's Your Health*,⁶ a component of Health Canada's Web site, provides periodic updates on topics relating to the health of Canadians, including the relationship between some environmental exposures and cancer. Readers interested in the topics discussed here may wish to look at the sections for dioxins and furans, electric and magnetic fields, occupational exposure to radiation and PCBs.

The following chapter discusses general principles and some of the methodological challenges in environmental cancer epidemiology.

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Basic Concepts in Epidemiology

Several of the exposure-specific chapters that follow deal with methodological issues unique to the exposure being examined. This chapter briefly sets out general principles and strategies in environmental cancer epidemiology and uses specific exposures to illustrate concepts. These concepts provide context for the critiques of the evidence that are contained in the exposure reviews and may be helpful for readers not familiar with epidemiological methods. Detail on methods can be found in publications devoted to environmental epidemiology, medicine and statistics.¹⁻⁹

Types of evidence from epidemiological studies

For both ethical and practical reasons, studies to investigate the effects of environmental exposures on human populations must be observational rather than experimental. Unlike the experiment, where only the agent of interest is manipulated and all other extraneous factors are held constant, the observational study must contend with the difficulty of identifying, measuring and controlling (either by design or analysis) the many factors, other than the one of interest, that could influence outcome. In addition, measuring both the exposure and the disease outcome can be problematic. The ability of an epidemiological study to provide accurate risk estimates depends heavily on the strength of its design and the types of information it uses.

A strong study design uses accurate measurements that result in little misclassification, controls extraneous factors that could confound the results and permits causal inference. General criteria for concluding that a relationship is causal rather than only an association include a strong association, consistency, specificity, a relationship in time, a biological gradient (dose-

response effect), biological plausibility and coherence of the evidence.⁹ Generally speaking, the stronger the association, the less likely it is to have occurred as a result of chance or to be the result of confounding by another factor. An association that has been repeatedly observed by different persons in different places, under different circumstances and over time is considered to be consistent and unlikely the result of some constant error or fallacy that permeates every enquiry. Specificity is a more difficult concept. Suffice it to say that an association that is limited to specific individuals and to particular sites and types of diseases is a strong argument in favour of causation. Demonstration that the suspected causal factor preceded the effect (and is consistent with the known latency of the disease) is further evidence for a causal association, as is a biological gradient or dose-response effect (i.e., the greater the exposure, the higher the risk of disease). Biological plausibility lends further strength to the argument for causation, but often cannot be demonstrated; what is biologically plausible depends upon the biological knowledge of the day. And finally, coherence means that the cause-and-effect interpretation of an association should not seriously conflict with the generally known facts of the natural history and biology of the disease. In his discussion of this criterion, Hill gives the example that the association of lung cancer with cigarette smoking is coherent with the temporal rise in the two variables and with the sex difference in both smoking rates and mortality from lung cancer.⁹

In terms of the strength of a design, a continuum extends from descriptive analyses (useful for formulating hypotheses) to the “natural experiment” (in which an exposure has occurred to a defined group of people who can be compared to a similar group of individuals not exposed). In between, lie study designs that yield evidence of varying degrees of strength. These approaches are described below.

Ecological (or cross-sectional) studies relate cancer mortality or incidence rates (usually age- and sex-adjusted) with characteristics of regions. The units of analysis in these studies are populations or groups,

rather than individuals. Thus, the ecological design provides no information on the relationship between exposure and disease at the individual level. The measure of association is the *correlation coefficient*. Values for the correlation coefficient range from -1 through 0 to $+1$, representing, respectively, a perfect negative correlation, no relationship and a perfect positive relationship. Example of ecological studies could be the rates of bladder cancer of various communities by water supply (chlorinated municipal water as opposed to well water), or skin cancer rates of communities with different average numbers of hours of sunlight per day.

Although this study design can be a useful preliminary step in investigating an association between disease and a suspected causal factor, the evidence it provides for a cause-effect relationship is relatively weak for at least three reasons. First, a relationship that applies with respect to groups of people does not necessarily apply at the individual level. This is referred to as the *ecological fallacy*. For example, it is conceivable that people who developed bladder cancer used well water rather than chlorinated municipal water even though they lived in communities with a chlorinated water supply. Second, to impute a cause-and-effect relationship, the suspected “cause” must precede the effect. If both “cause” and “effect” are measured at the same time, there is no assurance that the cause has preceded the effect. This is a particular problem in cancer epidemiology where a long latency between exposure and the development of cancer is the norm. Third, there is little opportunity in this type of study design to control for other factors, besides the study factor, that could affect outcome. For example, if the population of the sunnier communities tended to be more prone to skin cancer (e.g., have fair skin), than those of the less sunny communities, an apparent relationship between average daily sunshine exposure and skin cancer could be overestimated.

In *case-control studies*, individuals with the disease of interest are compared with individuals without the disease on factors being investigated as potential causes. The measure of association in this context is

the *odds ratio* (OR). When the control group is representative of the general population with respect to the suspected causal factor, the odds ratio provides a good estimate of the degree of risk of the disease for persons with the attribute relative to those without it. For example, an odds ratio of two means that the risk of disease for persons with the attribute is approximately twice the risk for those without it. The case-control design is stronger than the ecological design for the three reasons mentioned above: the unit of analysis is the individual, a time interval between exposure and disease onset can be approximated, and information on a variety of other factors can be collected. It may be weaker than other designs discussed below in that measurement of the potential exposure factors can be limited. The case-control study is of particular value for diseases, such as cancer, that are relatively rare.

A *cohort* is a group of persons who share a common experience within a defined time period. In *cohort studies*, the disease status of individuals known to be exposed to a particular factor is determined at a later date and compared to the disease status of individuals known not to have been exposed. The measure of association in the cohort study is the *relative risk* (RR). This is the risk of disease in the exposed group, expressed as a rate, divided by the risk in the unexposed group. The cohort study is often much more costly than the case-control study when the disease is rare because a very large number of people must be included in order to accumulate a sufficiently large number of participants with the outcome of interest. Also, depending upon the time between the exposure and the disease, selective losses to follow-up can be a major weakness.

A *nested case-control study* is a case-control study conducted within a cohort. For example, workers in a factory (the cohort) who have developed cancer can be compared with those who have not, in terms of their specific jobs and/or exposure to the agent of interest. This study design can benefit from the advantages of both the case-control and cohort approaches in that similar information is collected for both the case and control groups. The nested case-control study is especially useful where

biological specimens have been procured in a cohort study, particularly if they can provide data on biological markers of exposure, susceptibility or disease natural history.

The *natural experiment* is one that arises from the activities of humanity. It is a variant of the cohort design, and one in which a group of individuals exposed to an event that would not normally occur without the actions of humankind—a nuclear accident, for example—are then followed for disease occurrence relative to individuals not exposed. For example, much of the information we know about the effects of radiation exposure has been derived from follow-up studies of individuals exposed to radiation fallout from the atomic bombings of Hiroshima and Nagasaki.

It is not uncommon for the different types of studies of an exposure-disease relationship to yield different results. A cause-effect relationship is increasingly likely if various study designs, executed in different populations, suggest the same relationship (even though the strength of the relationship may differ) and if the association increases with the magnitude of the exposure (i.e., a dose-response relationship is observed).

The results of multiple epidemiological studies are often aggregated using two techniques: a *meta-analysis* and a *pooled analysis*. A meta-analysis produces a weighted average of risk estimates from previously published studies. Studies are often weighted on the basis of the variability of the risk estimates or to reflect in some other fashion the quality of the studies. A pooled analysis combines the original data on individual exposures and outcomes from multiple studies. It is methodologically generally preferred to a meta-analysis.

Measuring outcome

Cancer epidemiology studies can use either incidence or mortality as a measure of outcome. Mortality information is often more readily available because mortality data are part of the vital statistics that most countries collect. Cancer mortality data approximate incidence data for cancers that are highly fatal. Mortality data are less use-

ful in epidemiological studies for cancers where mortality is low since factors, other than those that cause cancer may contribute to death from cancer and, thus, obscure the etiology. Also, use of cancer mortality information usually limits the amount of other information that can be collected, such as occupational and residential histories, and behaviours such as smoking.

One way of obtaining more comprehensive exposure information is through studies using incident cancer cases and personal interviews. This greater detail and precision renders incidence studies better able to detect relationships than mortality studies. Canada is fortunate to have the Canadian Cancer Registry as part of a national cancer registration system to which all provinces and territories contribute information.¹⁰

Measuring exposure

In order to estimate risk, it is important to assess the amount of exposure to the person, group or area being monitored. Exposure assessment can be either direct or indirect. An example of direct exposure measurement is the use of radiation monitors worn by workers. Indirect exposure assessment includes predicting exposure from levels monitored in various media (air, water, food, soil) and reconstructing historical exposure patterns (e.g., by using job classifications and exposures known to be associated with specific jobs).

Examples of exposure indices in order of increasing accuracy are as follows: 1) a binary categorical assessment (when, in fact, there are a range of individual exposures); 2) a matrix of categories associated with a person's exposure, along with a length of exposure; 3) subject-specific exposure measurements; 4) the effective biological dose received by an individual; and 5) extending the previous index to incorporate information on the genetic susceptibility of the individual to the dose received. Cumulative exposure is a commonly used index, calculated by multiplying exposure intensity by duration of exposure.

Assessment of exposure to any environmental contaminant is difficult because the general population is often not aware of

specific exposures and may have difficulty remembering proxy indicators of exposure, such as residential history, drinking water sources and dietary intakes from 10 to 40 or more years ago. Environmental measurements may not be available for the earlier periods. Thus for many studies there has been an element of misclassification. To the extent that this misclassification is non-differential (e.g., random error), elevated risks probably represent an underestimation of the true risk. Where misclassification is systematic (e.g., the tendency of persons with the disease to report exposures of concern more often than those without the disease), overestimation of risk is likely to occur. This is referred to as *exposure bias*.

Controlling extraneous factors

Controlling extraneous factors that can distort the risk estimate is one of the biggest challenges in epidemiology and various design and analysis strategies have been developed for this purpose. One design approach is to restrict participant inclusion so that the study groups are as homogeneous as possible and sources of variability are reduced. One example is the inclusion of people of one sex and/or within a limited age range. A second approach is matching, whereby controls are selected for inclusion in the study if they match individual cases on certain attributes (e.g., age group and sex). A third approach is to collect as much descriptive information about the study participants as possible so that the study groups can be compared to determine how similar they are on factors other than those of interest. A factor that differs between the comparison groups and is associated with the outcome of interest is a potential confounder which can distort the relationship being studied. Analytic strategies for controlling potentially confounding factors involve mathematical models to adjust the risk estimate for the distorting effects of the confounders. Direct and indirect age-adjustment of rates, logistic regression, multiple linear regression and the Cox proportional hazards model are some of these techniques.

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Glossary

The chapters in which each item is discussed are given in brackets, using the legend: AP (Air Pollution), DB (Disinfection By-Products), EF (Electromagnetic Fields), ET

(Environmental Tobacco Smoke), MM (Metal Mining), OC (Organochlorines), PE (Pesticides), PP (Pulp and Paper), R (Radon), UR (Ultraviolet Radiation). Where no chapters are indicated, the term is considered generic to environmental cancer epidemiology.

Although chemical compounds can have several names, only one is given here for each. Very complex names are not included. Where possible, the CAS (Chemical Abstract Service) registration number is provided in brackets at the end of each entry. This number can be used to search for information on a compound.

The Canadian spelling (“ph”) is used in the glossary whenever there is an option of “ph” or “f” even though the “f” variant may appear in the text at the discretion of the author and particularly when referring to a product name.

µg/L: Micrograms per liter. For aqueous (water) samples 1 µg/L is equal to one part per billion (ppb).

1,1-dichloro-2,2-bis(p-chlorophenyl) ethylene (DDE): (C₁₄H₈Cl₄). The stable breakdown product of DDT that is a persistent widespread environmental contaminant, is readily stored in fatty tissues, and has been identified in human tissues such as blood and milk. (72-55-9) (OC, PE)

1,1,1-trichloro-2,2-bis(4-chlorophenyl) ethane/dichlorodiphenyltrichloroethane (DDT): (C₁₄H₉Cl₅). An organochlorine implemented largely during WWII as an insecticide to control body lice and insect vectors of malaria and typhus, and subsequently used for agricultural purposes. Its registration for use in Canada was discontinued in 1985. Although DDT is no longer manufactured in North America, trace amounts still enter our environment as a result of leakage from waste sites and long-range transport in the atmosphere. (50-29-3) (OC, PE)

1,2-dibromo-3-chloropropane (DBCP): (C₃H₅Br₂Cl). An organohalide fungicide/fumigant and nematicide. Any that leaches into surface water evaporates within a few

days. In air, it takes several months to break down, and it may remain in soil for several years. Exposure is mainly from consuming contaminated water or food. (96-12-8) (PE)

1,3-dichloropropane: (C₃H₆Cl₂). A contaminant of soil fumigants containing 1,3-dichloropropene. It is rarely found in water and is of low toxicity. (142-28-9) (PE)

1,3-dichloropropene: (C₃H₄Cl₂). Used in Canada as a soil fumigant to control fungi and nematodes. A colourless liquid at room temperature, it is soluble in water and evaporates quickly from it and from soil into air, where it is broken down by sunlight. It may leach into and travel in ground water. Trade name is Telone II. (542-75-6) (PE)

1,3,7-trichlorodioxins: By-product contaminants of some pesticides. (PE)

2,3,7,8 congener: (C₈H₅Cl₃O₃). 2,3,7,8-TCDD. The most toxic congener of TCDD. (93-76-5) (PE)

2,3,7,8-TCDD: See 2,3,7,8, congener.

2,3,7,8-tetrachlorodibenzo-p-dioxin: First discovered as a by-product of chlorinated phenol production in the 1950s, TCDD was industrially produced as the by-product of manufacture of 2,4,5-trichlorophenol. It is the most potent carcinogen known to some animals, and is known to bind to some human receptors. (1746-01-6) (PE, OC, PP)

2,4-D acid: Acid form of 2,4-D. (PE)

2,4-D: See 2,4-dichlorophenoxyacetic acid.

2,4-dichlorophenoxyacetic acid (2,4-D): (C₈H₆Cl₂O₃). One of the chlorophenoxyacetic acid herbicides. Its crystals are prismatic, white to pale yellow in colour, and have a phenolic-like odour. A chlorinated phenoxy compound that functions as a systemic herbicide and is used to control many types of annual and perennial broadleaf weeds in fruit, vegetable, turf, and ornamental plantings. It serves a secondary purpose as a plant growth regulator and is applied to crops to induce rooting and blossom set, to control ripening of bananas and citrus fruits, and to prolong fruit life on the tree. As with 2,4,5-T, 2,4-D chemically stimulates

plant growth hormones, causing uncontrolled cell proliferation. It contains chlorine, thus posing a risk for dioxin formation, as seen with its use as one of the ingredients of Agent Orange. There are many forms or derivatives (esters, amines, salts) of 2,4-D and these vary in solubility and volatility. (94-75-7) (OC, PE)

2,4,5-T: See 2,4,5-trichlorophenoxyacetic acid.

2,4,5-trichlorophenol (TCP): (C₆H₃Cl₃O). An organochlorine precursor of 2,4,5-T that is structurally similar to phenoxy herbicides and is used as an antiseptic and fungicide/fumigant. A yellow solid, also known as Omal, 2,4,6-T, and Phenochlor, it is broken down in 1 to 9 days by sunlight and by bacteria in soil. (95-95-4) (PE)

2,4,5-trichlorophenoxyacetic acid (2,4,5-T): (C₈H₅Cl₃O₃). A chlorophenoxyacetic acid herbicide that was used in Canada in the past as a defoliant to control undesirable brush and woody plants. The crystals can be formulated as soluble or emulsifiable concentrates and are white and pale brown in colour. It should be stated which salt or ester is present: i.e., 2,4,5-T-trolamine; 2,4,5-T-triethylammonium. (93-76-5) (OC, PE)

3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone (MX): A very potent mutagen and genotoxic compound in laboratory animals; it has also been shown to be carcinogenic in rats. MX appears to account for about one third of the mutagenicity of chlorinated drinking water, as determined in *in vitro* tests.

4-aminobiphenyl: See Para-aminobiphenyl (PAB).

4-chloro-2-methylphenoxy acetic acid (MCPA): (C₉H₉ClO₃). A systemic phenoxy herbicide used to control annual and perennial weeds (including thistle, dock, buttercup and horsetail) in cereals, grasslands, trees and turf. The herbicide works by concentrating in the actively growing regions of a plant where it interferes with protein synthesis, cell division and ultimately the growth of the plant. It should be stated which acid, salt or ester is present. (94-74-6) (PE)

A priori: Based on an hypothesis or theory rather than on experiment or experience. Heuristic.

Acetic acid: (CH₃COOH). A colourless pungent liquid that is the chief acid of vinegar; may be a component of vapours emitted from wood pulp. (PP)

Acryl group: (C₃H₃O₂). An unsaturated group that is part of compounds such as acrolein, acrylonitrile, acrylic acid.

Additivity: A mathematical model based on the assumption that the combined effects of several factors is the sum of the effects that would be produced by each of the factors in the absence of others.

Adduct: A complex that forms when a chemical binds to a biological molecule, such as DNA or a protein.

Adenocarcinomas: Tumours in which the cancerous cells are arranged in the form of glands. Cancers of the lung, stomach, pancreas, prostate gland, and ovary are most often adenocarcinomas.

Adjusted odds ratio: An odds ratio that represents the association between two factors after the effects of other confounding effects have been mathematically removed.

Adjustment: A summarizing procedure for a statistical measure in which the effects of differences in composition of the population being compared are minimized. (PE)

Aerated stabilization basin: A water basin with an on-going flow of air bubbles, used to treat waste water. (PP)

Aerosol: A gaseous suspension of fine solid or liquid particles, such as paint, a detergent, or insecticide, packaged under pressure with a gaseous propellant for release as a spray of fine particles.

Aerosolize: Disperse as an aerosol. Radon daughters, which are solid particles, disperse into the atmosphere as an aerosol.

Age-adjusted rates: A mathematical procedure designed to minimize the effects of

differences in age composition when comparing rates for different populations. In direct adjustment, the observed age-specific rates in the two populations are applied to a third “standard” population with a known age structure to calculate the expected number of deaths in each of the comparison populations. Indirect adjustment is the mirror image of direct adjustment and is used when the rates in the populations to be compared are either unstable or unknown. In this situation, the expected numbers of deaths in the study populations are calculated by applying the standard population age-specific rates to the study populations.

Agent Orange: A code name for the orange band that was used to mark the drums in which a herbicide, developed for the military, was stored. Primarily for use on broadleaf foliage, such as the dense jungle found in Southeast Asia, Agent Orange was a 50-50 mix of 2,4-D and 2,4,5-T. The earliest health concerns about Agent Orange were about the product’s contamination with TCDD. (OC)

Ah: See Aryl hydrocarbons.

Ah receptor: A receptor that binds a wide variety of aromatic compounds, including polycyclic hydrocarbons, among which are dioxins (e.g., TCDD), dibenzofurans, and biphenyls (PCBs). Detectable in many tissues and organs, the Ah receptor is responsible for mediating the carcinogenic effects of these agents. (OC)

Alachlor: 2-chloro-2’,6’-diethyl-*N*-methoxy-methylacetanilide (C₁₄H₂₀ClNO₂). An aniline herbicide used to control annual grasses and certain broadleaf weeds in crops such as field corn and soybeans. It is a selective systemic herbicide, absorbed by germinating shoots and by roots. (15972-60-8) (PE)

Aldehydes: Organic chemical compounds belonging to a class of highly reactive substances obtained mainly by the oxidation of primary alcohols. Aldehydes are characterized by the group – CHO and are used industrially in the manufacture of resins, dyes and other organic compounds. (PP, PE)

Aldicarb: 2-methyl-2-(methylthio)propionaldehyde *O*-methylcarbamoyloxime (C₇H₁₄N₂O₂S). A broad spectrum, systemic oxime carbamate insecticide and nematicide that is the most toxic of the carbamate insecticides. (116-06-3) (PE)

Aldrin: (C₁₂H₈Cl₆). A cyclodiene insecticide. Aldrin is the name for material containing 95% pure compound. The pure compound has the common name HHDN. Aldrin degrades to dieldrin quickly in the body and the environment. Once used around the world to control soil insects and mosquitoes, in the 1970s its use was restricted to licensed pest control operators for the removal of underground termites. Today it is no longer manufactured or used in Canada. (309-00-2) (PE)

Aliphatic: Saturated or unsaturated hydrocarbon compounds of the open chain formation. (PE)

Alkaline oxide: See Hypochlorite.

Alkyl bromide: An alkyl halide with one or more bromine atoms in its structure. (PE)

Alkyl halide: A chemical compound made up of an alkyl group (C_nH_{2n+1}) and a halide atom. Halides are compounds containing a halogen atom (chlorine, bromine, fluorine and iodine). (PE)

Alkylation: A chemical reaction in which a hydrogen atom in an organic compound is replaced by an alkyl group (C_nH_{2n+1}). (PE)

Alpha particle: A positively charged particle ejected spontaneously from the nuclei of some radioactive elements. It is identical to a helium nucleus that has a mass number of 4 and an electrostatic charge of +2. It has low penetrating power and a short range (a few centimeters in air). The most energetic alpha particle will generally fail to penetrate the dead layers of cells covering the skin and can be easily stopped by a sheet of paper. (R, MM)

Ambient: A term used to describe the surrounding environment.

Ames reversion assay: A quantitative measurement of the mutagenicity of a chemical substance by the Ames test. The greater the number of bacterial colonies that grow in the presence of the chemical, the more mutagenic the chemical. (PE)

Ames test: A test for mutagenicity of chemical compounds that uses a special strain of the bacterium, *Salmonella typhimurium*. The bacteria are incubated in the presence of the suspected mutagen. Growth of bacterial colonies indicates mutagenicity of the chemical. (PE)

Amides: Compounds with the formula RCONH₂. (PE)

Amines: A class of organic compounds having a nitrogen atom attached to a carbon framework by single bonds. (PE)

Aminotriazole: See Amitrole.

Amitrole: 1-*H*-1,2,4-triazol-3-ylamine (C₂H₄N₄). A triazole herbicide that is applied as a liquid. Trade names include Amerol, Amino Triazole, Amitrol, Amizine, Amizol, Azolan, Azole, Cytrol, Diurol, and Weedazol. (61-82-5) (PE)

Ampere: A unit for measuring the rate of flow of an electric current, defined in terms of the force which a current produces. Approximately one ampere of current is required to produce 100 watts of electric power. (EF)

Amphibole: Any of a group of rock-forming silicate minerals, including hornblende and asbestos. (MM)

Androgen receptor: A member of the subfamily of steroid hormone receptors. The gene for this receptor is localized on the human X chromosome. Androgens enter the cells by passive diffusion and bind to the androgen-binding domain of the receptor, initiating the production of androgen-specific proteins.

Angiosperms: Flowering plants and trees that form seeds inside a protective chamber called the ovary; includes hardwood trees, such as oak and maple. (PP)

Anilides: When aniline is heated with an organic acid, amides called anilides are produced. Commercially they are used as herbicides, such as alachlor, propachlor, pentanochlor and propanil. (PE)

Aniline: (Phenylamine C₆H₇N). A benzene ring with an amine (NH₂) group attached to one of the carbons in the ring. A degradation product of anilides. Pure aniline is a highly poisonous, oily, colourless substance with a pleasant odor. (62-53-3) (PE)

Anion: A negatively charged ion. (AP)

Ankerite: Ca(Mg,Fe⁺²,Mn)(CO₃)₂. A mineral belonging to the carbonate group, related to dolomite. (MM)

Antibody: A globulin (protein insoluble in water) in the blood or other body fluids which can be incited by the presence of an antigen.

Antibody producing cells: After encountering stimulating antigenic signals, B lymphocytes develop into plasma cells which produce antigenic-specific antibody molecules.

Antigen: A foreign substance that stimulates an immune response.

Antigenic transplanted UV related tumours: UV-induced tumours in the skin of rats or mice are antigenic and are rapidly rejected when transplanted into normal, genetically similar animals. If the tumours are transplanted into animals previously exposed to subcarcinogenic doses of UV-B, they are not rejected and instead grow progressively in the recipients. While the mechanism of suppression of tumour rejection is unknown, such a response might be a critical determinant of cancer risk in human skin. (UR)

Aramite®: Sulphurous acid, 2-chloroethyl 2-(4-(1,1 dimethylethyl)phenoxy)-1-methyl ester (C₁₅H₂₃ClO₄S). A colourless liquid organochlorine insecticide. (140-57-8) (PE)

Arithmetic mean: Sum of all values in a set of measurements, divided by the number of values in the set.

Aromatic amines: Amines in which one of the organic groups is an aromatic ring. (PE)

Aromatic compounds: A term applied to a large family of compounds structurally similar to benzene; i.e., a closed ring. (OC, PE, PP)

Aromatic hydrocarbons: Aromatic compounds made up of only carbon and hydrogen atoms. (OC, PE)

Aromatic ring: See Aromatic compounds.

Arsenic: (As). A highly poisonous chemical element having three allotropic forms, yellow, black, and grey, of which the brittle, crystalline grey is the most common. Arsenic is widely distributed in nature uncombined or in association with ores of antimony and silver. Extracted from arsenopyrite, arsenic and its compounds are used in insecticides, weed killers and various alloys. (R, PE, MM)

Arsenopyrite: (FeAsS). A primary source of arsenic. Arsenopyrite can be found in veins of lead or silver. (MM)

Aryl: A group derived from an aromatic hydrocarbon by removal of a hydrogen atom from the molecule. (PE)

Aryl hydrocarbons: (Ah). Aromatic hydrocarbons with a hydrocarbon group attached to the ring structure. (OC)

Ascertainment bias: Systematic failure to represent equally all classes of cases or persons supposed to be represented in a sample.

Atrazine: 6-chloro-N²-ethyl-N⁴-isopropyl-1,3,5-triazine-2,4-diamine (C₁₄H₂₀ClNO₂). A chloro triazine herbicide used to control broadleaf and grassy weeds in corn. It acts as a strong inhibitor of photosynthesis and is soluble in water. It is used as a non-selective, granular soil sterilant and can remain in the soil for two years. It has a high potential for ground water contamination. (1912-24-9) (PE)

Autosomal: Referring to the non-sex chromosomes.

Autosomal dominant pattern (of inheritance): The pattern of inheritance in which a trait or disease will be expressed in an organism when only one member of a gene pair (rather than both) on a non-sex chromosome contains the DNA code that carries that trait or disease. In a recessive pattern, both genes of the pair must be affected for the trait/disease to be expressed.

Auxin growth regulators: Chemical compounds that act as synthetic auxins or plant hormones, altering the plant's metabolism and hence growth characteristics (e.g., chlorophenoxy herbicides). (PE)

Axon: The part of a neuron that carries nerve impulses away from the nerve cell body to other nerve cells or effector organs.

Axonic poisons: Poisons that damage axons. (PE)

Azinphos-methyl: (C₁₀H₁₂N₃O₃PS). A white crystalline solid that is one of the most toxic of the organophosphate insecticides. It has low persistence in soil, the half life being 21 to 68 days under anaerobic conditions. It is unlikely to contaminate ground water and degrades in UV light. Use is being phased out in Canada. (86-50-0) (PE)

Backcasting: A method of estimating what might have happened in the past that relies on existing trends and statistics. (AP)

Basal cell carcinoma: The most common malignant skin tumour in Caucasians, basal cell carcinoma begins to occur in significant numbers in the fourth decade of life and increases with age. The lesions occur in fair-skinned persons and on areas of skin that receive a significant amount of intermittent or continuous sun exposure. Treatment with inorganic arsenical drugs and exposure to ionizing radiation (X-rays, radium) may also contribute fewer than five % of these cases. These cancers rarely metastasize but may be highly invasive locally. (UR)

Bayesian inferences: This method for inference involves working "backward" from effect to cause by estimating the conditional

probability of a cause given that certain events have occurred. (AP)

Benomyl: Methyl-1-(butylcarbamoyl) benzimidazol-2-yl carbamate (C₁₄H₁₈N₄O₃). A protective and eradicant benzimidazole fungicide and nematicide effective against a wide range of fungi, such as apple scab and black spot that affect fruits, nuts, vegetables, turf, and field crops. All uses have been discontinued. (17804-35-2) (PE)

Benzene: (C₆H₆). A thin, colourless, highly flammable liquid that is a coal-tar derivative used in the manufacture of numerous chemical products, including insecticides, detergents and motor fuels; commonly called benzol. (PP)

Benzene ring: Six carbon atoms forming a ring to which are attached six hydrogen atoms. (PP)

Benzimidazole: A compound having a benzene ring fused to an imidazole ring. It is a weak base and remarkably stable. It resists acids and bases and is not easily oxidized. (51-17-2) (PE)

Benzimidazoles: A group of compounds having benzimidazole in their structure, including benomyl, carbendazim, thiabendazole, thiophanate and thiophanate-methyl. They are used as fungicides/fumigants. (PE)

Benzoic acid: Benzenecarboxylic acid, a fungistatic compound widely used as a food preservative. (65-85-0) (PE)

Benzoic acids: Aryl aliphatic acids that are used as herbicides (e.g., Dicamba). They are applied to soil to prevent germination, or as a post-emergent herbicide. (PE)

Benzo[a]pyrene: A type of polycyclic aromatic hydrocarbon, or PAH, that is probably carcinogenic to human beings. (ET)

Beta rays/particles: A charged particle emitted from a nucleus during radioactive decay, with a mass equal to 1/1837 that of a proton. A negatively charged beta particle is identical to an electron. A positively charged beta particle is called a positron. Large amounts of beta radiation may cause skin burns, and beta emitters are harmful

if they enter the body. Beta particles may be stopped by thin sheets of metal or plastic. (R)

Bioconcentrate (bioaccumulate): A chemical present at infinitesimal concentrations in air or water may be increasingly concentrated as it moves up the food chain, until humans eating meat or fish ingest relatively high concentrations. Such chemicals enter the bodies of plants and animals, are not easily expelled, and accumulate over time.

Biodegradable: Can be chemically degraded using natural effectors such as soil bacteria, weather, plants or animals. Bacteria are considered “a biodegradable detergent” because they break down substances in the soil for resorption and uptake in the natural environment.

Biomarkers: A biological indicator (e.g., a genetic locus or a biochemical) useful for measuring the effects of a particular hazardous exposure (e.g., cotinine). Once an exposure has occurred, a continuum of biological events can be detected. These events may serve as indicators of exposure, of susceptibility, or of effect. For example, metabolites of exogenous substances may be detected in the body and indicate exposure. An important metabolite of heptachlor is heptachlor epoxide, which is an oxidation product formed from heptachlor by many plant and animal species.

Biota: Animal and plant life characterizing a given region.

Biotite: Black or dark-coloured mica (a mineral that divides into thin, partly transparent layers, withstands heat, and is used for insulation). (MM)

Biphenyl: An aromatic hydrocarbon, also known as diphenyl, that is composed of two benzene rings. It is used alone or with diphenyl ether, as a heat-transfer fluid. Pure biphenyl is a colourless crystalline solid with a pleasant odour; it is insoluble in water but soluble in ordinary organic solvents. (OC)

Bisdithiocarbamate: A class of fungicide used on potatoes, fruits and vegetables (e.g., Mancozeb). (PE)

Blind assessment: The person doing the assessment does not know whether the subject is a case or control.

Boron compounds: Compounds containing boron (B), a non-metallic chemical element. (PP)

Brachiopod crustaceans: Small invertebrate, predominantly aquatic animals, having segmented bodies covered with an exoskeleton and two coiled arms called brachia on either side of the mouth, used to draw in food-bearing water; includes lobsters, shrimps, crabs, barnacles, wood lice. (PP)

Bromide: A compound of bromine with a positive radical. (DB)

Bromine: (Br). In its diatomic form, Br₂, bromine is a deep reddish brown liquid at room temperature, but if exposed to air, will emit a pungent brown coloured vapour. Like chlorine, bromine is a halogen. It is found naturally in seawater and saline springs, though at small concentrations. Bromine is used as a fire retardant and pesticide and to make brominated organic compounds. (DB)

Bromodichloromethane: (CHBrCl₂). Methane (a colourless, odourless, flammable gas) that has one bromine and two chlorine atoms in place of the hydrogen atoms. Bromodichloromethane is a product of the reaction between chlorine and naturally-occurring organic matter in water. (DB, PP)

Bromoform: (CHBr₃). A volatile organic compound found in chlorinated water supplies as a consequence of the reaction between chlorine during water treatment and natural organic substances in the presence of bromide ion. One of the four compounds constituting trihalomethanes. (DB)

Bromoxynil: 3,5-dibromo-4-hydroxybenzoxynitrile (C₇H₃Br₂NO). A nitrile herbicide. Trade names: Brominal, Buctril. It is used on grain, vegetables and grass for post emergent control of broadleaf weeds

(1689-84-5). It should be stated which salt or ester is present: Bromoxynil-potassium (2961-68-4) or bromoxynil-octanoate (1689-99-2). (PE)

Bronchiolitis obliterans: Dense, irreversible scarring of the terminal and respiratory bronchioles of the lung. This scarring may partially or totally close off the airway. (PP)

Butylate: S-ethyl-di-isobutylthiocarbamate (C₁₁H₂₃NOS). A thiocarbamate herbicide used on corn. The half-life under crop growing conditions is 1.5-3 weeks. All uses have been discontinued in Canada. Trade name: Sutan (2008-41-5) (PE)

Calcinate: To heat (a substance) to a high temperature but below the melting or fusing point, causing loss of moisture, reduction, or oxidation and the decomposition of carbonates and other compounds. (PP)

Calcining: Heating an inorganic substance to a high temperature, but not high enough to melt or fuse it, in order to bring about evaporation of certain matter in it or cause chemical changes such as oxidation. Limestone is calcined to produce lime. (MM)

Calcite: (CaCO₃). A mineral composed of calcium carbonate. It occurs as limestone, chalk, marble etc. (MM)

Calcium carbonate: (CaCO₃). An inorganic chemical found in nature as calcite (limestone, chalk, marble, etc.) and aragonite (a crystalline carbonate of lime) and in plant ashes, bones etc. (PP)

Captafol/captofol: N-(1,1,2,2-tetrachloroethylthio)cyclohex-4-ene-1,2-dicarboximide (C₁₀H₉Cl₄NO₂S). A broad-spectrum dicarboximide fungicide, also called Captafol and Difolatan, that is effective for the control of almost all fungal diseases of plants, except powdery mildews, and is widely used to control foliage and fruit disease. Captafol is also used in the lumber and timber industry. (2425-06-1) (PE)

Captan: N-(trichloromethylthio)cyclohex-4-ene-1,2-dicarboximide (C₉H₈Cl₃NO₂S). A dicarboximide fungicide powder used to

control diseases on many fruit, ornamental, and vegetable crops. It is used in agricultural production as well as by the home gardener. It is also applied to packing and shipping boxes for fruits and vegetables. (133-06-2) (PE)

Carbamates: Derivatives of carbamic acid that inhibit cholinesterase (ChE) and are used as insecticides. Many are designated as N-Methyl carbamates; others have an amide functional group with substituents other than a methyl group. (PE)

Carbamic acid: (H₂NCOOH). A compound that exists only in the form of salts or esters (carbamates), amides (carbamides), and other derivatives. (PE)

Carbaryl: 1-naphthyl methylcarbamate (C₁₂H₁₁NO₂). Also known as Sevin. A wide-spectrum, general use carbamate pesticide that controls insects on citrus, fruit, cotton, forests, lawns, nuts, ornamentals, shade trees, and other crops, as well as on poultry, livestock and pets. It is also used as a molluscicide and an acaricide. (63-25-2) (PE)

Carbathiin: See Carboxin.

Carbofuran: 2,3-dihydro-2,2-dimethyl benzofuran-7-ylmethylcarbamate (C₁₂H₁₅NO₃). A carbamate insecticide of lesser toxicity than aldicarb. (1536-66-2) (PE)

Carbon tetrachloride or tetrachloromethane: (CCl₄). A colourless oily, combustible liquid; formerly used as a cleaning agent, but no longer recommended because of its toxicity to the liver and kidney. (PP)

Carboximide: A class of fungicides that includes Carboxin and Folpet. (133-07-3) (PE)

Carboxin: 5,6-dihydro-2-methyl-1,4-oxathiazine-3-carboxanilide (C₁₂H₁₃NO₂S). A systemic anilide fungicide used as a seed treatment for control of smut, rot, and blight on barley, oats, rice, cotton, vegetables, corn and wheat. One of the leading fungicides in Canada, carboxin is also used to control fairy rings on turf grass. (5234-68-4) (PE)

Carcinogen: An agent capable of initiating development of malignant tumours. May

be a chemical, a form of electromagnetic radiation, or an inert solid body.

Case: A person in the population or study group identified as having the particular disease or condition under investigation. Various sources may be used to identify cases (e.g., physicians' diagnoses, cancer registries and notifications, and abstracts of clinical records).

Case-control study: A study that starts with the identification of persons with the disease or other outcome of interest, and compares them to a suitable control group (comparison or a reference group) of persons without the disease.

Cation: A positively charged ion. (AP)

CDKN2A: A germline mutation at human chromosome 9p21 present in 10–15% of individuals developing two or more independent melanomas. The mutation is also present in many families with two or more affected first degree relatives. At the present time, these germline mutations are thought to be transmitted from one generation to another in an autosomal dominant pattern, with variable penetrance, and individuals with them appear to be at high risk for the disease. (UR)

Cell cycle: An ordered set of events, culminating in cell growth and division into two daughter cells. These events include protein synthesis, DNA replication, DNA repair and mitosis (cell division).

Cell signaling cascade: A chain of events, initiated by an environmental agent, that leads to aberrant cell proliferation and carcinogenesis.

Cellulose: (C₆H₁₀O₅)_n. The main constituent of the cell walls of plants. (PP)

Chalcopyrite: (CuFeS₂). The most common mineral containing copper, found in porphyry copper deposits, skarns, contact metamorphism, hydro-thermal vents and other places. Consists of a sulphide of copper and iron. (MM)

Chinese hamster: An animal whose cells (ovary, lung, bone marrow etc.) are isolated

and cultured for use in tests to determine the outcome of hazardous exposures (e.g., pollutants, herbicides). (PE)

Chip chute: A piece of machinery that feeds logs into a heavy, vertically rotating disk where they are shredded into small chips. (PP)

Chloracne: A skin disease that is one of the most sensitive indicators of exposure to dioxins and related chemicals. Clinically it is a persistent acne on the cheeks and behind the ears. (OC, PP, PE)

Chloramination: Treating drinking water by applying chlorine before or after applying ammonia. (DB)

Chloramines: ($\text{CH}_3\text{C}_6\text{H}_4\text{SO}_2\text{NClNa} - 3\text{H}_2\text{O}$). Compounds formed by the reaction of hypochlorous acid (or aqueous chlorine) with ammonia for the purpose of water disinfection. Mono-, di-, and trichloramines may be formed depending on the ratio of chlorine to ammonia, the pH, and the temperature of the water. (DB)

Chlordane: ($\text{C}_{10}\text{H}_6\text{Cl}_8$). An organochlorine (cyclodiene) insecticide that can cause potentially fatal neurotoxic symptoms, such as muscle spasms and seizures. It is no longer registered as an active ingredient in Canada. (57-74-9) (PE)

Chlordecone: ($\text{C}_{10}\text{Cl}_{10}$). A cyclodiene insecticide used on tobacco, ornamental shrubs, bananas and citrus trees and in ant and roach traps. It breaks down slowly in the environment and does not readily dissolve in water. (143-50-0) (PE)

Chlorinated cyclodienes: A group of organochlorines (including dieldrin, mirex, chlordecone – kepone) that are stable in soils and under solar UV radiation and hence are persistent insecticides. Their toxicity increases with the environmental temperature. (OC, PE)

Chlorinated ketones: Ketones in which the hydrogen atom(s) is/are replaced by an equal number of chlorine atoms. Ketones are a group of compounds having a carbonyl group (CO) linked to hydrocarbon groups. (DB)

Chlorinated organic compounds/chemicals/hydrocarbons/synthetics: Compounds having one or more chlorine atoms in place of a hydrogen atom. (PP, OC, PE)

Chlorination: The process of adding chlorine to water, for the purpose of disinfection. (DB)

Chlorine: (Cl). Normally existing in its gaseous diatomic form, Cl_2 , chlorine is produced for industry principally by electrolysis of sodium chloride (salt), and is used as a disinfectant and bleaching agent, as well as to disinfect water. Chlorine gas can combine with nearly all other elements, and especially with water, causing it to be highly irritating to the lungs and other mucous membranes at high levels when inhaled. However, under normal conditions of use, the inhalation of mists or vapours from dilute chlorine solutions is not expected to be significant or to result in any health effects in the general population. (PP, DB)

Chlorine dioxide: (ClO_2). A gas generated through the reaction of sodium chlorite and chlorine or by acidification of strong sodium chlorite solution. ClO_2 is a highly effective, environmentally-friendly microbiocide that eliminates planktonic and sessile bacteria, disinfects surfaces, and destroys biofilms. (PP, DB)

Chlorite: A salt of chlorous acid. (MM)

Chloroacetanilide: A benzene ring where one hydrogen atom is replaced by the $-\text{NHCOCH}_3$ group and also having one or more hydrogen atoms replaced by chlorine atoms. (PE)

Chlorodibromomethane: See Dibromochloromethane.

Chloroform/chloroformtrichloromethane: (CHCl_3). A volatile organic compound found in water as a consequence of the reaction between chlorine and naturally-occurring substances. One of the four compounds constituting trihalomethanes. (DB, PP)

Chloronitrile: A nitrile having one or more chlorine atoms in its structure. (PE)

Chlorophenols: Organic chemicals in which one or more hydrogen atoms of phenol are replaced by one or more atoms of chlorine. Chlorophenols are formed as a result of the chlorination of humic matter or of natural carboxylic acids during the treatment of water. They are well-known chlorination by-products, since they can confer objectionable taste and odour. Chlorophenols are also a class of pesticides with widespread use. There are 19 chlorophenol congeners, many of which are used in Canada in pesticide products or wood preservatives. (PP, PE, DB)

Chlorophenoxyacetic acid herbicides: Chlorophenoxyacetic acid is synthesized from phenol (a benzene ring with a hydroxyl group on the ring) and acetic acid. The chlorinated derivatives include 2,4-D and 2,4,5-T which would have two and three chlorine atoms on the ring respectively. (OC, PE)

Chloropicrin: Trichloronitromethane (CCl_3NO_2). A clear, colourless, oily liquid with a strong, sharp, highly irritating odour used primarily for preplant soil fumigation to control soil borne fungi, diseases and nematodes. It also is used to treat wood poles and timbers for internal decay by fungi and insects. (76-06-2) (PE)

Chlorothalonil: Tetrachloroisophthalonitrile ($\text{C}_8\text{Cl}_3\text{N}_2$). An aromatic fungicide sprayed on vegetables, trees, small fruits, turf, ornamentals, and other agricultural crops. It also controls fruit rot in cranberry bogs and snow moulds and is used in paints. (1897-45-6) (PE)

Chlorotriazine: ($\text{C}_3\text{Cl}_3\text{N}_3$). Colourless crystals that react violently with water. Decomposes when heated or burned to produce toxic fumes including hydrogen chloride and nitrogen oxides. (PE)

Chlorovanillins and chlorosyringols: Aromatic or low molecular weight compounds that are by-products of the degradation of lignin using alkaline or chlorine treatment. (PP)

Chloroxanthins: Xanthine (2,6-dihydroxypurine) is found in tea and in animal tissues. Chloroxanthines (having one or more

chlorine atoms as substituents) are toxic by-products of some pesticides. Purine is an aromatic heterocyclic compound. (PE)

Chlorpyrifos: *O,O*-diethyl *O*-3,5,6-trichloro-2-pyridylphosphorothioate (C₉H₁₁Cl₃NO₃PS). An organothiophosphate that acts by interfering with the activities of cholinesterase, an enzyme essential for the proper working of the nervous systems of both humans and insects. Chlorpyrifos is a contact dust, foam or liquid spray used against flying and non-flying insects such as hornets, wasps, ants, cutworms, fungus gnats and spiders. (2921-88-2) (PE)

Cholinesterase: One of many important enzymes needed for the proper functioning of the nervous systems of humans, other vertebrates, and insects. Certain chemical classes of pesticides, such as organophosphates (OPs) and carbamates (CMs) work by interfering with, or 'inhibiting' cholinesterase. While the effects of cholinesterase inhibiting products are intended for insect pests, these chemicals can also be poisonous, or toxic, to humans in some situations. (PE)

Chromate: A salt or ester of chromic acid. (PP)

Chromic acid: A solution of potassium dichromate in sulphuric acid. It is a strong oxidant, commonly used as a cleaning agent. (PP)

Chromosome 14q32 (or Band 14q32): A genetic locus on human chromosome 14 (an autosomal chromosome).

Chromosome 18q21: A genetic locus on human chromosome 18 (an autosomal chromosome).

Chromosome breaks: Chromosomes break and rearrange with heterologous and homologous chromosomes during both types of cell divisions (mitosis and meiosis).

CMM: See Cutaneous malignant melanoma.

Co-kriging: A version of kriging that predicts more than one response. (AP)

Co-mutagens: Mutagens that act together or synergistically.

Cobalt: (Co). A silver-white metallic element with a pinkish tint that occurs with and is similar to nickel and iron, used especially in alloys and for making pigments. (MM)

Cohort study: A study in which subsets of a defined population are identified who are, have been, or in the future may be exposed to the agent under investigation. The identified individuals are followed over time for the occurrence of disease.

Conazole: The active part of these compounds is the triazole ring which is a Cytochrome P450 inhibitor. A triazole ring is a five-membered ring of two carbon atoms adjacent to each other, and three nitrogen atoms. (PE)

Confidence interval (CI): A range of values for a variable of interest having a specified probability of including the true value of the variable (e.g., 95%). The end points of the confidence interval are called the confidence limits.

Confounder: A variable/factor, related to both the outcome of interest and the study factor, that can obscure the relationship being studied.

Confounding: A mixing of effects between the exposure, the disease, and a third factor (confounder) that is associated with the exposure and independently affects the risk of developing the disease.

Congeners: A group of chemical substances that share chemical properties and structure. They are derivatives of the same or a similar compound or element belonging to the same family in the periodic table. Unlike isomers, congeners do not necessarily have the same molecular formula. (OC, PE)

Conifer: Trees or shrubs bearing their seeds in cones (e.g., pines, spruces, firs, hemlocks, junipers and cypresses). (PP)

Contact metamorphism: The alteration of a rock due to the introduction of heat (no pressure effects), from an adjacent igneous rock (such as a lava flow). Contact metamorphism does not affect the entire rock,

just a relatively thin zone next to the heat source. (MM)

Control: (noun) A person in a comparison group without the factor of interest – exposure in a cohort study, disease in a case-control study. (verb) During analyses, to adjust for or take into account extraneous influences and observations. (adjective) A "control variable" is a variable which has a potential effect on the outcome or disease under study, and which is subject to control by analysis. See Confounder.

Coplanar PCBs: PCBs with atoms arranged in a single plane, resembling dioxins, and with dioxin-like activity via binding with the Ah receptor. (OC)

Correlate: (noun) A variable that changes as another variable changes. (verb) Show the connection or relationship between two variables.

Correlation: The degree to which variables change together; the mutual relation of two or more things.

Correlation coefficient: A measure of association that indicates how closely two variables are linearly related.

Cotinine: ((C₆H₁₂N₂O₂)₂ C₄H₄O₄). A major urinary metabolite of nicotine, used as a biomarker of exposure to tobacco smoke. (ET)

Coumaphos: (C₁₄H₁₆ClO₅PS). An organothiophosphate insecticide of moderate to high toxicity. All uses have been discontinued in Canada. (56-72-4) (PE)

Covariance: A measure of the joint variance of two or more variables.

Covariate: A variable that is possibly predictive of the outcome of the study. A covariate may be of direct interest to the study or may be a confounding variable or effect modifier.

Cox proportional hazards model: A statistical model in survival analysis that relates the time until death (survival time) to a series of measurements thought to influence an individual's survival.

Credible regions: Sets that contain an uncertain quantity or vector of uncertain quantities with a specific probability. (AP)

Creosote: A complex organic mixture produced from coal that contains more than 300 compounds, including polycyclic aromatic hydrocarbons (PAHs), which account for up to 90% of the total mixture. Creosote is one of the most popular wood preservatives used in Canada. (PE)

Cumingtonite: $((\text{Mg}, \text{Fe})_7\text{Si}_8\text{O}_{22}(\text{OH})_2)$. A common member of the amphibole mineral group, that contains more magnesium than iron. (MM)

Curie (Ci): The basic unit used to describe the intensity of radioactivity in a sample of material. The curie is equal to 37 billion (3.7×10^{10}) disintegrations per second, which is approximately the activity of 1 gram of radium. A curie is also a quantity of any radionuclide that decays at a rate of 37 billion disintegrations per second. It is named for Marie and Pierre Curie, who discovered radium in 1898. (MM)

Cutaneous malignant melanoma (CMM): See melanoma. (UR)

Cyanazine: 2-(4-chloro-6-ethylamino-1,3,5-triazin-2-ylamino)-2-methyl propionitrile ($\text{C}_9\text{H}_{13}\text{ClN}_6$). A triazine herbicide used for pre- and post-emergence weed control for corn, canola and mixed grains. All uses have been discontinued in Canada. (21725-46-2) (PE)

Cyclodienes (cyclodienes): Chlorinated hydrocarbon insecticides (such as chlordane, aldrin, dieldrin, heptachlor, endrin and mirex). Cyclodienes have a positive temperature correlation – their toxicity increases with increases in the surrounding temperature. Cyclodienes appear to affect all animals in generally the same way, first with nervous activity followed by tremors, convulsions and prostration. (PE)

CYP1A1 gene: A gene whose enzyme induction and DNA adducts in placental tissue constitute useful biomarkers of early effects induced by environmental exposure to organochlorines. The gene is activated

by the binding of organochlorines to the Ah receptor. (OC)

Cytochrome: A respiratory enzyme, chemically related to haemoglobin, capable of alternate reduction and oxidation. (OC)

Cytochrome P450: A cytochrome that has been studied to monitor the bioaccumulation of dioxins and furans. Specifically, cytochrome P450IA1 can be used as a measure of Ah receptor activation resultant from environmental exposure. (OC)

Daphnea: Minute freshwater brachiopod crustaceans. (PP)

DBCP: See 1,2-dibromo-3-chloropropane.

DBPs: See Disinfection by-products.

DCM: See Dichloromethane.

DDE: See 1,1-dichloro-2,2-bis (p-chlorophenyl) ethylene.

DDT: See 1,1,1-trichloro-2,2-bis (4-chlorophenyl) ethane.

Deoxyribonucleic acid (DNA): The basic hereditary material in all cells. DNA contains all the information necessary for protein synthesis. (R)

Diallate: S-2,3-dichloroallyl di-isopropyl (thiocarbamate). A thiocarbamate herbicide that inhibits growth of broad-leaf weeds, such as wild oats, in croplands. (2303-16-4) (PE)

Diazinon: O,O-diethyl O-2-isopropyl-6-methylpyrimidin-4-yl phosphorothioate ($\text{C}_{12}\text{H}_{21}\text{N}_2\text{O}_3\text{PS}$). Also known as dimpylate. An organothiophosphate insecticide used on outdoor lawns and gardens or as a soil drench to control most insects, such as ants, cutworms, gnats and springtails. Diazinon is a colourless oil that is stable in sunlight and unstable in acid and alkali media. It can pollute surface and ground waters. (333-41-5) (PE)

Dibenzofurans: Furans with two benzene groups attached to carbon atoms that normally bind hydrogen. (OC)

Dibromochloromethane: (CHBr_2Cl). A volatile organic compound found in chlorinated water supplies as a consequence of the reaction between chlorine during water treatment and naturally occurring substances. (DB, PP)

Dicamba: 3,6-dichloro-*o*-anisic acid ($\text{C}_8\text{H}_6\text{Cl}_2\text{O}_3$). Also known as Disugran and dianat. A benzoic herbicide used in large quantities for broad leaf weed control on lawns, grain crops, pastures and non-crop areas. It should be stated which salt or ester is present: dicambadimethylammonium (2300-66-5), dicambapotassium (10007-85-0), dicamba-sodium (1982-69-0), or dicamba-methyl (6597-78-0). (PE)

Dichlorodiphenyltrichloroethane (DDT): A synthetic insecticide that was introduced for agricultural purposes in 1945. Although DDT is no longer manufactured in North America, trace amounts still enter our environment as a result of leakage from waste sites and long-range transport in the atmosphere. Registrations of the remaining uses of DDT in Canada were discontinued in 1985. (OC, PE)

Dichloromethane (DCM)/methylene chloride: (CH_2Cl_2). A colourless liquid with a sweet, chloroform-like odour, used as a solvent in a variety of industries and as a fumigant for strawberries and grains. (75-09-2). (PP)

Dichlorvos: 2,2-dichlorovinyl dimethylphosphate ($\text{C}_4\text{H}_7\text{Cl}_2\text{O}_4\text{P}$). An organophosphate insecticide used in no-pest strips. (62-73-7) (PE)

Diclofop-methyl: Methyl 2-[4-(2,4-dichlorophenoxy) phenoxy] propanoate ($\text{C}_{16}\text{H}_{14}\text{Cl}_2\text{O}_4$). A diphenylether/chlorphenoxy selective post-emergence herbicide. (51338-27-3) (PE)

Dieldrin: ($\text{C}_{12}\text{H}_8\text{Cl}_6\text{O}$). A cyclodiene insecticide that was a popular pesticide for crops such as corn and cotton. It breaks down very slowly. In the 1970s use was restricted to licensed pest control operators for the removal of underground termites. Dieldrin is no longer registered for use in Canada. (60-57-1) (PE)

Digester fluid: A digester is a vessel in which substances are softened or decomposed, usually for further processing. In chemical pulping, chips and chemicals (sulphates or sulphites) in aqueous solution are cooked together in a pressure vessel (a digester) from which de-lignified pulp is produced for further processing. The cooking mixtures are also called “liquors” (white or black, depending on the process used). (PP)

Dimethoate: *O,O*-dimethyl-S-methylcarbamoylmethyl phosphorodithioate (C₅H₁₂NO₃PS₂). Also known as phosphamide, dimethoate has many trade names. An organothiophosphate insecticide and nematocide used on field and orchard crops and on ornamentals, as a residual wall spray for house flies in farm buildings, and to control botflies on livestock. It is biodegradable and breaks down quickly in soils. In water it is highly soluble and therefore subject to leaching. (60-51-5) (PE)

Dimethyl sulphide: A reagent used in the wood pulping process to break down the carbon bonds in lignin. (PP)

Dimethylbenz[a]anthracene: A polycyclic aromatic hydrocarbon (PAH) in tobacco smoke. (ET)

Dimethylcarbamoyl chloride: (C₃H₆ClNO). A colourless liquid that decomposes in the presence of water to dimethylamine, carbon dioxide and hydrogen chloride. Three registered pesticides derived from it are Tandex (Karbutilate), dimethilan and Pirimor (primicarb). It is an air pollutant and a chemical intermediate in the production of dyes, pharmaceuticals and pesticides. (79-44-7) (PE)

Dinitroaniline herbicides: Also known as dinitrobenzenamines, these herbicides act by inhibiting the steps in plant cell division responsible for cell wall formation and chromosome separation. The most commonly used dinitroanilines in Canada are trifluralin and ethalfluralin; both are selective, pre-emergence herbicides used to control annual grasses and broadleaf weeds in a variety of crops. (PE)

Dinitrobenzenamines: A group of compounds having two hydrogen atoms of the benzene ring replaced by nitro groups (NO₂) and another hydrogen atom replaced by an amino group. (PE)

Dioxins: See Polychlorinated dibenzo-p-dioxins.

Diphenyl aliphatics: Aliphatic compounds having two phenyl groups as part of their structure. (PE)

Direct standardized comparison: A mathematical method for removing the potential confounding effect of age when comparing rates in two populations with differing age structure. The observed age-specific rates in the two populations are applied to a third “standard” population with a known age structure to calculate the expected number of deaths in each of the comparison populations.

Disinfection by-products (DBPs): A group of chemicals that can form in drinking water when chlorine or another disinfectant reacts with the naturally occurring organic matter. Examples of DBPs are haloacetic acids and trihalomethanes. (DB)

Dithiocarbamates: Typically fungicides with a carbamate structure, where sulphurs replace both oxygens in the amide functional group. They are also used as accelerators in the vulcanization of rubber, as antioxidants in polymer chemistry, and as drugs. The most frequently used dithiocarbamate fungicide in Canada is mancozeb. (PE)

Diuron: 3-(3,4-dichlorophenyl)-1,1-dimethylurea (C₉H₁₀Cl₂N₂O). Also known as dichlorfenidim, trade names include Crisuron, Diater, Di-on, Direx, Karmex and Unidron. A phenylurea herbicide used to control broadleaf and grassy weeds as well as mosses by inhibiting photosynthesis on field and orchard crops and ornamentals. It is moderately to highly persistent in soils and relatively stable in water. (330-54-1) (PE)

DNA: See Deoxyribonucleic acid.

DNA adduct: DNA modified by external chemicals added onto its molecule. (OC)

Dolostone: A sedimentary rock composed of more than ninety percent dolomite (CaMg(CO₃)₂) and less than ten percent calcite (CaCO₃). (MM)

Dose, absorbed: The amount of energy from ionizing radiation deposited in any substance per unit mass. It is expressed numerically in grays (the international system of units).

Dose, effective: A measure of the total potential harm from ionizing radiation over different organs, expressed in Sv (sieverts) or mSv (millisieverts). It is obtained by summing the products of the *equivalent dose* multiplied by the tissue weighting factor for each organ. Weighting factors account for the different potentials for adverse effects in different tissues.

Dose, equivalent (or biological dose): A measure, expressed in sieverts (Sv), of the potential biological damage to living tissue from various types of ionizing radiation exposure. It is obtained by summing the products of the *absorbed dose* of each radiation type multiplied by its weighting factor. Weighting factors account for the different potentials for adverse effects of the different types of radiation.

Dose-response relationship: A relationship in which a change in amount, intensity and duration of exposure is associated with a change – either an increase or a decrease – in a specific outcome.

Dysplastic nevus syndrome: A hereditary condition in which affected family members have dysplastic (abnormally developing) nevi (moles) and greatly increased risk of malignant melanoma. (UR)

Ecologic(al) correlation: A correlation in which the units studied are populations rather than individuals. Correlations found in this manner may not hold true for the individual members of the population(s).

Ecologic(al) fallacy: Bias that may occur because an association observed between variables on an aggregate level may not

represent the association that exists at an individual level.

Ecologic(al) study: Study in which the units of analysis are populations or groups of people rather than individuals.

Effluent: The liquid waste of sewage and industrial processing. (PP)

Electrical field: A space throughout which an electric force operates. (EF)

Electrical field strength: The force on a stationary positive charge per unit charge at a point in an electric field. Also known as electric field vector, electric field intensity. Electric fields are measured in volts per metre (V/m). (EF)

Electrolytic tanks: Tanks containing an electrolyte (a substance, such as water, that conducts electricity by dissociation into positively and negatively charged ions) and negatively and positively charged electrodes apart from each other. Positive ions in the electrolyte migrate to the negative electrode (cathode), where they combine with one or more electrons; negative ions move to the positive electrode (anode) and transfer one or more electrons to it. Used in the extraction and purification of metals from ores, in electroplating, and to separate compounds (e.g., NaCl (salt) into sodium metal and chlorine gas). (MM)

Electromagnetic field (EMF): Electrical devices and systems produce two different fields—an electric field and a magnetic field. These fields, in combination, are referred to as electromagnetic fields or EMFs. Electromagnetic fields are generated by current-carrying electric wiring, (especially if the conductors are apart, as in the wiring in old homes, or are poorly grounded), radio or TV station transmitters, microwave ovens, power transmission lines and generators, and electrical appliances, especially those with electric motors. (EF)

Electron: An elementary particle with a negative charge and a mass 1/1837 that of the proton. Electrons surround the positively charged nucleus and determine the chemical properties of the atom. (R)

Endocrine disruptors: Chemical substances that mimic the structure and activity of a natural hormone. It is suggested that some chemicals acting as hormonal disruptors may lead to infertility, some cancers, and other hormonally-induced disorders. (PE)

Endrin: (C₁₂H₈Cl₆O). Also known as nendrin. A cyclodiene insecticide that is a highly toxic chlorinated hydrocarbon; if ingested or absorbed through the skin, it can cause potentially fatal neurotoxicity such as tremors and convulsions. Endrin is no longer registered as an active ingredient in Canada. (72-20-8) (PE)

Epidermal Langerhans' cells: Langerhans cells can be looked upon as “sentinel” cells of the immune system. They are among the first cells to come into contact with foreign particulate substances encountering the skin. By means of specialized receptors on the cell membrane, the Langerhans cell recognizes invading as opposed to host molecules. By conveying this information to the lymphoid system, the body is able to mount a defensive immunological response to the foreign material. (UR)

Epigenetic events: Events that do not initiate a tumour but, rather, influence the time to the appearance of the tumour.

Erythema: An abnormal redness of the skin due to capillary congestion as in inflammation (sunburn). (UR)

Ester: A compound resulting from the reaction of an acid with an alcohol, so that the hydrogen of the acid is replaced by the hydrocarbon radical of the alcohol. Animal and vegetable fats and oils are esters. (PE, OC, PP)

Estrogen receptor agonist activity: A chemical compound similar to estrogen (in structure) can bind with estrogen's natural receptor and compete with estrogen for space on the estrogen receptors.

Estrogen receptor-negative cases: Breast cancer cases with levels of estrogen receptor protein equal to or less than 10 fmol/mg; as measured in breast cancer cells.

Estrogen receptor-positive cases: Breast cancer cases with levels of receptor protein above 10 fmol/mg as measured in the cytoplasm of breast cancer cells.

Ethalfuralin/ethyl fluralin: *N*-ethyl- α,α,α -trifluoro-*N*-(2-methylallyl)-2,6-dinitro-*p*-toluidine (C₁₃H₁₄F₃N₃O₄). A dinitroaniline selective pre-emergence herbicide commonly used in Canada to control annual grasses and broadleaf weeds in a variety of crops. Trade names are Sonalan and Curbit. (55283-68-6) (PE)

Ethoprop: *O*-ethyl *SS*-dipropyl phosphorodithioate (C₈H₁₉O₂PS₂). A thiophosphate insecticide and nematocide. Trade names: Mocap, Ethoporphos, Propfos, Rovokil. It acts by inhibiting photosynthesis and is used on sugar cane, potatoes, tobacco, corn, pineapples, beans and cucumbers and for golf course and industrial lawn applications. (13194-48-4) (PE)

Ethyl mercaptan: Mercaptans are thiols. They are analogs of alcohols, having a sulphur atom instead of the oxygen atom in the alcohol. The sulphur atom gives them a strong disagreeable odour, akin to the smell of skunk. Ethyl mercaptan (CH₃CH₂SH) is the analog of ethanol (CH₃CH₂OH). (PP)

Ethylan: 1,1-dichloro-2,2-bis(4-ethylphenyl) ethane (C₁₈H₂₀Cl₂). An organochlorine insecticide. It is also called Perthane and ethyl-DDD. It has been discontinued. Practically insoluble in water. It was used for home mothproofing and for moths and carpet beetles in the dry cleaning and textile industries. It was also used on fruit and vegetable crops. (72-56-0) (PE)

Ethylene dibromide: (C₂H₄Br₂). A soil and post harvest fumigant insecticide. (106-93-4) (PE)

Ethylene oxide (Oxirane): (C₂H₄O). Used as a fumigant. (72-21-8) (PE)

Etiological period: A period of exposure, prior to the onset of disease, during which the disease process was likely initiated.

Excess relative risk model: A mathematical model derived to calculate relative risks of developing the disease based on

multiplicative effects (multiple causes). The model implies that the risk is greater than the sum of the risks calculated independently.

Exposure-response relationship: The intensity, duration, and the onset of the response (or manifestation) caused by the exposure. The science of toxicology is based on the principle that there is a relationship between a toxic reaction (the response) and the amount of poison received (the dose). An important assumption in this relationship is that there is almost always a dose below which no response occurs or can be measured. A second assumption is that once a maximum response is reached any further increases in the dose will not result in any increased effect. The toxic effects on an organism are related to the amount of exposure.

Extractives: Products of industries that specialize in obtaining natural substances, such as fossil fuels, from the Earth. Extractive industries include mining, and coal and gas production. (PP)

Familial atypical multiple mole – melanoma syndrome: See Dysplastic nevus syndrome.

Fatty acids: Any of a large group of organic acids made up of molecules containing a carboxyl group (COOH) at the end of a long hydrocarbon chain; the carbon content may vary from C₂ to C₃₄. The more common fatty acid residues that occur in higher plants and animals are palmitic, oleic, linoleic and stearic acids. (PP)

Fenitrothion: *O,O*-dimethyl *O*-4-nitro-*m*-tolyl phosphorodithioate (C₉H₁₂NO₅PS). A thiophosphate insecticide and selective acaricide of low ovicidal properties. (122-14-5) (PE)

Fibroblasts: The principal nonmotile cells of connective tissue. Fibroblasts produce an amorphous, gel-like substance that fills the spaces between cells and fibres in connective tissue. (UR)

Fibrotic lung: Formation of fibrosis tissue in the lung. (MM)

Fluorite: (CaF₂). A transparent, crystalline mineral that occurs in many colours; calcium fluoride. It is used for fusing metals, making glass etc. (MM)

Fmol (femtomole): One quadrillionth of a mole or 10⁻¹⁵ mole.

Folpet: *N*-(trichloromethylthio)phthalimide (C₉H₄Cl₃NO₂S). A carboximide compound and protective foliage fungicide. Its mode of action inhibits normal cell division of a broad spectrum of microorganisms. It is used to control cherry leaf spot, rose mildew, rose black spot, and apple scab. Used on berries, flowers, ornamentals, fruits and vegetables, and for seed- and plant-bed treatment. Also used as a fungicide in paints and plastics, and for treatment of internal and external structural surfaces of buildings. (133-07-3) (PE)

Fonofos: *O*-ethyl *S*-phenyl(*RS*)-ethylphosphonodithioate (C₁₀H₁₅OPS₂). A soil organophosphate insecticide primarily used on corn. It is also used on sugar cane, peanuts, tobacco, turf, and some vegetable crops. Fonofos controls aphids, corn borer, corn rootworm, corn wireworm, cutworms, white grubs, and some maggots. All uses have been discontinued in Canada. (944-22-9) (PE)

Formaldehyde: (CH₂O). An unclassified fungicide and bactericide. (50-00-0) (PE)

Formic acid: (CH₂O₂). A colourless caustic liquid found especially in ants and in many plants and used chiefly in the dyeing industry. (PP)

Free radicals: Reactive molecular fragment with one un-paired electron. (PE)

Fugitive emissions: Toxic emissions released by the pulp and paper and other industries. They include the group of reduced sulphur compounds (collectively called total reduced sulphur or TRS) and the oxides of sulphur and nitrogen. (PP)

Fumigant: Small, volatile, organic molecules that become gases at temperatures above 40°F. They are usually heavier than air and commonly contain one or more of the halogens (Cl, Br, or F). Most are highly

penetrating, reaching through large masses of material. They are used to kill insects, insect eggs, nematodes, and certain microorganisms in buildings, warehouses, grain elevators, soils, and greenhouses and in packaged products such as dried fruits, beans, grain, and breakfast cereals. (PE)

Fungicide: An agent that destroys fungi including their spores. (PE)

Furans: See Polychlorinated dibenzofurans (PCDFs).

Furfural: A furan ring having an aldehyde group attached to it. Furan is a five-member ring having four carbons and one oxygen atom in it. (PP)

Galena: (PbS). A grey metallic ore consisting of lead sulphide. It is the most important source of lead. (MM)

Gamma rays/radiation: High-energy, short wavelength, electromagnetic radiation emitted from the nucleus. Gamma radiation frequently accompanies alpha and beta emissions and always accompanies fission. Gamma rays are very penetrating and are best stopped or shielded by dense materials, such as lead or depleted uranium. Gamma rays are similar to X rays. (R)

Garnet: A brittle silicate mineral occurring mainly in red crystals. The transparent, deep-red variety is used as a semiprecious gemstone; other varieties are used as abrasives. (MM)

Generalized estimating equation: A unified and flexible approach to estimating model parameters when it is not desirable and/or possible to make particular distributional assumptions about the observed data. (AP)

Genetic epidemiology: The science that deals with the manifestation, distribution and control of heritable diseases in populations.

Genotoxic effects/genotoxicity: Damage of cellular DNA by a chemical or other agent, resulting in mutations or cancer.

Genotype: An individual's genetic makeup underlying a specific trait or constellation of traits.

Geological-tectonic setting: A description of the conditions (climate, faulting, etc.) that were in force at the particular place and time that the rocks were formed. (MM)

Geometric mean: A measure of central tendency based on the logarithm of the individual values.

Germline mutation: A change in the genetic material (DNA) of the germ cells (sperm and ovum) with a potential to transmit the change from one generation to the other.

Glioma: A type of brain cancer. (ET)

Gluconic acid: (C₆H₁₂O₇). A crystalline acid obtained by oxidation of glucose and used chiefly in cleaning metals. (PP)

Glutathione depletion: Glutathione is a compound in the body that prevents oxidative stress in most cells and helps to trap free radicals that can damage DNA and RNA. As individuals grow older, glutathione levels drop, and the ability to detoxify free radicals decreases. (MM)

Glyphosate: *N*-(phosphonomethyl) glycine (C₃H₈NO₅P). A broad-spectrum non-selective systemic herbicide used to control annual and perennial plants. (1071-83-6) It should be stated which salt or ester is present: glyphosate-isopropylammonium (38641-94-0), glyphosate-sesquisodium (10393-85-0), or glyphosate-trimesium (81591-81-3). (PE)

Granulomatous lung disease: A granuloma (tumour-like mass or nodule) in the lung. (MM)

Gravimetric sampling: A method of quantitative chemical analysis in which the constituent sought is converted into a substance of known composition that can be separated from the sample and weighed, or a weight difference can be applied without any separation. (MM)

Gray (Gy): The international system (SI) unit of *absorbed dose*. One gray is equal to an absorbed dose of 1 Joule/kilogram.

Ground water: That portion of the water below the surface of the ground whose pressure is greater than atmospheric pressure. (DB)

Guanine: (C₆H₆N₄O). One of the bases in DNA and RNA. It is a purine, an aromatic heterocyclic compound made up of two fused rings, a six-membered ring of four carbon atoms and one nitrogen atom with an oxygen attached to one of the carbons and an amino (NH₂) group attached to another of the carbon atoms, fused to a five-membered ring that shares two carbon atoms with the six-membered ring. This ring is made up of three carbon atoms and two nitrogen atoms. (73-40-5) (PE)

Gymnosperms: Vascular plants that bear naked seeds not enclosed in any specialised chambers such as ovaries. Softwoods, such as pines and firs, are gymnosperms. (PP)

Gypsum: (CaSO₄·2H₂O). A mineral used for making plaster of Paris, fertilizer, etc.; hydrated calcium sulphate. Alabaster is one form of gypsum. (MM)

Half-life: The period required for half of the atoms of a particular radioactive isotope to decay and become an isotope of another element. Half-lives can range from less than a millionth of a second to millions of years depending upon the element concerned. After one half-life, the level of radioactivity of a substance is halved, after two half-lives it is reduced to one quarter, after three half-lives to one-eighth and so on. (R)

Halocarbon: Any compound of carbon and one or more halogen (bromine, chlorine, iodine, fluorine) atoms. (PE)

Halogen: Any one of the chemical elements, iodine, bromine, chlorine, fluorine and astatine, that combine directly with metals to form salts. The halogens are the most active elements. (DB)

Halogenated: Containing one or more halogen atoms, i.e., fluorine, chlorine, iodine, bromine or astatine. (DB)

Halogenated acetic acids (HAAs): Acetic acid in which one or more hydrogen atoms

are substituted with appropriate numbers of halogen atoms (e.g., chlorine). HAAs are formed along with other disinfection by-products when chlorine or other disinfectants used to control microbial contaminants in drinking water react with naturally occurring organic and inorganic matter in water. The major haloacetic acids are: mono-, di-, and trihaloacetic acids, and mono- and dibromoacetic. (DB)

Halogenated acetonitriles: Various halogenated acetonitriles have been detected in chlorinated drinking water samples, the brominated acetonitriles being formed when bromide is present in the water during chlorination. Dichloroacetonitrile is the most abundant of the acetonitriles. (DB)

Halogenated hydrocarbons: One of a group of halogen derivatives of organic compounds. (DB)

Halogenated volatile organics: See Volatile organic compounds. (VOCs)

Halogenation: The introduction of a halogen atom (fluorine, chlorine, bromine, iodine and astatine) into an organic compound (or molecule) by addition or substitution. (DB)

Hazard ratio (relative rate, rate ratio, incidence density ratio, instantaneous relative risk): A useful measure in etiological research that quantifies the strength of the relationship between exposure and risk.

HCB: See Hexachlorobenzene.

HCH: See Hexachlorocyclohexane.

Healthy worker bias: A bias resulting from generalizing findings from studies conducted on occupational groups because working people are relatively more fit and healthy compared to the population in general.

Hemicellulose: (C₆H₁₀O₅)_n. A type of polysaccharide in plant cell walls whose chemical composition is more complex than sugar and less complex than cellulose. (PP)

Heptachlor: (C₁₀H₅Cl₇). A cyclodiene insecticide first isolated from technical chlordane in 1946. During the 1960s and 1970s, it was used primarily by farmers to kill ants, and soil insects in seed grains and on crops, as well as by exterminators and homeowners to kill termites. Before heptachlor was banned, formulations available included dusts, wettable powders, emulsifiable concentrates, and oil solutions. It acts as a nonsystemic stomach and contact insecticide. (76-44-8) (PE)

Heterocyclic aromatic compounds: Aromatic compounds with an atom other than carbon (e.g., oxygen, nitrogen or sulphur). (OC)

Heterogeneity: The condition or state of being different in kind or nature. The quality of certain genetic disorders that consist of two or more fundamentally distinct entities.

Hexachlorobenzene (HCB): (C₆Cl₆). An aromatic compound used as a selective fungicide for seed protectant treatment (usually for wheat) against common and dwarf bunt. It acts as a fumigant on fungal spores. It is highly persistent. Registration in Canada was discontinued in 1976. Today, trace amounts continue to enter our environment through long-range atmospheric transport, the manufacture and use of industrial chemicals that contain HCB and various industrial and municipal emissions. (OC, PE)

Hexachlorocyclohexane (HCH): (C₆H₆Cl₆). An organochlorine (also known as benzhexachloride - BHC) which has five isomers, alpha, beta, gamma, delta and epsilon. The gamma isomer was isolated and sold as an insecticide under the name lindane. HCH acts in the body similarly to DDT, but much more rapidly. (58-89-9) (OC, PE)

Host factors: Host factors are traits which make an individual at risk (or susceptible) of acquiring a particular disease or health disorder. For instance, the host factors for melanoma are: racial/ethnic origin, pigmentation, skin reaction to sunlight, nevus and freckle density.

HPV: See Human papilloma virus.

Human papilloma virus (HPV): A group of relatively small DNA viruses, many of which are oncogenic or potentially oncogenic.

Human T-lymphocytes: Lymphocytes (white blood cells) originate, in postnatal life, from stem cells in the bone marrow; these stem cells divide continuously, releasing immature lymphocytes into the bloodstream. Some of these travel to the thymus, where they multiply and differentiate (i.e., acquire special properties and functions). The term T lymphocyte (or T cell) stands for thymus-derived lymphocyte (or cell). Once they have left the thymus, T cells join the bloodstream and circulate to and within the rest of the lymphoid organs, where they can multiply further in response to appropriate stimulation. About half of all lymphocytes are T cells.

Hydrocarbons: A class of organic compounds composed entirely of hydrogen and carbon atoms. (DB, OC, PE, PP)

Hydrogen sulphide: (H₂S). An ill-smelling, colourless, flammable, highly toxic gas, used as a reagent in chemical manufacturing. (MM, PP)

Hydrometallurgy: The extraction of metal from ore by using aqueous solutions. It usually involves dissolution of the metal or metal compound by water (sometimes with additional agents such as dilute sulphuric acid), purification of the solution, and recovery of metal from the solution by chemical or electrolytic means. Gold, silver, copper, zinc and many other metals are extracted in this way. (MM)

Hydroxymethylfurfural: Furfural with an hydroxyl methyl (CH₂OH) group attached to the ring. (PP)

Hypochlorite: A salt of hypochlorous acid used during the treatment of pulp to remove lignin and bleach the pulp. The velocity of this reaction is directly proportional to the amount of hypochlorite used, but the risk with a fast reaction with high concentrations of hypochlorite is a subsequent decrease in paper strength. (PP)

Hypochlorous acid: (HOCl). An unstable acid used as a bleach and disinfectant. (PP)

IARC: International Agency for Research on Cancer.

Imide: A compound containing the -CO-NH-CO- group. (PE)

Immunosuppression: The artificial prevention or diminution of the immune response.

In-vivo: Within a living organism: metabolic studies conducted *in vivo*; *in vivo* techniques. As opposed to *in vitro* in which the experiment is conducted in a laboratory environment or in a test tube.

Induction period: See Latency period.

Interaction: The effect of one factor varies according to the level of another factor.

Interpolate: To infer or to estimate the value of a variable within the range sampled.

Interpolation error: Unwarranted high confidence in the interpolated values.

Intrusions/intrusive rock: Rock that was forced into fissures or between strata when molten. (MM)

Inverse exposure/dose-rate effect: For equal total exposure, a high exposure rate and short duration is less harmful than a low exposure rate and long duration. When a more protracted dose is delivered, a higher percentage of the cells have the potential to be affected during a sensitive part of their cell cycle. This results in a higher chance of malignant transformation. (R)

Ionizing radiation: Highly penetrating radiation that results in the formation of ions by displacement of electrons from their path of orbit. Ionizing radiation is capable of breaking chemical bonds, thus causing damage to living tissue through which it passes. (EF, R)

Iron oxides: The main types of iron ore that can be mined profitably for iron. The most common forms are hematite (Fe₂O₃), goethite (α-FeO(OH)), magnetite (Fe₃O₄) and siderite (FeCO₃). (MM)

Isomers: Two or more compounds identical in molecular formula, but having different structural arrangements and exhibiting different properties. (PP, OC, PE)

Isoprene: (C₅H₈). A volatile liquid hydrocarbon used in synthetic rubber and turpentine. (PP)

Isotopes: Any two or more forms of an element having identical or very closely related chemical properties and the same atomic number but different atomic weights or mass numbers. (R)

Isotropy: The condition of having the same or similar values in all directions. For air pollution studies it states that the closer the distance between the two locations, the more similar the concentration levels are. (AP)

Job-exposure matrix: An array of data in rows and columns specially designed to present the duration and intensity of exposure(s) associated with a particular job and to translate job task histories into estimates of exposure to specific agents. It consists of jobs on one axis and specific exposures on the other, with the matrix elements describing the likelihood of an individual's exposure to a specific substance in a given job either in binary or polytomous categories.

Joule: A unit for measuring energy. One joule is the amount of work done, or energy used, in applying one newton of force to move a body one metre in the direction of the force. (EF)

K-ras gene: K-ras is one member of the Ras family of genes. These genes code for a group of closely-related proteins that are involved in the regulation of normal cell growth and proliferation. K-ras is located on chromosome 12, and is involved in cell cycle control. Mutations in this gene have been associated with several types of cancer, including lung cancer, such that it is considered to be a proto-oncogene. K-ras oncogene activation is known to occur at an early stage in tumorigenesis and maybe an important diagnostic marker. See Biomarkers.

Kaiser Permanente cohort: A cohort of individuals enrolled in the Kaiser Permanente health insurance plan that has been extensively studied by epidemiologists.

Ketones: Any of a class of organic compounds having a carbonyl group (CO) linked to hydrocarbon groups. (PP)

Komatiitic: Like a komatiite or containing komatiite. A komatiite is a series of very old (older than 590 million years) lava flows that were very hot (> 1600 degrees C) when they were extruded onto the Earth's surface. (MM)

Konimeter: A device for measuring the number of particles in the air, as in a mine or cement plant. (MM)

Kraft (sulphate) pulping process: The principal method of chemical pulping. It involves using sodium hydroxide and sodium sulphate to break down the wood and separate the cellulose fibre from the lignin. (PP)

Kriging: A weighted moving average interpolation (extrapolation) method that minimizes the estimated variance of a predicted point (node) with the weighted average of its neighbors. (AP)

Latency/induction period: Delay between the exposure to a disease-causing agent and the appearance or manifestation of the disease.

Lateritic: Similar to, or containing, a laterite. A laterite is a red soil with large amounts of iron and/or aluminum oxides created by weathering. It forms in forested areas in tropical or temperate climates. (MM)

Leaching: Preferential dissolution of a component using an aqueous solution in order to separate it from other components. (MM)

Lead-210: In the series of unstable products from the radioactive decay of uranium-238, lead-210 results from the decay of radon-222 and is a precursor of the stable isotope lead-206. (R)

LET: See Linear energy transfer.

Lignin: After cellulose, the complex polymer, lignin, is the largest component of wood, accounting for about 25% of wood composition. (PP)

Lime: Calcium oxide (CaO). Manufactured by heating limestone, coral, sea shells, or chalk (made of CaCO₃) to drive off the carbon dioxide (CO₂), leaving CaO. (PP)

Lime kiln: A furnace used to calcinate limestone. (PP)

Lindane: (C₆H₆Cl₆). Gamma HCH. One of the eight isomers of hexachlorocyclohexane (HCH) and the only organochlorine insecticide still licensed for use in Canada. An ingredient in Kwell® shampoo used to control head lice. (58-89-9) (PE)

Linear energy transfer (LET): The amount of energy deposited by an ejected particle per unit of the track length over which it is deposited. Generally speaking, high LET radiation is more effective at inducing cell damage than low LET radiation. (R)

Linear regression analysis/model: A method of describing the relationship between two or more variables by calculating a best fitting straight line.

Linuron: 3-(3,4-dichlorophenyl)-1-methoxy-1-methylurea (C₉H₁₀Cl₂N₂O₂). A phenylurea herbicide. Controls broadleaf and grassy weeds by inhibiting photosynthesis. Used on crop and non-crop sites for a variety of vegetable and fruit crops as well as for wheat. It is slightly to moderately soluble in water and is not readily broken down in water. (330-55-2) (PE)

Lipid fractionation: The procedure for separating lipids from other cellular constituents, using organic solvents (e.g., chloroform, methanol), in which they dissolve.

Lipophilic: Tending to combine with or dissolve in lipids. PCBs, for example, dissolve in the lipids of cells.

Lode gold deposits: Veins of gold. (MM)

Logistic regression: Statistical analysis estimating the magnitude of the association between an exposure and a binary outcome after adjusting simultaneously for a number of potential confounding factors.

Long-Evans cinnamon rat: A mutant strain displaying hereditary hepatitis and spontaneous hepatocellular carcinoma, and showing abnormal hepatic copper accumulation, similar to Wilson's disease in humans.

Macrophage: A large mononuclear cell that ingests degenerated cells, blood tissue, and small exogenous particles; found in large numbers throughout the body, with the greatest accumulation in the spleen, where they remove damaged or aging red blood cells from the circulation.

Mafic-ultramafic: One of three classifications of igneous rocks based on chemical composition (the others are alkaline and calc-alkaline). These rocks are typically dark in colouration, and make up most oceanic crust. They are also found on continents, typically in rift valleys (where continents are pulled apart and new ocean basins form the break), and in flood basalts (a type of lava flow involving a very large volume of lava). (MM)

Magmatic bodies/hosts: See Intrusions.

Magnetic field: The region of magnetic influence or force around a magnet, a magnetic body such as the Earth, or a body carrying an electric current. Also the magnetic forces present in such a region. (EF)

Magnetic flux density: A measure of magnetic field strength per unit area, quantified by units of tesla (T) or gauss. (EF)

Malathion: diethyl (dimethoxythiophosphorylthio)succinate (C₁₀H₁₉O₆S₂). Also known as carbophos, maldison, and mercaptotion. A wide-spectrum aliphatic organophosphate insecticide commonly used in Canada to kill insects on fruits and vegetables, for mosquito control and to kill head and body lice. (121-75-5) (PE)

Mammary tumours: A mass or a tumour located in human breasts or mammary glands.

Mancozeb: Manganese ethylene bis(dithiocarbamate) (polymeric) complex with zinc salt. A dithiocarbamate fungicide that has a very low acute toxicity to mammals. The major routes of exposure to mancozeb are through the skin or from inhalation. Mancozeb sprays and dusts are moderately irritating to the skin and respiratory mucous membranes. (8018-01-7) (PE)

Matched case-control study: A case-control study in which the controls are matched to the cases on factors that could confound the results, should they differ between the two groups. Some commonly matched variables are age, gender, race, and socio-economic status.

Matching: The process of making a study group and a comparison group comparable with respect to variables such as age and sex.

MCPA: See 4-chloro-2-methylphenoxy acetic acid.

Meiotic chromosomal aberrations: Germline mutation resulting from meiosis (cell division whereby each daughter cell receives half the number of chromosomes). These mutations may be transmitted to the progeny.

Melamine formaldehyde: A thermosetting resin made from melamine (a white crystalline compound, C₃H₆N₆) and formaldehyde (a colourless, pungent gaseous aldehyde, CH₂O) used in solution as a disinfectant and preservative. (PP)

Melanoma: A spreading and frequently recurring cancer of specialized skin cells (melanocytes) that produce the protective skin-darkening pigment melanin. Although it represents approximately five % of all cases of skin cancer, melanoma is responsible for nearly three-quarters of all skin cancer deaths.

Meningioma: A common type of benign brain tumour that infiltrates adjacent brain tissue, but does not metastasize. Includes

astrocytoma, oligodendroglioma and ependymoma.

Mercaptans: Any substance containing the radical -SH bound to carbon; analogous to alcohols and phenols, but containing sulphur instead of oxygen. (PP)

Mesothelioma: A benign or malignant tumour affecting the lining of the chest or abdomen. Pleural mesothelioma has been associated with exposure to asbestos. (MM, PE)

Meta-analysis: The process of using statistical methods to combine the results of several different studies to produce a weighted summary estimate of risk.

Metabolites: Substances produced by metabolism or metabolic processes. Any substance involved in metabolism (either as a product of metabolism or as necessary for metabolism).

Metallic nickel: A silvery white metal that is moderately hard. It is both malleable and fairly ductile. Metallic nickel is an important industrial metal used in the manufacture of special alloy steels and cast irons. (MM)

Metam sodium: Sodium methylthiocarbamate (C₂H₅NS₂Na). Also known as metham, methylthiocarbamic acid, carbam and carbathion. A leading broad spectrum fumigant used in Canada, primarily as a liquid fumigant for pre-planting control of soil-borne fungi. It is also used to control nematodes and weeds affecting a variety of important fruit and vegetable crops. It degrades rapidly to methyl isothiocyanate the primary bio-active agent. (137-42-8) (PE)

Metamorphic rock: Rock derived from either igneous or sedimentary rock that has undergone changes in composition, texture, or internal structure through the action of pressure, heat, moisture, etc. Slate is a metamorphic rock formed from shale. (MM)

Methidathion: (C₆H₁₁N₂O₄PS₃). An organothiophosphate insecticide and acaricide. The compound is used to control a variety of insects and mites in many crops such as fruits, vegetables, tobacco, alfalfa and sunflowers and is also used in greenhouses. All

uses have been discontinued in Canada. (950-37-8) (PE)

Methyl isothiocyanate: (CH_3NCS). Also known as MITC, Methyl Mustard, Isothianic Acid Methyl Ester, Vorlex and MIT. A colourless solid, the vapors are heavier than air and it can cause severe burns. It is an unclassified fungicide, herbicide and nematicide. All uses have been discontinued in Canada. (556-61-6) (PE)

Methyl mercuric chloride/methyl mercury chloride: Methyl mercury (II) chloride (chloromethyl mercury) (CH_3ClHg). White crystals used in the manufacture of pharmaceuticals and pesticides. (115-09-3) (PE)

Methylene chloride: See Dichloromethane.

Metolachlor: (α -RS, 1RS)-2-chloro-6'-ethyl-N-(2-methoxy-1-methylethyl) acetotoluidide ($\text{C}_{15}\text{H}_{22}\text{NO}_2$). Trade names are Bicep, CGA-24705, Dual, Pennant, and Pimagram. A chloroacetanilide general use herbicide used in Canada primarily for the control of grasses in corn, beans, soybeans and other crops. It is often used in formulations with other pesticides, often herbicides that control broad leaf weeds. (51218-45-2) (PE)

Mirex: ($\text{C}_{10}\text{H}_{12}$). A chlorinated cyclodiene insecticide used especially against ants. It is no longer registered as an active ingredient in Canada. (2385-85-5) (OC) (PE)

Misclassification: The erroneous classification of an individual, a value, or an attribute into a category other than that to which it should be assigned. The probability of misclassification may be the same in all study groups (non-differential misclassification) or may vary between groups (differential misclassification).

Mitotic chromosomal aberrations: Mutations or chromosomal changes (sister chromatid exchange, chromosome breakages) during mitosis (cell division without dividing the number of chromosomes). These mutations are typically not transmitted to the progeny. (PE)

Modelling: The act of representing or describing a phenomenon or set of relationships in mathematical terms to aid understanding;

set assumptions about relationships used to study their interactions.

Mole: A unit for measuring amounts of substances that take part in chemical reactions. (OC)

Molecular epidemiology: A branch of epidemiology where the researcher studies specific gene behaviour (or other biological molecules) with the aim of associating cancer-related genetic alterations with specific exposures.

Monomer: A chemical compound consisting of single molecules that can join together to form a polymer. (PP)

Monotonically increases: A sequence is said to increase monotonically if each value is greater than or equal to the previous one, and monotonically decreasing if each value is less than or equal to the previous one.

Moving average: A method of smoothing the curve representing the data. Each observation is replaced by a mean of the observation and the observations on either side of it.

Multiple traversals: Multiple 'hits' of individual cell nuclei by alpha particles. (R)

Mutagen: An agent (e.g., radiation) capable of altering the genetic material in living organisms, causing chromosomal damage, point mutations, sister chromatid exchanges, or functional defects in gene replication or cell division.

Mutagenic: Capable of inducing alteration (mutation) in genetic material.

Mutagenicity: The property of an agent (e.g., chemical substance, radiation) to induce mutation.

Mutation: A structural change within genetic material of an organism resulting in the creation of a new character or trait not found in the parental type.

MX: See 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone.

N-acetylation phenotype: The genetically-determined rate at which the liver enzyme N-acetyltransferase detoxifies compounds in the body. (ET)

N-nitroso-di-n-propylamine (NDPA): An unavoidable contaminant in trifluralin-containing products. (621-64-9) (PE)

Nabam: Disodium ethylene bis(dithiocarbamate) ($\text{C}_4\text{H}_6\text{N}_2\text{Na}_2\text{S}_4$). A dithiocarbamate fungicide/fumigant. (142-59-6) (PE)

Natural killer (NK) cells: Cells produced by the body's immune system to destroy or damage a variety of malignant target cells.

NDPA: See N-nitroso-di-n-propylamine.

Nested case-control design study: A case-control study in which cases and controls are drawn from the population in a cohort study.

Neutron: An uncharged elementary particle with a mass slightly greater than that of the proton, and found in the nucleus of every atom heavier than hydrogen. (R)

Newton: A unit for measuring force. One newton is the force required to give an acceleration of one metre per second to a mass of 1 kg. (EF)

Nickel carbonyl: ($\text{Ni}(\text{CO})_4$). Carbon monoxide reacts with nickel to produce the volatile compound nickel carbonyl. (MM)

Nickel carbonyl process: A process used to separate nickel from other metals and impurities. After iron and copper have been removed by smelting the ore and slow-cooking the nickel matte, the impure nickel is combined with carbon monoxide at 60°C to make the compound tetracarbonylnickel, $\text{Ni}(\text{CO})_4$, which is subsequently decomposed at above 200°C to yield metallic nickel that is 99.8% pure. (MM)

Nickel matte: An impure mixture of sulphides produced during the smelting of nickel sulphide ore. (MM)

Nickel subsulphide: (Ni_3S_2). A major component in the refining of nickel ores.

Synonyms: heazlewoodite, nickel sulphide (3:2), and trinickel disulphide. (MM)

Nickel sulphate hexhydrate: ($\text{NiSO}_4 \cdot 6\text{H}_2\text{O}$). A water-soluble compound of nickel that is used in nickel plating, as a mordant in dyeing and printing textiles, as a blackening agent for zinc and brass, and in the manufacture of organic nickel salts. (MM)

Nitriles: Compounds containing the cyano (CN) group. (PE)

Nitrogen oxides: Inorganic oxides that contain nitrogen (e.g., nitrogen oxide (NO), nitrous oxide (N_2O), and nitrogen dioxide (NO_2)). (AP)

Nitrophen: 2,4-dichlorophenyl 4-nitrophenylether ($\text{C}_{12}\text{H}_7\text{Cl}_2\text{NO}_3$). Also known as NIP and niclofen. A nitrophenyl ether herbicide. A pre- and post emergent herbicide for grasses and broadleaf weeds. It was used on food and ornamental crops but is no longer sold or manufactured in the US and Canada. (1836-75-5) (PE)

Nitrophenyl: A benzene ring where one of the hydrogen atoms has been replaced by a nitro (NO_2) group. (PE)

Nitrosamines: A group of chemical compounds with the structure $\text{R}_2\text{N-N}=\text{O}$. (ET)

Nitrosomethylurea (NMU): ($\text{C}_2\text{H}_5\text{N}_3\text{O}_2$). A solid material with a half life of 2-20 days in water. It degrades in ultraviolet and visible light. It is potentially explosive at room temperature and when heated gives off toxic fumes of nitrogen oxides. (684-93-5) (PE)

NK: See Natural killer cells.

NMU: See Nitrosomethylurea.

No-observed-(adverse)-effect level (NOEL)/ (NOAEL): A term from toxicology, meaning the highest dose at which no health effects are detected in the animal population. (PP)

NOEL (NOAEL): See No-observed-(adverse)-effect level.

Non-asbestiform amphibole: A mineral of the amphibole group that is not in the form

of fibrous needle-like crystals. The general definition of asbestos can include any fibrous mineral from the amphibole and serpentinite mineral groups. (MM)

Non-Hodgkin lymphoma: A group of lymphomas (cancer of the lymphatic system) which differ in important ways from Hodgkin lymphoma (also a type of lymphoma) and are classified according to the microscopic appearance of the cancer cells. The disease is classified as either low grade (slowly growing), intermediate grade or high grade (rapidly growing) and may be treated in a variety of ways depending on the exact diagnosis. Previously called lymphosarcoma.

Non-ionizing radiation: Radiation insufficient to split the chemical bonds of compounds. (EF)

Non-linear regression: A regression problem in which the parameters are nonlinear, which prevents the use of least squares criteria.

Non-parametric model: A statistical model that assumes that the population contributing the sample is not normally distributed regarding the variable under study i.e., the resulting statistical test is distribution free.

Non-selective herbicide: A herbicide that kills any vegetation. (PE)

Nucleotide: One of the compounds into which nucleic acid splits on hydrolysis, consisting of a nitrogenous base, a sugar, and a phosphate group. (PE)

Null hypothesis (H_0): The statistical hypothesis that two or more variables are not related or that two or more populations do not differ from one another. The null hypothesis states that the results observed in a study or an experiment are no different from what might have occurred just by chance.

Octachlorodibenzodioxin: A compound having eight chlorine atoms on the two

benzene rings that are attached to either side of the dioxin ring. This compound has no hydrogen atoms in its structure. (PP)

Odds ratio (OR): Main measure of risk derived from case-control studies that quantifies the relationship between an exposure and a health outcome. The ratio of two odds. Mathematically it is represented as ad/bc : a = number of people exposed who have the disease, b = number of people not exposed but have the disease, c = number of people exposed but do not have the disease, and d = number of individuals who have not been exposed and do not have the disease.

Ohm: Unit for measuring the resistance of a conductor to an electric current. A conductor has a resistance of one ohm if it takes one volt of pressure to send a current of one ampere through it. (EF)

Olfactometer: An instrument to test the sense of smell. (PP)

Olfactometry: A procedure to assess the sense of smell. (PP)

Oncogene: A mutated and/or over-expressed version of a normal gene of animal cells (the proto-oncogene) that, in a dominant fashion, can release the cell from normal restraints on growth and thus, alone or in concert with other changes, convert a cell into a tumour cell.

OPs: See Organophosphates.

Optical radiation: Optical radiation (10 nm–1 mm) is radiant energy within the broad region of the electromagnetic spectrum that includes ultraviolet radiation (UR), visible light, and infrared radiation. One nanometre [nm] is one billionth (10^{-9}) of a metre, or 10 angstrom units. (UR)

OR: See Odds ratio.

Organic compound: A compound containing carbon. (DB, OC, PP)

Organic materials: Natural substances derived from organisms and containing compounds of carbon (e.g., hydrocarbons, such

as crude oils and fossil fuels, or plant decay in soils). (DB)

Organobromides: Organic compounds, also known as brominated hydrocarbons, brominated organics and brominated synthetics, that contain hydrogen and bromine strongly bound to carbon. (PE)

Organochlorines: Organic compounds (also known as chlorinated hydrocarbons, chlorinated organics and chlorinated synthetics) that contain hydrogen and chlorine strongly bound to carbon. Many organochlorines are strongly lipophilic (fat-seeking) and tend to build up in the fatty parts of living creatures where they become more concentrated and toxic. (PP, OC, PE)

Organohalide: Any organic compound having one or more halogen atoms in its structure. See halocarbon. (PE)

Organophosphates (OPs): A class of insecticides (including also one or two herbicides and fungicides) derived from phosphoric esters. With the decision to phase out many of the persistent organochlorines, there was an increase use of organophosphates, despite their much greater acute human toxicity. Organophosphates are generally divided into three groups based on chemical similarities: aliphatics (e.g., malathion, dimethoate and dichlorvos), phenyl derivatives (e.g., parathion, fenitrothion) and heterocyclic derivatives (e.g., azinphos-methyl, chlorpyrifos, phosmet). OPs inhibit certain important enzymes of the nervous system, namely cholinesterase (ChE). This inhibition results in the accumulation of acetylcholine (ACh) at the neuron/neuron and neuron/muscle (neuromuscular) junctions or synapses, causing rapid twitching of voluntary muscles and finally paralysis. (PE, OC)

Organophosphorous: A compound containing phosphorous bound to an organic compound; several organophosphorous compounds are insecticides, as they are highly toxic cholinesterase inhibitors. (PE)

Organothiophosphate: An organic compound having a thiophosphate group in its structure. (PE)

Outlier: A subject or other unit of analysis that has extreme values on a variable. Outliers can distort the interpretation of the data and result in misleading statistics.

Oxidative damage: The action of free radicals on DNA.

Oxidative stress: A harmful condition that occurs when there is an excess of free radicals, a decrease in antioxidant levels or both.

Oxidic nickel: Nickel compounds that contain oxygen (e.g., NiO, (NiCu)O). (MM)

Oxime: Compounds containing the group C-NOH. (PE)

Ozonation: The application of ozone to water, wastewater, or air, generally for the purposes of disinfection or odour control. (DB)

Ozone: (O₃). A form of oxygen, containing three oxygen atoms per molecule. A very powerful oxidant which destroys small organisms in water, including cryptosporidium. Used in water treatment for disinfection or for taste and odour control. Ozone is an key indoor and outdoor air pollutant, and is associated with deleterious human health and environmental effects. (DB)

p53 gene: A gene involved in the control of the cell cycle. p53 is considered to be a tumour suppressor gene, because when the protein function is lost due to a mutation, tumour cells may be more likely to continue to grow and proliferate.

PAB: See Para-aminobiphenyl.

PAHs: See Polycyclic aromatic hydrocarbons.

Para-aminobiphenyl (4-aminobiphenyl/PAB): (C₁₂H₁₁N). A colourless solid with characteristic odour, used as a herbicide and also found in tobacco smoke. (92-67-1) (PE)

Parathion: *O,O*-diethyl *O*-4-nitrophenyl phosphorodithioate (C₁₀H₁₄NO₅PS). Also known as thiophos. An organothiophosphate insecticide. These chemicals act by interfering with the activities of cholinesterase. (56-38-2) (PE)

Parenchymal cells: Cells forming the parenchyma. Parenchyma is the essential or functional elements of an organ, as distinguished from its stroma or framework.

Particulate: Referring to, or produced by, particles (a tiny mass of material.), such as dust, minute germs, etc. (AP, PP)

Particulate matter (PM): Microscopic particles that vary in size and chemical make-up. For monitoring purposes, PM levels are classified as total suspended particulates (TSP), particles with diameters of 10 micrometers (µm) or less (PM₁₀), particles between 10 and 2.5 µm (PM_{10-2.5}), and particles with diameters of 2.5 µm or less (PM_{2.5}). Major sources of outdoor PM include industrial and vehicle emissions, road dust, agriculture, construction, wood burning, forest fires, pollen, spores, bacteria and volcanoes. PM can also be formed through atmospheric chemical reactions.

PCBs: See Polychlorinated biphenyls.

PCDFs: See Polychlorinated dibenzofurans.

PCP: See Pentachlorophenol.

Penetrance: The frequency with which a heritable trait is manifested in individuals known to carry the gene that causes it. Clinically, definition of penetrance often depends on the quality of clinical methodologies; for example, magnetic resonance imaging might demonstrate findings not previously recognizable. In the medical context, the gene is usually considered penetrant if diagnostic abnormalities can be demonstrated even if the individual is asymptomatic. In the biological context, the gene can be considered penetrant if it affects the function of the individual.

Pentachlorophenol (PCP): (C₆HCl₅O). A chlorinated hydrocarbon insecticide and fungicide. Pentachlorophenol is phenol with five chlorine atoms in place of the five hydrogen atoms on the ring. It is a solid that is used primarily to protect timber from fungal rot and wood-boring insects. PCP products are very toxic to plants and are used as pre-harvest defoliants and general herbicides. Their use as herbicides is currently restricted to nonagricultural uses

along drainage ditches, driveways, and fence rows. PCP, which is found throughout our environment, has been voluntarily withdrawn by manufacturers of wood for domestic use. PCP is classified as a possible human carcinogen, as it can cause cancer in male mice. (87-86-5) (PE, PP)

Pentlandite: ((FeNi)₉S₈). The main mineral that is mined for nickel, typically found in association with other sulphide ores such as chalcopyrite. (MM)

Peroxisome: A liquid-filled sac surrounded by a single membrane. Peroxisomes break down fatty acids and amino acids. These reactions produce hydrogen peroxide, which could harm cells if it were allowed to persist. An enzyme (catalase) breaks down the hydrogen peroxide to water and oxygen, both of which can be used by the cell. Peroxisomes also break down alcohol. The peroxisomes of the liver and kidneys break down nearly half of the alcohol that a person consumes.

Peroxisome proliferation: Increase in the number of peroxisomes as a result of an environmental hazard (e.g., insecticide).

pH: A measure of the acidity or alkalinity of water.

Phagocyte: Any cell that ingests microorganisms, other cells or foreign bodies.

Phenol: (C₆H₅OH). A benzene ring with an hydroxyl group (OH) in place of one of the hydrogen atoms. Phenols/phenolic compounds are caustic, poisonous and crystalline aromatic organic compounds present in coal tar and wood tar that, in dilute solution, are used as a disinfectant. (DB, PE, PP)

Phenotype: In genetics, the visible appearance of an organism, produced by the interaction of its genetic constitution with the environment.

Phenoxy herbicides: A class of herbicides containing the radical (C₆H₅O). (PE)

Phenyl: (C₆H₅). A univalent radical derived from benzene that forms the basis of phenol, and other aromatic compounds. (PP)

Phenyl propane: A form of propane with a phenyl group attached at one of the hydrogen bonding locations. Monomers of phenyl propane make up the lignin macromolecule, which is aromatic. (PP)

Phenylurea: (C₆H₅NHCONH₂). A benzene ring where one hydrogen is replaced by a urea group. (64-10-8) (PE)

Phorate: O,O-diethyl S-ethylthiomethyl phosphorodithioate (C₇H₁₇O₂PS₃). An organothiophosphate insecticide and nematocide. Trade names: Thimet, Rampart, Granutox and Agrimet. Used on corn, potatoes and cotton. Half-life in the soil is 2-173 days. In water it hydrolyzes and one of the products is formaldehyde. (298-02-2) (PE)

Phosmet: O,O-dimethylS-phthalimidomethyl phosphorodithioate (C₁₁H₁₂NO₄PS₂). An organothiophosphate insecticide. Also known as phthaliphos and PMP. (732-11-6) (PE)

Phosphates: Esters of phosphoric acid. (OC, PE)

Phosphinic acid: (H₃PO₂). A weak monobasic acid, also called hypophosphorous acid, that is used as a herbicide. (6303-21-5) (PE)

Phosphoric esters: See Phosphates.

Photon: A quantum (or packet) of energy emitted in the form of electromagnetic radiation. Gamma rays and X rays are examples of photons. (R)

Phthalate: The di-ester of phthalic acid. (PE)

Phthalic acid: (C₈H₆O₄). A benzene ring having two COOH groups attached to the carbon ring in place of hydrogen. (PE)

Phthalimides: Imides of phthalic acid. The N-trihalomethyl dithio derivatives are referred to as phthalimides (e.g., folpet and captofol). They are fungicides and are structurally similar to thalidomide. They act as germination inhibitors. (PE)

Pigmentary factors: Host factors, such as fair skin, light eye and hair colour, that put an individual at increased risk of acquiring CMM (Cutaneous Malignant Melanoma). (UR)

Pitchblende: One of the primary mineral ores of uranium, containing three chemical elements – uranium, polonium and radium. (R)

PM₁₀: An airborne particle with a diameter of no more than 10 µm. See Particulate matter. (AP)

Point sources: Situations, places and events which increase the risk of exposures (e.g., concentrations of air pollutants may be higher in a heavily travelled road or an industry producing noxious fumes).

Point-in-time measures: Measurements (usually made under as-is conditions) taken at one time, as opposed to continuous measurements.

Polyaromatic hydrocarbon: Hydrocarbons having more than one aromatic (likely benzene) ring. (Hydrocarbons are a class of organic compounds composed entirely of hydrogen and carbon.) (OC)

Polychlorinated: A chemical compound with more than one chlorine atom. For example, a hydrocarbon with three chlorine atoms attached to either the main carbon chain or a side chain, would be polychlorinated. (PP)

Polychlorinated biphenyls (PCBs): A family of 209 structurally related chemical compounds consisting of two benzene rings and one to ten chlorine atoms. PCBs are stable and non-flammable, appearing as either a clear mobile oil (12%-48% chlorine content) to a white or off-white powder (68% chlorine content). They are hydrophobic (lack affinity to water) and lipophilic. Most are environmentally persistent. PCBs were first produced for industrial purposes in 1929 and were used for several decades in capacitors and transformers, hydraulic fluids, adhesives, plasticizers, heat exchange equipment, inks, lubricants, sealants, caulking compounds and carbonless copy paper. In 1968 an outbreak of PCB poisoning in Japan raised concerns about the toxicity of these substances. Significant quantities remain in certain types of electrical equipment. (OC)

Polychlorinated dibenzofurans (PCDFs):

Any of a class of organic compounds of the heterocyclic aromatic series characterized by a ring structure composed of one oxygen atom and four carbon atoms. The simplest member of the furan family is furan itself, a colourless, volatile, and somewhat toxic liquid. Furans are like dioxins, but they have one oxygen atom instead of two. They have a similar range of toxicity as dioxins. (OC, PP, MM)

Polychlorinated dibenzo-p-dioxins:

Any in a family of over 200 chlorinated organic chemicals of which 2,3,7,8-tetrachloro-p-dibenzo-dioxin (2,3,7,8-TCDD or TCDD) is the most toxic. TCDD was an impurity in the defoliant Agent Orange and in the pesticide 2,4,5-T. Dioxins are also produced when chlorinated materials, such as some plastics, are burned. (OC, MM, PE, PP)

Polychloroterpene:

A terpene is any of a group of hydrocarbons made up of building blocks of isoprene (C₅H₈). A polychlorinated terpene would have more than one chlorine atom in its structure. (PE)

Polycyclic aromatic hydrocarbons (PAHs):

A family of complex organic compounds derived by fusion of two or more benzene rings. PAHs are naturally present in fossil fuels and are also formed by the partial combustion of fossil fuels, organic matter and garbage. Canadians are exposed to PAHs primarily through tobacco smoke, wood smoke, contaminated air and food, particularly meat and fish. In Canada, the highest levels of PAHs in soil are found near former gas plants, coking plants and wood-preserving facilities. (AP, ET, MM, PE)

Polycyclic hydrocarbons:

Hydrocarbons having two or more rings sharing at least one carbon atom. (OC)

Polymer:

Any of a large number of natural or synthetic, organic or inorganic compounds composed of very large molecules that are made up of many light, simple molecules chemically linked together. Cellulose and proteins are naturally-occurring polymers; concrete, plastics and glass are synthetic polymers. (PP)

Polymerization: The chemical process that enables the bonding of two or more single unit or simple compounds (monomers) to form a larger compound (polymer) usually of high molecular weight. (PP)

Polymorphisms: Variant forms of a particular gene that occur simultaneously in a population. (AP)

Polysaccharide: A carbohydrate containing a large number of saccharide units, such as starch and glycogen. (PP)

Pooled analysis: The process of combining epidemiological data from several different studies at the level of the individual to produce a summary estimate of risk.

Population attributable risk: A measure of the proportion of disease in a population that can be attributed to a particular exposure.

Porphyry copper deposit: A low grade ore, less than one percent copper, that can be mined in bulk for copper. A porphyry is an igneous rock containing more than 25% large crystals (phenocrysts) embedded in a 'ground mass' of much smaller crystals. The copper is typically present in the form of chalcopyrite (CuFeS₂) within the ground mass. (MM)

Post-emergence herbicides: Herbicides used to destroy or inhibit plant growth after emergence. (PE)

Power boiler: See Recovery furnace.

Power frequency: The frequency at which power is generated and distributed; in most of North America it is 60 HZ (hertz). (EF)

ppb: Parts per billion; a measure of concentration. May represent the concentration of a residue in soil, water or whole animals. For example, one ppb is equivalent to one second in 32 years.

ppm: Parts per million; a measure of concentration. May represent the concentration of a residue in soil, water or whole animals. For example, one ppm is equivalent to one minute in 2 years.

Pre-emergence herbicides: Herbicides used to destroy the plant before emergence. (PE)

Profluralin: N-cyclopropylmethyl- α,α,α -trifluoro-2,6-dinitro-N-propyl-p-toluidine (C₁₄H₁₆F₃N₃O₄). A dinitroaniline herbicide. Trade name: Tolban 4E. Used on cotton, vegetable, turf and woody ornamentals to control grasses and broadleaf weeds. It is strongly absorbed to organic matter and clay and therefore does not leach. (26399-36-0) (PE)

Propane side chain: Polymers may have side chains that are other hydrocarbons. One such side chain is the hydrocarbon propane, C₃H₈. On its own, propane is a colourless gas found in natural gas and petroleum that is used as a fuel. (PP)

Propoxur: 2-isopropoxyphenyl methyl carbamate (C₁₁H₁₅NO₃). A carbamate contact insecticide used against silverfish, hornets and wasps. (114-26-1) (PE)

Prospective cohort: Any designated group of persons who are followed or traced over a period of time.

Proteases: A class of enzymes capable of splitting the peptide bonds of a protein. (MM)

Proxy/surrogate respondent: One who speaks for a subject in a study (e.g., when a subject has died or is too ill to participate).

Pulsed electromagnetic field exposure: Electromagnetic fields that deliver their exposures in short pulses as opposed to a continuous flow. (EF)

Pyrethroids: Synthetic forms of pyrethrins. Pyrethrins are two highly insecticidal compounds that were isolated from pyrethrum flower heads in 1924: Pyrethrin I (C₂₁H₂₈O₃) (121-21-1) and Pyrethrin II (C₂₂H₂₈O₅) (121-29-9). Natural pyrethroids are expensive and unstable in sunlight. Synthetic pyrethroids are very stable in sunlight and are effective at extremely low rates of application. They function as axonic poisons. Type I Pyrethroids include allethrin, tetramethrin, resmethrin, d-phenothrin, bioresmethrin, and permethrin. Type II

Pyrethroids include cypermethrin, cyfluthrin, deltamethrin, cyphenothrin, fenvalerate and fluvinate. (PE)

Pyrite: (FeS₂). A common mineral consisting of iron sulphide having a yellow colour and a metallic glitter that suggests gold; “fool’s gold”. (MM)

Pyrrhotite: A bronze-coloured, slightly magnetic iron sulphide, sometimes containing nickel. (MM)

Quasi-controls: A control group in which members have not been assigned randomly along with the experimental group. Quasi controls are used when it is impossible to achieve random assignment of subjects to both experimental and control groups.

Quetelet index: An anthropometric measure of body mass defined as (weight)/(height)². This measure has the highest correlation with skinfold thickness or body density. Also known as body mass index (BMI).

Radiation: The emission and propagation of energy by means of electromagnetic waves or particles. (R)

Radical: An atom or group of atoms acting as a unit in reactions. For example, ammonium (NH₄) is a radical in ammonium hydroxide (NH₄OH) and ammonium chloride (NH₄Cl). (OC, DB, PP)

Radioactive decay: Breakdown of atoms of radioactive substances into other radioactive products (e.g., radium 226 decays to radon-222). Atoms in a radioactive substance decay in a random fashion but at a characteristic rate. The length of time this takes, the number of steps required and the kinds of radiation released at each step are well known. (R)

Radioactivity: The spontaneous decay of an unstable atomic nucleus, giving rise to the emission of radiation. (R)

Radioisotope: A radioactive isotope, i.e., one whose atoms undergo radioactive decay emitting alpha, beta or gamma radiation. Radioisotopes are produced by decay

of other radioisotopes or irradiation of a stable isotope. (MM)

Radium: (Ra). A radioactive metallic element with atomic number 88. As found in nature, the most common isotope has a mass number of 226. It occurs in minute quantities associated with uranium in pitchblende, camotite, and other minerals. (MM, R)

Radon: (Rn). A radioactive element that is one of the heaviest gases known. Its atomic number is 86. It is a decay product of radium. (MM, R)

Radon daughters/progeny: Short-lived decay products of radon-222. Radon progeny are gasses that become attached (adsorbed) to solid particles that are inhaled and trapped within the lungs. The progeny can thereby irradiate cells in the immediate vicinity of the particles to which they are attached. While most of the progeny attach to larger aerosols immediately after forming, a variable proportion remains unattached and is referred to as the “unattached fraction”. (R, MM)

Random-digit dialling: The procedure for selecting a population sample from telephone subscribers in a region. It is based on every possible permutation and combination of seven digits from a set of 10 (0-9). The area code is constant and unlisted numbers can be accessed.

Rat liver activation system: In a standard Ames assay a rat liver homogenate is used to provide the P450 cytochromes necessary for activation of mutagens to their reactive forms. (PE)

Raw water: Water that has not been treated in any way; it is generally considered to be unsafe to drink. (DB)

Recall bias: The distortion in the results respondents’ foggy memories about their exposure history.

Receptor: A cellular protein that binds with a specific drug, chemical or hormone, effecting a change in the cell’s function.

Recovery furnace/power boiler: Spent digester liquors are sent here to recover and reconstitute digestion chemicals from the spent cooking liquor, and to recover heat energy by burning the dissolved organic material from the wood. (PP)

Reduced sulphur compounds: The vile-smelling gases emitted from the kraft process. They include include hydrogen sulfide (H₂S), Methyl mercaptan (CH₃-SH), Dimethyl sulfide (CH₃-S-CH₃), and Dimethyl disulfide (CH₃-S-S-CH₃). (PP)

Regionalized variable: A variable that has properties that are intermediate between a fully random variable and a fully deterministic one. This means that although they are continuous over an entire surface, the complexity of the surface is such that it cannot be described easily by a deterministic function such as a trend surface. (AP)

Regression statistics: The relationship between the mean value of a random variable and the corresponding values of one or more independent variables.

Relative risk: A ratio of the risk of disease or death among the exposed to the risk among the unexposed.

Repeated sampling paradigm: A sequence of two or more cross-sectional studies conducted within the same dynamic target population generally spaced at least a few years apart. In this model the investigator follows the population rather than individuals. It is unlikely that a single respondent will appear in more than one sample.

Resins: Sticky yellow or brown substances that flow from certain plants and trees, especially the pine and fir, and normally harden upon exposure to air into brittle, amorphous, solids that are insoluble in water. They are soluble, however, in alcohol, ether and other organic solvents. There are three types of resins: hard resins, oleoresins, and gum resins. The oleoresins are perhaps the most commercially important. The most widely used of the oleoresins being rosin, used in sizing paper, soap making and for the bows of stringed instruments. It is obtained by the distillation of the oleoresin, turpentine.

Resmethrin: 5-benzyl-3-furylmethyl (1RS, 2RS; 1RS, 3SR)-2,2-dimethyl-3-(2-methylprop-1-enyl) cyclopropane carboxylate (C₂₂H₂₆O₃). A pyrethroid ester insecticide used to control flying and crawling insects and for fabric protection, pet sprays and shampoos. (10453-86-8) (PE)

Robertson-Berger metre: A metre used to measure ultraviolet radiation. (UR)

Saccharomyces cerevisiae: A yeast that is an ideal eukaryotic (having a nucleus) micro-organism for biological studies because the complete sequence of its genome is known and genetic manipulation is relatively easy. It can be used to functionally dissect gene products from other eukaryotes. (PE)

Salmonella typhimurium: A strain of gram negative bacteria belonging to genus *Salmonella*. It is responsible for food poisoning in man. (PE)

SCE: See Sister chromatid exchange.

Schist: A crystalline metamorphic rock that splits easily into layers. (MM)

Serum: The clear portion of any liquid separated from its solid particles. The pale yellowish fluid which exudes from the clot formed in the coagulation of the blood; the liquid portion of the blood, after removal of the blood corpuscles and the fibrin.

Siderite: (FeCO₃). An iron ore composed of iron carbonate. Siderite occurs in various forms and colours. (MM)

Sidestream smoke: The stream of smoke from the burning end of a cigar, cigarette, or pipe. (ET)

Sievert (Sv): The international system (SI) unit for equivalent dose equal to 1 Joule/kilogram.

Silica: Silicon dioxide (SiO₂). The main ingredient in sand and a compound of the two most abundant elements in the Earth's crust, silicon and oxygen. The crystalline form exists in three different forms or morphs (i.e., it is polymorphic) namely

quartz, cristobalite, and tridymite. Quartz is mainly diffused in the planet as sand. The other two occur in lava and are formed by heating quartz or amorphous silica. (MM, R)

Silicosis: A disease of the lungs caused by continued inhalation of the dust of minerals containing silicon; characterized by progressive fibrosis and a chronic shortness of breath. (R)

Sintering: Fusing together fine particles to form larger masses by the combined action of heat and pressure. (MM)

Sister chromatid exchange (SCE): A genetic exchange between two sister chromatids or genetic material in the prophase of mitosis (cell division in the body cells – as opposed to the germ cells) thereby producing different genetic architecture between the two daughter cells. The frequency of such exchanges in an experimental biological system (e.g., Chinese hamster cells) indicates the degree of carcinogenicity of an exposure.

Sister chromatids: In the prophase of mitosis of eukaryote organisms (cells containing nuclei), each chromosome in each cell replicates to constitute a pair of daughter chromosomes, called sister chromatids at this stage, that are in close association with each other.

Skarn: A rock, created from limestone or dolomite by contact metamorphism, that contains large amounts of silicon, aluminum, iron and magnesium that have moved from the adjacent igneous rock (typically granite). Skarns can be economically mined for iron and copper. (MM)

Small cell carcinoma: A type of cancer in which the tumour cells have endocrine-like characteristics and may secrete one or more of a wide range of hormones.

Smelting: A complex set of chemical reactions that result in the formation of slag (waste) and a valuable matte (an impure mixture of sulphides that is processed further). (MM)

Smelting dissolving tanks: The unburned inorganic component that collects at the bottom of the recovery boiler/furnace is molten smelt. The smelt flows out of the furnace and is dissolved in a weak caustic solution producing “green liquor”. (PP)

Sodium hydroxide: A brittle, white, opaque solid with the chemical formula NaOH. It is strongly alkaline, and is used in the making of wood pulp for paper, and in the manufacture of soap. Sodium hydroxide is also known as sodium hydrate, caustic soda, and lye. (PP)

Sodium sulphide (Na₂S): A reddish brown amorphous solid that is deliquescent (becomes liquid by absorbing moisture from the air) and is used in the manufacture of dyes. (PP)

Soil sterilant: A chemical that kills everything growing in the soil where it is applied. Can be carried by water and persist in the soil for several years. (PE)

Soluble nickel: All forms of soluble nickel salts: nitrates, citrates, acetate, sulfamates.

Somatic mutation: A change in the genetic material in the somatic cells (or body cells) which does not transmit to the next generation.

Spatial interpolation: Interpolation carried out on a spatial or geographic domain.

Sprague-Dawley rats: A strain of rats commonly used to conduct toxicological experiments into the health effects of various exposures.

Squamous cell carcinoma: A skin cancer that is less common than basal cell carcinoma but has a higher rate of metastasis (spread). It is estimated that 90-95% of SCCs are caused by sunlight exposure. Squamous cell carcinoma is also an occupational hazard, occurring in workers who distill tar vapour in the manufacture of coal gas and in machinery operators whose clothes and skin become soaked in mineral oil.

Standardized (standardised) incidence/morbidity/mortality ratio (SIR/SMR):

The ratio of the number of events observed in the study group or population to the number that would be expected if the study group had the same age-specific rates as the standard population.

Statistical power/power of a statistical test:

A gauge of the sensitivity of a statistical test; i.e., its ability to detect effects of a specific size, given the particular variance and sample sizes of the study.

Statistical significance:

The probability, expressed as a p-value, that an observed effect has occurred purely as a result of chance. The smaller the p-value, the less likely the observed effect is the result of chance, and the greater the statistical significance.

Sub-multiplicative interaction:

Unmeasurable and complex interaction between two or more factors (e.g., between smoking and radon exposure in lung cancer).

Substituted amides:

A class of herbicide also known as chloracetamides that act as shoot inhibitors, and are used as pre-emergence herbicides. The leading examples of amide herbicides used in Canada are alachlor and metolachlor. (PE)

Sulphallate:

2-chloroallyl diethyldithiocarbamate ($C_8H_{14}ClNS_2$). A thiocarbamate herbicide. (95-06-7) (PE)

Sulphanilamide:

p-aminobenzenesulphonamide ($C_6H_8N_2O_2S$). The amide of sulphanilic acid (sulphanilamide) and certain related substituted amides are of importance as the *sulpha drugs*. Antibacterial activity and toxicity of the substituted sulphanilamides depend on the nature of the group attached to the amido nitrogen. It is nearly always heterocyclic-a ring structure in which one or more of the carbon atoms is replaced by a different atom (nitrogen, oxygen or sulphur). (63-91-2) (PE)

Sulphates:

Salts of sulphuric acid (H_2SO_4) that occur naturally in numerous minerals and have numerous practical uses (e.g., in

the manufacture of chemicals, dyes and fertilizers). (AP)

Sulphide matrix breccias:

A sedimentary rock containing very large angular grains held together by a matrix (thick glue) of very small grains of some type of sulphide. Some common sulphides are galena (PbS), sphalerite (ZnS), pyrite (FeS_2). (MM)

Sulphidic nickel:

Nickel compounds that contain sulphur, including nickel subsulphide and nickel sulphide. (MM)

Sulphite pulping process:

An alternative to the Kraft (sulphate) pulping process, that uses sulphuric acid and one of its base salts. One of the major drawbacks of this alternative is that it creates more pollutants, uses more water, and produces a poorer quality product than the sulphate process. (PP)

Sulphonation:

Treating wood chips with hydrosulphide, and exposing them to increased acidity in a bisulphate solution to remove the lignin. (PP)

Sulphonyl ureas:

Herbicides with a urea functional group having a sulfonyl substituent. Examples include Bensulfuron-methyl and Chlorsulphuron ($(C_{12}H_{12}ClN_5O_4S)$ 1-(chlorophenylsulphonyl)-3-(4-methoxy-6-methyl-1,3,5-triazin-2-yl) urea) (6490-27-23), trade names Glean® and Telar®. Used to control many broadleaf weeds and some annual grass weeds, sulphonyl urea herbicides block the synthesis of essential branched chain amino acids. They have a high potential to contaminate ground water. (PE)

Sulphur:

A lemon-yellow-coloured non-metallic element sometimes known as "brimstone". (PP)

Sulphur dioxide:

(SO_2). A colourless, non-flammable, extremely irritating gas or liquid used in many industrial processes. (MM, PP)

Summary relative risks:

Relative risk calculated by pooling relative risks emerging from meta-analysis.

Suppressor T-cells:

Antigen-specific suppressor T lymphocytes (white blood cells) that diminish an organism's immune response.

Surface water:

Water which is open to the atmosphere and subject to surface runoff; generally lakes, streams, rivers. (DB)

Surfactants:

Surface-active lipoproteins that normally serve to decrease the surface tension of fluids. In the lung, they thereby permit the pulmonary tissues to expand during inspiration. (PE)

Susceptibility genes:

Genetic loci that put individuals into a higher risk of morbidity or mortality from a specific condition.

Synergistic effect:

A situation in which the combined effect of two or more factors is greater than the sum of their solitary effects.

Tankhouse:

Where the electrolytic tanks are located in a smelter. (MM)

TCDD:

See 2,3,7,8-tetrachlorodibenzo-p-dioxin.

TCP:

See 2,4,5-trichlorophenol.

Terbuphos:

S-tert-butylthiomethyl-0,0-diethyl phosphorodithioate ($C_9H_{21}O_2PS_3$). A highly toxic aliphatic organo thiophosphate insecticide and nematicide used to control soil pests on corn and sugar beets. Primarily formulated as granules, it is applied at planting. Terbufos controls wireworms, seed-corn maggots, white grubs, corn rootworm larvae and other pests. It breaks down rapidly. Two of the primary degradation products, terbufos sulphoxide and terbufos sulphone are highly toxic and more persistent in terrestrial and aquatic environments than the terbufos itself. Use is being phased out in Canada. (13071-79-9) (PE)

Tesla:

The unit of magnetic flux density, equal to one weber per square meter and symbolized as T. A micro-tesla (μT) is one millionth of a tesla. (EF)

Tetrachlorodioxins:

Pesticide by-products/contaminants. (PE)

Tetrachloroethylene: (CCl₂; CCl₂). A halogenated volatile organic compound (VOC) organic solvent that can become airborne from pulp and paper mill waste water. (PP)

Thiocarbamate: Typically herbicides with a carbamate structure where sulfur replaces one of the oxygens in the amide functional group (-S-CO-N- instead of -OCO-N-). They are weak cholinesterase inhibitors. (PE)

Thiocyanate: A compound having the SCN group in its structure. (PE)

Thiol-containing molecules: An organic compound containing SH (sulphydryl). (MM)

Thiophanate methyl: Dimethyl 4,4'-(*O*-phenylene) bis (3-thioallophanate) (C₁₂H₁₄N₄O₄S₂). A carbamate fungicide. (23564-05-8) (PE)

Thiophosphate: A phosphate in which one of the oxygen atoms has been replaced by a sulphur atom. (PE)

THMs: See Trihalomethanes.

Threshold-limit value (TLV): Air borne concentration of substances which represent conditions under which it is believed that nearly all workers may be repeatedly exposed day after day, for the entire working life, without adverse effects. (MM)

Threshold-limit value time-weighted average (TLV-TWA): Average concentration of an airborne substance for a normal eight hour work day or 40-hour work week to which nearly all workers may be repeatedly exposed day after day without adverse effects. (MM)

TLV: See Threshold limit value.

Toxaphene: (C₁₀H₁₀C₁₈). Polychlorcamphene, camphechlor. A reaction mixture of chlorinated camphenes containing 67-69% chlorine. A polychloroterpene (organochlorine) insecticide. The use of toxaphene on Canadian crops was discontinued in 1970. It is a common fish contaminant in the Yukon and NWT. For Canadians, the principal route of exposure is eating contaminated fish. (8001-35-2) (PE)

Transition: A mutation in which a chemical in DNA is replaced by a different chemical but of a similar type.

Translocation: An exchange of chromosomal fragments between two non-homologous chromosomes in a diploid organism during cell division.

Transversion: A mutation in which a chemical in DNA is replaced by a chemical of a different type.

Treated water: Disinfected and/or filtered water served to water system customers. (DB)

Triadimefon: 1-(4-chlorophenoxy)-3,3-dimethyl-1-(1*H*-1,2,4-triazol-1-yl)butan-2-one. A triazole fungicide used to control powdery mildews, rusts, and other fungal pests on cereals, fruits, and vegetables. (43121-43-3) (PE)

Triallate: *S*-2,3,3-trichloroallyl diisopropylthiocarbamate (C₁₀H₁₆Cl₃NOS). A thiocarbamate herbicide used to control wild oats, primarily in wheat and barley and one of the thiocarbamate herbicides used most commonly in Canada. (2303-17-5) (PE)

Triazines: Herbicides that act by stopping photosynthesis, used on fruit, grain and vegetable crops. They include Atrazine (AATREX), Cyanazine (BLADEx), Hexazinone (VELPAR), Metribuzin (LEXONE, SENCOR) and Simazine (PRINCEP). Triazine is a heterocyclic aromatic 6-membered ring made up of 3 nitrogen atoms and 3 carbon atoms. (PE)

Triazoles: A class of herbicide and fungicide/fumigant including Amitrole, Fluconazole, Guanazole, Itraconazole, and Trapidil. Triazole is a heterocyclic aromatic 5-membered ring made up of three nitrogen atoms and two carbon atoms. (PE)

Trichloroethylene: (CHCl; CCl₂). A halogenated volatile organic compound (VOC) in the form of a heavy, stable toxic liquid with a chloroform aroma, slightly soluble in water. (PP)

Trichlorophenol: (C₆H₃Cl₃O). An organochlorine fungicide/fumigant. A man-made chemical no longer made in the US. It is a germicidal agent used to preserve wood and glue as well as to protect textiles against mildew. (88-06-2) (PE)

Trifluralin: α,α,α -trifluoro-2,6-dinitro-*N,N*-dipropyl-*p*-toluidine (C₁₃H₁₆F₃N₃O₄). One of the dinitroaniline herbicides most commonly used in Canada; a selective, pre-emergence herbicide used to control annual grasses and broadleaf weeds in a variety of crops. (1582-09-8) (PE)

Triflusuifuron: 2-[4-dimethylamino-6-(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl]carbamoylsulfamoyl]-*m*-toluic acid (C₁₆H₁₇F₃N₆O₆S). A sulfonyl urea herbicide. (PE)

Trihalomethanes (THMs): Halogen-substituted single-carbon compounds with the general formula CHX₃, where X may be one or a combination of chlorine, bromine, fluorine, or iodine. These compounds are formed in treated water primarily as a result of chlorination of organic matter present naturally in raw water supplies. The THMs most commonly present in drinking water are chloroform, bromodichloromethane, chlorodibromomethane, and bromoform. (DB)

Trivalent arsenicals: Arsenic compounds possessing a valence of three (e.g., Arsenic trichloride (AsCl₃), Arsenic Trioxide (As₂O₃)). (MM)

Tumour-promoting agent: A stimulus or substance (chemical or otherwise) which has the potential to stimulate the growth of either benign or malignant tumours.

Turpenes: Any of the group of isomeric unsaturated hydrocarbons with the formula C₁₀H₁₆, also known as turpentines. They have a pleasant aromatic odour, and occur in essential oils and oleoresins of plants, especially conifers. Terpenes are emitted from outside chip piles in the pulp and paper industry and they constitute a group of volatile organic compounds that have no practical collection or disposal method. Forest trees also emit vast amounts of terpenes, and in the typical rural kraft mill, terpenes emitted by a chip pile are negligible compared to natural terpene emissions. (PP)

Turpenoids: A group of plant secondary metabolites based on one or more isoprene units, and constituents of many essential oils. (PP)

Ultraviolet radiation (UVR): That portion of the electromagnetic spectrum extending from the violet, or short wavelength, end of the visible light range to the X ray region. Ultraviolet (UV) radiation is undetectable by the human eye, although when it falls on certain materials it may cause them to fluoresce; i.e., emit electromagnetic radiation of lower energy, such as visible light. (UR)

Uncertainty factor: All those factors (or confounders) for which the investigator has only probabilistic data.

Unit risk: The excess probability of developing a disease, given continuous exposure to one unit (e.g. 1 µg/m³) of a substance over a lifetime. (MM)

Uracil: (C₄H₄N₂O₂). One of the bases in RNA. It is a pyrimidine(1,3-diazine), an aromatic heterocyclic compound that is a six-membered ring made up four carbon atoms and two nitrogen atoms. There are two oxygen atoms attached to two of the carbons in the ring. Uracil herbicides, derived from Uracil, can cause ground water contamination. Examples of Uracil herbicides include Bromacil (314-40-9) and Teracil (5902-51-2). (PE)

Uranium: (U). A heavy silvery-white metallic element with the atomic number 92, radioactive and toxic, easily oxidized, and having 14 known isotopes of which U 238 is the most abundant in nature. The element occurs in several minerals from which it is extracted and processed for use in research and nuclear fuels and weapons. (R)

Urea: (CO(NH₂)₂). A water-soluble crystalline compound, that is the major nitrogenous end product of protein metabolism and is the chief nitrogenous component of the urine of mammals and other organisms. Also called carbamide. Urea is manufactured synthetically for use in making fertilizers. (57-14-7) (PE, PP)

Uvea: The portion of the eye composed of the iris and ciliary bodies together with the choroid coat.

Uveal melanoma: Melanoma which occurs in human uvea.

UVR: See Ultraviolet radiation.

Valence: A measure of the possible ways an atom can combine with other atoms. It is dependent on the electron configurations of the reacting elements.

Variable penetrance: In the medical context, penetrance is the proportion of individuals with a given genotype who present with any phenotypic features of the disorder (i.e., it is an all-or-none phenomenon). However, in one sense penetrance may vary with age, as in the case of Huntington's disease. Variation in age of onset is most often considered as an aspect of variable expression.

Variance: A measure of the variation shown by a set of observations.

Variogram: A plot reflecting several measurements of a spatial or regionalized variable along a specified area or distance. Measurements are taken at a number of locations and the relationship between observations at the various locations can be explored by variogram analysis. (AP)

Vitamin D photochemistry: Cutaneous exposure to UV-B converts epidermal pre-vitamin D3 (7-dehydrocholesterol) to the stable hormone vitamin D3. This compound then diffuses through the skin to blood vessels and circulates systemically, where it is converted to the functional hormone 1,25-dihydroxy vitamin D3[1,25(OH)2D3]. Aging substantially decreases the ability of human skin to produce vitamin D3. This, coupled with the widespread use of sunscreens that filter out UV-B, has led to concern that vitamin D deficiency may become a significant clinical problem in the elderly. Indeed, studies have shown that the use of sunscreens can prevent the production of vitamin D3 in human skin. (UR)

VOCs: See Volatile organic compounds.

Volatile organic compounds (VOCs): Organic compounds that convert into vapour or gas without a chemical reaction. (DB, AP, PP)

Volt: The electrical unit equal to the potential difference between two points on a conductor carrying a current of 1 ampere when the power dissipated between the two points is 1 watt; equivalent to the potential difference across a resistance of 1 ohm when 1 ampere of current flows through it. (EF)

Watt: The unit for measuring electric power or energy available per second. One watt is equal to one joule of energy per second. (EF)

Weber: The unit of magnetic flux. (EF)

Wertheimer-Leeper wire code: A categorization of wiring configurations developed by Nancy Wertheimer and Ed Leeper. Power lines close to residences are categorized according to the number of conductors and their diameters, location of transformers and service drops, as well as the distance of the conductors from the home. (EF)

Wood volatiles: Extractives naturally present in wood that vapourize over time. (PP)

Working level month: A WL (Working Level) is any combination of radon progeny in one litre of air that results in the average emission of 1.3 X 10⁵ MeV of alpha energy during decay. Exposure to 1 WL for 170 hours equals 1 Working Level Month (WLM) of exposure, a unit developed to describe exposure sustained by miners during the average number of hours spent underground. (R)

Xenoestrogen hypothesis: A convention that states: "some environmental chemicals (e.g., organochlorines) exhibit estrogen receptor agonistic activity." It is unclear whether this is an important mechanism whereby cancer is induced in humans. (PE)

Xiphophorus fish model: Heavily pigmented backcross hybrids of the genus Xiphophorus (platyfish and swordtails) are very sensitive to melanoma induction by single exposures to UVR. They are therefore used in experiments involving melanoma induction by UVR. (UR)

Radiation

Radiation is energy in the form of particles or electromagnetic waves. Based on the effects it can produce in matter, two classes of radiation have been defined: ionizing and non-ionizing.¹ Ionizing radiation has sufficient energy to remove electrons from atoms and break atomic bonds. Both classes can alter the genetic material (DNA) of a cell. Approximately 80% of our exposure to ionizing radiation is from *natural* sources, usually at very low dose rates, such as cosmic rays and naturally occurring radioactive elements in the Earth's crust and air.² Most of the *artificial* (man-made) radionuclides (unstable nuclei of atoms) released into the global environment have come from nuclear weapons tests. Other artificial sources of ionizing radiation include nuclear facilities, uranium mines, mills and plants and X ray devices.

Non-ionizing radiation has lower energy than ionizing radiation and does not ordinarily have enough intensity to endanger living things from acute exposure. Exposure to non-ionizing radiation includes ultraviolet radiation (UVR) from the sun, radiofrequency radiation (radar, radio and television towers, mobile telephones) and extremely low frequency electric and magnetic fields (ELF EMF) from electrical wires and appliances. Although a portion of the ultraviolet spectrum has sufficient energy to ionize atoms, it is traditionally considered a non-ionizing form of radiation. Human exposure to ELF EMF has risen dramatically this century because of our increasing use of electricity, giving rise to concerns about the effects of long-term exposures. Also, over the past few years, the ozone layer—a thin veil of gas in the atmosphere that screens out harmful solar UVR—has become thinner, resulting in slightly more of the sun's harmful radiation reaching the Earth's surface.³

Sources of radiation may be taken into the body by inhalation or ingestion and some forms of electromagnetic radiation can penetrate skin to reach other organs of the body. Gamma rays penetrates skin with ease, while alpha particles do not and exposure occurs primarily through inhalation or ingestion. Energy absorbed by

tissue produces reactive chemicals called free radicals, which can induce other chemical changes and ultimately biological effects.¹ Radioactive sources taken into the body may persist in tissues, irradiating organs for extended periods of time.

Radiation doses can be high or low, and can be received over a short or long period of time. Effects on humans can be acute or chronic, somatic or genetic. Somatic effects are limited to the exposed individual, whereas genetic effects may also affect subsequent unexposed generations.

High doses of absorbed ionizing radiation, delivered at high dose rates, (e.g., from a nuclear accident) can produce a variety of clinical effects including localized burns, acute radiation syndrome (ARS), increased circulatory disease and death. ARS and death result from damage to critical organs and tissues, such as bone marrow and the gastrointestinal tract. Lower doses of radiation may result in effects manifested later in life as a result of damage to DNA. Usually, cellular damage is repaired through a natural process; however, if it is not adequately repaired, it may result in a viable but modified cell. After a prolonged and variable latency period, reproduction of a modified somatic cell may result in the appearance of a cancer.²

Units used to measure radiation dose to the body reflect the damage that may result to tissues and organs from the dose received.¹ Three dose measurements are used: the absorbed dose, the equivalent dose and the effective dose. The *absorbed dose* is the amount of energy absorbed as a result of the radiation. Its SI unit, or *Système International d'Unités*, is the gray (abbreviated as "Gy"). One Gy is an absorbed dose of one joule per kilogram of material irradiated. However, tissue damage also depends on the type of radiation, as some types of radiation are potentially more harmful than others. Consequently, the absorbed dose is multiplied by a weighting factor for each radiation type to obtain the *equivalent dose*. X rays, gamma rays and beta particles have a weighting factor of one, while

neutrons and alpha particles have a factor of 20. The unit of equivalent dose is the sievert (abbreviated as "Sv"). Doses commonly received by occupational groups and the public are much smaller than a sievert and are commonly expressed in millisieverts (mSv), or one thousandth of a sievert. The average individual dose from natural sources in Canada is about 2 mSv per year.¹ Thirdly, the risk to an individual also depends on which organs in the body have been exposed. The *effective dose* has been developed to summarize the total potential harm over different organs and is also measured in Sv or mSv. Tissue weighting factors have been developed which sum to a whole body total of 1.0. Effective doses are obtained by multiplying the equivalent dose by the organ weighting factor. As a result, the potential harm from an effective dose of 1 mSv to a specific organ should be similar to that from an effective dose of 1 mSv of whole body irradiation.¹

Units of Working Levels (WL) and Working Level Months (WLM) are often used in studies of exposure to radon and its decay products. A WL is any combination of radon progeny in one litre of air that results in the average emission of 1.3×10^5 MeV of alpha energy. A WLM is the product of a WL and time (M) in working months (170 working hours).⁴

Radiation risk estimates are derived largely from extrapolation of epidemiological studies of human populations that were exposed to high doses of radiation as well as by residential and occupational studies at lower levels. The main source of information on the risk of radiation-induced cancer following whole-body exposure to external ionizing radiation comes from the follow-up studies of Japanese survivors of the 1945 atomic bombings of Hiroshima and Nagasaki. Other studied populations include hard rock miners exposed to high concentrations of radon and its decay products in air, early radium dial painters who inadvertently ingested appreciable amounts of radium and patients treated in the past with high doses of medical X rays, who received repeated fluoroscopies for

the management of tuberculosis or who were given radium-224, radium-226 or Thorotrast (thorium oxide) for treatment or diagnosis. While evidence is growing that there may be an effective threshold below which there are no adverse effects from low doses of radiation, the linear non-threshold assumption of biological response to dose (dose-response) continues to be used as a prudent approach to radiation protection.² For a more detailed discussion of radiation, the reader is referred to two publications by Canada's Atomic Energy Control Board (AECB)—*Canada: Living with Radiation*¹ and *Assessment and management of cancer risks from radiological and chemical hazards*.⁵

The following three chapters present the epidemiological evidence relating cancer to specific types of radiation exposure. Radon, a source of ionizing radiation, is presented first, followed by two types of non-ionizing radiation—UVR and ELF EMF. Radon and ultraviolet radiation emanate primarily from the natural environment, but are mediated by the built environment and personal behaviours. Electromagnetic fields, although occurring naturally (e.g., during thunderstorms), are primarily associated with the built environment.

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Radon

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Radon is a radioactive gas that emanates from uranium-bearing soil and porous rock. Although radon is most highly concentrated in areas of high uranium concentration, the presence of trace amounts of uranium in most ground sources means that all humans are exposed to radon to some degree. Radon migrates out of soil and rock into the surrounding air, resulting in accumulation in poorly ventilated or closed areas. Such areas represent the primary environments in which humans are exposed to radioactivity from radon to experience detrimental health effects.

There is no convincing evidence that any cancers other than lung cancer are associated with exposure to radon. There is, on the other hand, consistent evidence of a substantially elevated risk of lung cancer among Canadians exposed to radon in certain occupational settings, particularly uranium mining. While the combined evidence for a positive association between residential radon exposure and lung cancer is less compelling, the inherent methodological difficulties in mounting such studies may render it impossible for any single study to detect the relationship more conclusively. The best available evidence to date from pooled analyses indicates a positive, but weak association between residential radon and lung cancer risk.

Residential radon is of critical importance because it is ubiquitous; a small excess risk that may exist in relation to radon exposures encountered in a residential setting translates into the potential for a far greater number of excess cancers in the general population than does exposure of a relatively small number of miners, even though the latter may be exposed to much higher levels of ionizing radiation. Fortunately, a number of techniques are available to homeowners to reduce radon concentrations in their homes.

Introduction

Radon-222 is a radioactive gas that is a daughter product in the radioactive decay sequence of uranium-238 and its daughter product radium-226. It is the gaseous nature of radon that makes it of particular interest to epidemiologists. Although radon is most concentrated in the atmosphere above ground with high uranium concentration, the presence of trace amounts of uranium in ground sources means that all humans are exposed to radon, to some degree, due to its emanation from uranium-bearing substrate. This property allows it to migrate out of soil and porous or broken rock, into the surrounding air, resulting in accumulation in poorly ventilated or closed areas. Such areas represent the primary environments in which humans are exposed to sufficient levels of radioactivity from radon (alpha particles) to experience detrimental health effects.

The adverse health effects associated with exposure to radon were recognized even before the discovery of the radioactive properties of radium by Becquerel and Curie in the late 1890s. Schüttmann¹ gives an excellent historical account of the identification of “Schneeberg lung disease” in the mines of the Saxony area of Germany as early as the 16th century. This “miners’ disease” was described as a progressive illness, with symptoms of increasing cough, expectoration and shortness of breath. It resulted in the early deaths of a large proportion of miners who had worked in the mines of the Saxony area. Schneeberg lung disease later came to be recognized as a form of lung cancer and, over time, evidence mounted that it was associated with mines where pitchblende (uranium-bearing waste) was extracted. It was later discovered that mines in the Saxony area were associated with levels of radon among the highest in the world, and that this factor seemed to be more strongly associated with the development of Schneeberg lung disease than with other potential exposures such as silica. Schneeberg lung disease, which had

already come to be known as lung cancer, was first listed as an occupational disease in 1925.¹ This led to the first organized attempts to protect miners from the deleterious effects of radon through use of ventilation in the mines to reduce the concentration of radon in the mine air.

Most of the adverse health effects identified as associated with exposure to radon relate to development of malignant disease (though cardiovascular disease has been studied in recent years as well). In the sections that follow, we describe the biological basis for the mechanisms by which radiation, and radon in particular, are thought to cause cancer, the epidemiological evidence for the association between cancer and radon, and potential health implications in Canada.

The biological basis for radon-induced malignancy in humans

Radiobiology of cancer

The potential for radiation to induce malignant transformation in mammalian cells has been extensively studied and some of the biological mechanisms have been elucidated.² When radioactive materials decay, photons (gamma rays), high speed electrons (beta rays) or nuclear fragments (charged particles or neutrons) are ejected from the radioactive atoms. These ejected particles can then interact with other materials, including mammalian cells, with which they may come in close proximity. For biological damage resulting in malignant potential to occur, the ejected particles must pass into a cell and deposit some or all of their energy within the cell. The relationship between the amount of energy deposited and the track length over which it is deposited is known as the linear energy transfer (LET).³ Generally speaking, high LET radiation is more effective at inducing cell damage than low LET radiation.

The types of radiation emitted from radioactive materials such as radon are referred

to as ionizing radiation. The term “ionizing” refers to the mechanism by which the radiation interacts with matter through which it passes. Whether passing through air or water or solid material, ionizing radiation interacts with matter at an atomic level through deposition of energy and the resulting ejection of electrons from the atoms. This leaves the atom ionized and changes its chemical properties. This in turn can result in breakage of chemical bonds between atoms. Ionizing radiation can also result in changes to the nucleus of atoms in which it is deposited.

Mammalian cells are mostly water, which means that in tissues, the energy deposition is mainly in water. In this medium, ionizing radiation can cause formation of negatively charged hydroxyl radicals (OH⁻) through fragmentation of water molecules. Because of the instability of these “free radicals”, they have a high propensity to bind with other molecules, changing the chemical properties of these molecules.³

From the standpoint of malignant transformation of cells, the most important molecules within the cell that can be affected by ionizing radiation are the double-helix DNA (deoxyribonucleic acid) molecules. These can be damaged by either direct or indirect processes. Direct damage involves breakage of chemical bonds between base pairs by the ionizing radiation itself. Indirect damage entails alteration of base pair chemistry and resulting loss of chemical bonds between base pairs through interaction with hydroxyl radicals created by the ionizing radiation.

Damage to DNA strands can result in a number of outcomes: the breaks may be repaired by the normal repair mechanisms of the cell, resulting in a normal DNA molecule; there may be loss of a base, resulting in permanent change in the DNA; there may be a break in the strand on one side of the double-helix molecule, or there may be breaks in both strands. Any of the latter three may result in mutations that can give rise to malignant potential.²

Malignant potential is only significant if the cell divides, the offspring cells survive the cell division, and the mutation which

confers the malignant potential is passed on to one of the offspring. Furthermore, the cells which result will only give rise to malignancy if the mutation is of a type that changes the cell in some way or ways that lead to an altered phenotype capable of tumour formation. Typical changes, among others, that lead to such phenotypes include activation or deregulation of oncogenes and loss of tumour suppressor genes.⁴

Biological effects of radon related to cancer

Radon decays into Polonium-218 through emission of an alpha particle. Polonium-218 itself emits an alpha particle as it decays. Another radon daughter, Polonium-214 also emits an alpha particle in decaying to Lead-210. Both Polonium isotopes have very short half-lives and both, unlike radon itself, are solid rather than gaseous elements. It is believed that these solid elements, in aerosolized form, or, in their charged state, attached to other particulate matter, result in most of the biological damage attributed to exposure to radon.⁵ Damage results when these radioactive elements come into close proximity to lung tissue, particularly in the larger airways of the lung, where they have a propensity to settle out. This is supported by evidence that miners exposed to moderate to high levels of radon have a higher ratio of central to peripheral lung tumours than non-miner smokers, whose carcinogen (tobacco smoke) tends to settle out in more peripheral airways.⁶

There is evidence of radon-associated mutations in both tumour suppressor genes and oncogenes. Taylor et al.⁷ described a series of lung cancer samples from 52 uranium miners of the Colorado plateau, which showed mutations in the p53 tumour suppressor gene in 55 to 73% of lung cancers, depending on histological subtype. Of particular interest was that 16 of 29 mutation-positive cancers had the same transversion mutation, potentially indicating that this was a specific hotspot for p53 mutation induced by radon exposure. Vähäkangas et al.⁸ failed to find this same mutation, but did report that other types of mutation in the p53 tumour suppressor gene occurred in 37% of tumour samples in their series. Furthermore, there was another difference between the types of mutations in their

series and those series reporting non-radon related lung tumour mutations: namely, that 22% of the mutations were deletion mutations, whereas other series had rarely reported this type of mutation in lung tumours. Subsequent series^{9,10} failed to confirm the findings of Taylor et al. with respect to a specific hotspot for p53 mutation caused by radon, but these studies involved individuals for whom the exposures to radon were lower than those in the Taylor series. A further analysis of lung adenocarcinoma specimens from the Colorado plateau miners by McDonald et al. did not find a specific p53 hotspot.¹¹

Both Vähäkangas et al.⁸ and McDonald et al.¹¹ also examined rates and types of mutation in the K-ras oncogene commonly found in lung tumours. Whereas Vähäkangas reported finding zero out of 19 tumours containing K-ras mutations, McDonald reported 9 out of 23 (37%) containing such mutations. However, McDonald et al. concluded that the rate and pattern of K-ras mutations in their series of adenocarcinomas in the Colorado plateau miners was similar to the rate found in smoking-induced adenocarcinomas.

Thus, although the molecular biology evidence for mutation-induced malignant transformation is consistent with mechanisms postulated above, the published literature is not clear on this issue.

The inverse-dose-rate effect

Another important consideration regarding the biological mechanisms by which exposure to radon results in carcinogenesis, relates to a phenomenon known as the inverse-dose-rate effect. This concept has as its central tenet that the same dose of radiation will be more effective in causing cancer if it is delivered over an extended period of time rather than as an acute dose. Thus, for a given dose of radiation, a lower dose rate is more effective in causing cancer. The biological rationale for this is that cells are more susceptible to genetic damage during specific parts of their cell cycle.^{12,13} When exposed to an acute dose of radiation, only a small proportion of cells will be at a point in their cycle where they are susceptible to genetic damage. When a more protracted dose is delivered, a higher

percentage of the cells have the potential to be affected during a sensitive part of their cell cycle. This results in a higher chance of malignant transformation. However, a dose rate effect is only plausible when the total dose is sufficiently high that multiple traversals of individual cell nuclei are likely. In other words, a cell which experiences only a single “hit” by an alpha particle cannot express a dose rate effect.¹² There is evidence in support of this effect in the literature dealing with miners exposed to radon.¹⁴⁻¹⁶

This theory has a direct bearing on the interpretation of studies that involve very low dose rate and total dose from radon. In such exposures (as may be experienced in the residential setting), the exposure may be so low that the inverse-dose-rate effect disappears. This is important in understanding the epidemiological literature which has, more than occasionally, attempted to infer the risk associated with very low exposure to radon, as may occur in residences, from the data corresponding to much higher exposure rates and levels associated with uranium mining. Inferences of risk associated with one set of exposure conditions may be associated with large errors when applied to other exposure conditions. If the inverse-dose-rate effect is real at low doses, then simply extrapolating doses at levels typically found in association with occupational risk will result in an underestimate of true risk of residential exposure, whereas the reverse happens if the inverse-dose-rate effect is not real at dose levels found in residences.¹³

The linear no-threshold theory

Based on the empirical evidence and biological considerations, the Biological Effects of Ionizing Radiation (BEIR) Committee, in their fourth report (BEIR IV), proposed a model for relative risk of lung cancer mortality associated with radon exposure.¹⁷ The model was based on earlier work, some of which related to chemical carcinogenesis.¹⁸ This model implies that relative risk is linearly related to radon exposure in Working Level Months (WLM). A WL is any combination of radon progeny in one litre of air that results in the average emission of 1.3×10^5 MeV of alpha energy. A WLM is the product of a WL and time (M)

in working months (170 working hours).⁵ The model postulates that there is no threshold below which the risk of lung cancer associated with exposure to radon is zero. This model generated a great deal of controversy in the literature, most of which relates to data from some of the ecological studies of cancer risk from radon exposure that are discussed below. The discussion about the merits of this model has been ongoing since the BEIR Committee adopted it.¹⁹⁻²⁹

In a later report (BEIR VI),³⁰ the BEIR Committee used cellular and molecular evidence, in conjunction with epidemiological evidence, to update the specification of its model. The result was an Excess Relative Risk (ERR) model of a linear relationship between ERR and past exposure to radon. Consistent with the available data, the model also contains a parameter to explain the decrease in ERR with increasing age. Most recent studies of radon and risk of lung cancer have assumed or are consistent with this model. The most recent report (BEIR VII) supports the application of the linear no-threshold concept at low doses.³¹

Epidemiological evidence for the association between radon and malignant lung disease

Miner studies: Canada

The evidence for a relationship between occupational radon exposure and risks to health come from studies of a number of miner cohorts in a variety of countries. As mentioned above, the first evidence for a detrimental health effect of radon came from the Saxony area of Germany where miners were exposed to radon in pitchblende. More recently, health effects of exposure to radon have been studied in miners in Canada, the United States, France, Sweden, Finland, Czechoslovakia, Italy and China. Although exposures are highest in cohorts exposed in uranium mines, miners in certain non-uranium mines have also had moderate to high exposures.

In Canada, one of the earliest studies was conducted by Muller et al.³² using data from the Mining Master File held by the Ontario Ministry of Labour. This study examined exposure and outcome data for Ontario

miners who were classified as either uranium or non-uranium miners. The uranium miner cohort contained a total of 17,102 men who worked in the mines between 1955 and 1977. Unlike more recent studies that excluded subjects who had mined for less than one or two years, this study included miners who had worked for more than half a month. After exclusion of miners with known asbestos exposure or those who worked in uranium mines outside Ontario, the cohort consisted of 15,984 men. Exposures prior to 1968 were estimated using measures taken in each of the mines in individual calendar years and time spent in the mines on a calendar year basis for individual miners. Subsequent to 1968, personal exposure data were available for individual miners.

Muller et al.³² found a significantly elevated standardized mortality ratio (SMR) for carcinomas of the trachea, bronchus and lung of 1.81 (119 observed deaths, vs. 65.8 expected, $p < 0.01$). This elevated risk was demonstrated in both of the main sub-cohorts of miners based on location of mining activity (Bancroft mines: SMR 2.41; Elliot Lake mines: SMR 1.62). No increases in other types of malignancies were seen in this cohort. Among the non-neoplastic diseases, only silicosis and chronic interstitial pneumonia were associated with elevated SMRs, and only in the Elliot Lake mines (SMR 5.60).

Muller et al.³² stated that the mean cumulative exposure in this cohort, to radon progeny, was 53.5 WLM. The somewhat lower mean cumulative exposure, compared to that found in many other studies, was because uranium mining was a relatively new industry in Ontario in 1955 (when individuals became eligible to be included in the cohort). Also, they state that most men entered the study in the early years of uranium mining and worked for short periods only (median 1.5 years).

Muller et al.³² used the exposure data to quantify the ERR per additional WLM (ERR/WLM). This was calculated to be 0.015. Each additional WLM of exposure added 0.015 to the relative risk estimate. No attempt was made in this study to account for the effects of potential

confounders such as smoking history, exposure to arsenic, mineral fibres or silica. This is one important limitation of the study (in addition to relatively small sample size). However, the effects of exposure to mineral fibres were partially controlled for by eliminating miners with previous asbestos exposure from the cohort.

An updated study of this cohort³³ found a significantly elevated mortality from lung cancer in Ontario uranium miners (SMR 2.25, 95% Confidence Interval (CI): 1.91-2.64). Kusiak et al. reported the excess risk of dying from lung cancer in uranium miners was greatest in those exposed 5 to 14 years prior to diagnosis, and in men less than 55 years of age. This study also concluded that a part of the excess risk of lung cancer was due to exposure of some members of this cohort to arsenic while employed as gold miners previous to their employment as uranium miners. The ratio of small cell carcinomas to other histological types was also greater in the uranium miners than in the general population.

In 1996 Finkelstein³⁴ reported a study of lung cancer in Ontario uranium miners at the Elliot Lake mines. The study determined how risk of lung cancer due to radon exposure was modified by other factors, including smoking, silicosis, clinical symptoms, lung function and temporal pattern of radon exposure. Among 1,043 eligible uranium miners, 967 agreed to participate in the study and 733 had complete records. This included a respiratory health questionnaire, lung function tests and chest radiograph from 1974. These records contained information on smoking status as well as the other modifiers of risk under study. Data for individual miners were linked to the Ontario Mortality Database and the Ontario Cancer Registry up to the end of 1992. Both standardized incidence ratios (SIRs) and SMRs were calculated using the Ontario population as the standard. After controlling for confounders in Cox proportional hazards models, risk was found to be modified by older age at exposure, poorer lung function and exposure to radon in a time window 4 to 14 years before diagnosis. This study did not find smoking to be an effect modifier with respect to radon exposure.

Another attempt at determining the relative importance of silicosis as a modifier of the risk associated with exposure to radon in Ontario miners was published by Finkelstein in 1995.³⁵ This was a case-control study of the role of potential confounders of the link between lung cancer risk and silicosis. Miners with radiographic evidence of silicosis, identified through the Ontario Silicosis Surveillance Database, were matched by year of birth with three miners from the database who did not have evidence of silicosis. Miners with silicosis had a SIR for lung cancer of 2.55 (95% CI: 1.43-8.28). Smoking differences were considered unlikely to account for the difference in lung cancer risk. In a conditional logistic regression analysis, where radon and silicosis were added as variables, the effect of silicosis (Odds Ratio (OR) 6.99, 95% CI: 1.91-25) appeared to completely overwhelm the effect of radon as a risk factor (OR 1.00, 95% CI: 0.986-1.004). One limitation of this study was that the exposure of non-uranium miners was assumed to be the same as background and assigned a value of zero WLM, which may have introduced some differential misclassification.

A study of 7,057 gold miners in Ontario by Muller et al.^{36,37} detected a significantly elevated risk of lung cancer in this cohort (SMR 1.40, $p = 6 \times 10^{-6}$) relative to similarly aged Ontario males. However, it was not possible to attribute this risk to radon exposure due to lack of data regarding radon exposure levels in the mines for the period of study. Other factors, such as arsenic exposure, may have played a role in the increased lung cancer mortality of these miners. Smoking may have also influenced the SMR as expected greater prevalence of smoking among miners than general population.

Subsequently, Kusiak et al.³⁸ reported that radon measurements made in Ontario gold mines after 1961 (most in the 1980s) showed levels of radon in inactive areas to average 0.3 WL or greater, while levels in active gold mines averaged 0.02 WL. Kusiak³⁸ estimated that the levels in the inactive mines would have been the upper limit of exposure for miners working in gold mines prior to 1945, while exposures after 1945 were estimated from measurements in the active work areas and the

individual work histories of the miners. The study found a statistically significant elevated risk of dying from lung cancer in miners who started mining gold before 1945 and who never mined nickel. Poisson regression analysis found that both arsenic and radon had regression coefficients that were significantly different from zero, when analysed in the same model. The interaction term between radon and arsenic was not significantly different from zero. The authors concluded that the increased incidence of lung cancer in Ontario gold miners was due to the independent effects of arsenic and radon exposure.

Howe et al.¹⁴ have reported results of a study of lung cancer mortality in uranium miners employed at the Beaverlodge uranium mine in Saskatchewan. This cohort was comprised of 8,487 miners who mined between 1948 and 1980. A statistically significant SMR of 1.90 was found, relative to the general population. They also found a significant dose-response trend and determined that the ERR/WLM was 0.0328. This represents one of the largest dose-response relationships published to date and was thought to be due to the relatively low exposures experienced by this group of miners, who mined primarily in an era when the mine was ventilated. A reanalysis of the exposures of cohort members by SENES Consultants³⁹ concluded that the original exposure estimates were underestimated by about 50% and that a significant number of miners had exposures other than at Beaverlodge that were not accounted for in the original estimates.

Further analysis of this cohort by L'Abbé et al.⁴⁰ was performed to determine the relative importance of other potential modifiers of the risk-exposure relationship, particularly cigarette smoking and non-Beaverlodge mining experience. In this study, next of kin were traced for 46 of 89 men who died of lung cancer after working in the Beaverlodge mine between 1949 and 1980. Data on smoking and other mining experience were collected and compared to interviews of next of kin for 95 male controls who worked at the Beaverlodge mine and died of other causes. The cases in this study included 24 who had worked at the Port Radium mine in the

Northwest Territories in addition to the Beaverlodge mine. Their conclusion, based on logistic regression modeling of the confounding effects of smoking and other mining experience, were that neither of these variables appeared to substantially confound the relationship between risk and exposure. L'Abbé et al.⁴⁰ further concluded that the relatively high risk coefficients found in the original study cannot be explained by confounding by these two variables. However, the study was very limited since it represented only a small fraction of the original Beaverlodge cohort (N = 125 compared to N = 12,000 for the entire cohort) and it employed the original rather than the revised exposure estimates.

Howe et al.¹⁵ also reported results of studies involving a cohort of 2,103 uranium miners employed at the Eldorado Port Radium mine in Port Radium, Northwest Territories, Canada. These miners were employed at an earlier period than the Beaverlodge miners (1942-1960), during an era when the mine was not ventilated and they were therefore exposed to much higher levels of radon than the Beaverlodge miners. As with most other studies, this study found a highly significant relative risk (RR 3.37) associated with exposures greater than five WLMs. The risk of death was highest in the group of miners exposed five to nine years prior to diagnosis (RR 16.78) and declined in miners exposed for longer periods before diagnosis.

In contradistinction to the Beaverlodge cohort risk coefficient (0.0328), the ERR/WLM from Port Radium workers was 0.0027. The order of magnitude difference in these coefficients was explained by Howe et al.¹⁵ on the basis of the inverse-dose-rate effect. The average annual exposure rates for the Beaverlodge and Port Radium cohorts were five WLM and 109 WLM respectively. At the lower exposure rate of the Beaverlodge mine, the inverse-dose-rate effect would predict that similar cumulative doses received in the Beaverlodge mine would be associated with higher excess risk (and therefore higher risk coefficients) than would be those in the Port Radium mine. However, the Beaverlodge ERR would be reduced under the revised dose estimates discussed above.

The data for the Port Radium cohort were also consistent with a decrease in risk coefficient as age at observation increased. Howe et al.¹⁵ reported that those aged 70 or older showed no increase in risk over the general population, while no relationship was found between age at first exposure and risk.

Another group of miners who were exposed to high levels of radon in Canadian mines were the workers at the fluorspar mines of Newfoundland.⁴¹ It was noted in the 1950s that these miners had a growing number of lung cancer deaths. Measures of radon concentration, which were first recorded in the mines in 1960, revealed radon levels as high as 190 WL.⁴¹ It was found that the radon was entering the mines in ground water, presumably after the radioactive gas had leached into ground water in uranium-bearing rock nearby. Ventilation was introduced into the mines in 1960, after which the radon concentrations dropped to an average of 0.5 WL.

Morrison et al.⁴¹ examined the lung cancer risk in a cohort of 1,772 fluorspar miners. One hundred thirteen lung cancers were observed, compared to an expected number of 21.5 (RR 5.25, 95% CI: 4.33-6.32). The dose-response trend was highly significant, with an associated relative risk for miners exposed to >2500 WLM of 33.6 (95% CI: 22.47-48.18). No significant increase in risk was noted for the first ten years after exposure. For miners exposed to moderate (100-1000 WLM) or high (1000+ WLM) exposures, the risk was highest 10 to 19 years after exposure and declined thereafter. This pattern of declining risk after an initial latency period was consistent with results reported above for other groups of miners.^{14,15} Morrison et al. also found a decrease in attributable risk coefficient after age 70, as did the Beaverlodge cohort studies.¹⁴

The added strength of internal cohort comparisons, relative to SMR-related analyses may be noted. Also, a fundamental issue of these studies is trying to estimate exposures retrospectively; for the most part, the highest exposures occurred prior to monitoring.

Miner studies: Other countries

The Colorado Plateau uranium miner cohort⁴² has been followed since the 1950s.⁴³⁻⁴⁵ Roscoe⁴⁴ provided the latest update to the mortality experience of 3,238 white miners in the cohort, with vital status being ascertained until 1990. Occupational, medical and smoking histories were obtained in health surveys between 1950 and 1970. As in most other studies, exposures were estimated from a variety of methods, including actual measurements, and interpolation or extrapolation in time. For earlier time periods in the study, estimated doses were based on geographic features of the mines and ventilation practices. There were 371 deaths from lung cancer in the cohort members, which represented an SMR of 5.8 (95% CI: 5.2-6.4). In those who died from lung cancer, the average exposure to radon progeny was 1,574 WLMs. The test for trend for the relationship between exposure and risk of lung cancer was strongly positive ($p < 0.002$). In calculating the standard rate ratios (SRRs) for lung cancer, an internal comparison group (those with lifetime exposure < 120 WLM) was used. Duration of employment was found to be an important factor in the risk-exposure relationship, with those working longer than 15 years having a 3.1-fold increase in risk of lung cancer over those working less than five years.

A subsequent analysis of the Colorado Plateau cohort by Hornung et al.⁴³ examined the effects of age and smoking on the risk-exposure relationship. This analysis found no statistically significant interaction between radon exposure and smoking, which was contrary to the results of some studies, described below, that generally found a sub-multiplicative interaction between smoking and radon exposure.⁴⁶ However, a significant interaction was found between radon exposure, attained age and smoking. The meaning of this interaction is difficult to interpret due to the complexity of the relationship between the three variables, but Hornung et al. stated that it was consistent with a sub-multiplicative radon/smoking interaction that depended on attained age. The analysis was also consistent with other studies that showed an inverse-dose-rate effect that disappears at very low exposures (e.g., no dose rate effect below

10 WL). Significant interactions were also found between cumulative radon exposure and attained age, and age at last exposure and relative risk of lung cancer, also consistent with findings of other studies.

An interesting subgroup of the Colorado Plateau cohort consisted of miners of Navajo descent. Roscoe et al.⁴⁵ analysed the mortality data for this subgroup of 757 miners known to be light smokers (446 never smoked, 106 ex-smokers, 174 smoked < 1 pack/day). Consistent with other groups, a statistically significantly elevated SMR was found for lung cancers in the Navajo miners (SMR 3.3, 95% CI: 2.3-4.6). The relative risk of lung cancer for those in the 400-1000 WLM total exposure category was 6.9 (relative to those in the < 120 WLM category) while those in the > 1000 WLM category had a relative risk of 18.9 (both were statistically significant). Exposure rate was found to be inversely related to relative risk, with an increase of 10 WL in exposure rate being associated with a relative risk of 0.51. The SMRs for Navajo miners were lower for all categories of cumulative exposure than for the white miners. Roscoe et al.⁴⁵ interpreted this as consistent with the lower smoking exposures of the Navajos when compared to the white miners.

A cohort study was also done on New Mexico uranium miners,⁴⁷ who began working in an era when ventilation practices in the mines were becoming commonplace. The exposures received by the 3,469 miners in this cohort were less than those of the Colorado Plateau miners. Consistent with other studies, a significant excess of lung cancer deaths occurred (SMR 4.0, 95% CI: 3.1-5.1). After adjusting for smoking, relative risk in the highest exposure category (> 1000 WLM) was 12.3 times that of the lowest exposure category (< 100 WLM). Relative risk of lung cancer rose more steeply in those with attained age less than 55 years of age than in those 55 or older. Samet et al.⁴⁷ also found a decreasing risk with increasing time since last exposure, and that the relationship between ERR and WLM was 0.018 ERR/WLM, which was similar to other studies.

A brief report of a cohort of French uranium miners was published in 1992.⁴⁸

The reported exposures were less than those of the US miners, with exposures in the range of 1-4 WLM, except in the first ten years of operation of the mine (1946-1955). The lung cancer mortality for these miners was significantly elevated (SMR 2.13, $p < 10^{-4}$). Both the high exposure (those exposed before 1956) and the low exposure (those exposed after 1955) groups had significantly elevated SMRs (2.38 and 1.84, respectively). An interesting feature of the cohort study of French miners was that the relative risk estimates in the pre-ventilation era were about tenfold higher than in the post-ventilation era, which suggests that ventilation may be important in reducing risk.

Tomášek et al.,⁴⁹ following on earlier studies,⁵⁰ reported the mortality experience of uranium miners in West Bohemia. This was a cohort of 4,320 miners with relatively high exposure to radon (average 219 WLM) for whom detailed radon exposure measurements were available from shortly after the opening of the mine. The relative risk of lung cancer mortality in the cohort was 5.08 (95% CI: 4.71-5.47) when compared to the general Czech population. Consistent with other studies reporting a declining risk with increasing time since first exposure, this study found the greatest risk among miners 10 to 14 years from first exposure (RR 9.17, 95% CI: 7.5-11.1) and that it declined thereafter. No data regarding potential confounders, effect modifiers or the inverse-dose-rate effect were given.

Among non-uranium miners, the association between radon exposure and lung cancer was most extensively studied in Chinese tin miners.^{51,52} In 1990, Lubin et al. reported a case control study of miners of the Yunnan Tin Corporation (YTC).⁵¹ This study evaluated the role of radon and smoking in the genesis of the 74 cases of lung cancer, diagnosed within four years of interview and who were alive at the time of study. Controls were chosen from age-matched local residents who were YTC employees and who had not contracted lung cancer. Mean radon exposure was 507 WLM for cases and 247 WLM for controls. This study found that the best model for describing the relationship between radon exposure and smoking was intermediate between

additive and multiplicative; in other words, a sub-multiplicative model (although neither the additive nor multiplicative models could be ruled out definitively). They also found an ERR/WLM of 0.017, which is within the range reported by other studies.

Xuan et al.⁵² describe the largest series of radon exposed miners, consisting of 17,143 Chinese tin miners in whom 981 lung cancers had occurred at the time of study. Average exposure in the cohort was high at 275 WLM lifetime exposure. Relative risk decreased with increasing exposure rate, consistent with the inverse-dose-rate effect. A sub-multiplicative relationship between risk and smoking was found. The ERR/WLM was 0.006, which is lower than in many other studies, including the case-control study of miners from this same cohort that is reported above;⁵¹ however, this may be consistent with the finding of an inverse-dose-rate effect, because, with this cohort having a higher exposure rate, the inverse-dose-rate effect would give rise to a lower ERR/WLM.

Arsenic, a known lung carcinogen, was a potential confounder of the effect of radon exposure present in the cohort of tin miners.⁵² Age-adjusted relative risk reached 8.05 in the highest exposure category (> 800 WLM), but fell to 1.79 (95% CI: 1.0-3.1) when adjusted for arsenic exposure. The corresponding drop in ERR/WLM was 0.062 to 0.0016; however, the authors reported arsenic exposure was highly correlated with radon exposure ($r = 0.6$) and therefore the interpretation of the adjustment for arsenic exposure is problematic.

A number of other studies examined the relationship between radon exposure and risk of lung cancer in base metal miners.⁵³⁻⁵⁵ Although some are methodologically incapable of describing detailed relationships of risk, they are consistent with increased risk of lung cancer with exposure to radon above background levels.

The number, complexity and variability of studies dealing with this issue and the need to control for the important potential confounding factor smoking makes summarization of the literature difficult. Nevertheless, Lubin et al.^{46,56} performed a

pooled analysis of the 11 miner cohort studies for which individual exposure data were available. This pooled analysis included miners who had worked in uranium, iron, fluospar and tin mines, including all of the Canadian cohort studies discussed above. From this pooled analysis, which included 65,000 miners and 1.2 million person years of experience, Lubin et al. concluded that (1) the dose-response relationship was linear, despite differing slopes in the different cohorts; (2) excess relative risk (ERR/WLM) decreased with time since first exposure and attained age; (3) an inverse-dose-rate effect was supported, but was not found at exposures below 50-100 WLM; and (4) ERR/WLM was three times as high for never-smokers (ERR/WLM 0.0103) as for ever-smokers (ERR/WLM 0.0034). Although both the additive and multiplicative models of interaction between smoking and radon exposure were consistent with the pooled data, Lubin et al. concluded that a sub-multiplicative model provided the best fit.⁴⁶ No clear pattern emerged for the potential confounding effect of arsenic exposure, while silica exposure had little impact on the risk coefficients for radon. The BEIR VI pooled analysis used much the same data and approach.³⁰

The available data strongly support the conclusion that lung cancer risk is associated with radon exposures experienced by underground miners in the past. Furthermore, the combined evidence of consistent and strong associations, a biologically plausible mechanism and fully characterized temporal and dose-response relationships support the conclusion that radon exposures can cause lung cancer. While these conclusions relate in particular to high levels of exposure in occupational settings, recent attention has turned to estimation of the risk associated with radon exposures at much lower levels, in particular those found in residential dwellings. The evidence relating to lung cancer risk and residential radon exposure is discussed below.

Residential radon and lung cancer risk

Although the published literature is quite clear with respect to radon posing a risk for lung cancer in the occupational setting of mines with relatively high levels of radon progeny, the risk posed by levels of radon that are commonly encountered in residential settings is less clear. The issue is of critical importance, however, because of the ubiquitous nature of radon and that virtually everyone is exposed to it to some degree. A relatively small excess relative risk that may exist in relation to radon exposures encountered in a residential setting translates into the potential for a far greater number of excess cancers in the general population than does exposure of a relatively small number of miners, although the latter may be exposed to much higher levels of ionizing radiation. Furthermore, the potential risk of radon in the occupational setting resulted in widespread exposure monitoring and extensive efforts at mitigation of risk through use of appropriate ventilation of mining operations. This should result in much lower exposures and corresponding risk. While there has been as yet no widespread organized attempts at monitoring radon levels in homes and mitigation of radon levels where they are found to be excessive, in both the United States and Canada new recommendations have been made to significantly lower the concentration point for radon where mitigation action should be taken. In addition, both have taken steps to inform the public about the risk from radon and are encouraging homeowners to have their homes tested.^{57,58}

Evidence relating to the presence or absence of excess risk of lung cancer due to exposure to radon at levels typically found in homes comes from a large number of studies. These fall into two main groups: ecological studies and studies on individuals.

Ecological studies

Canadian studies

Two related publications described an ecological study of the relationship between lung cancer and residential radon exposure in Canada.^{59,60} In these studies, indoor

radon levels were estimated in 18 Canadian cities and correlated with age-adjusted lung cancer mortality rates for the same cities. A total of 34,380 deaths contributed to the mortality experience. Radon samples were obtained from an average of 778 homes in each of the cities in the summers of 1978 to 1980. No significant correlations were found between average indoor radon levels and lung cancer mortality rates for either males ($r = -0.34$, $p = 0.16$) or females ($r = 0.13$, $p = 0.62$), either before or after adjusting for average rates of smoking.

Stidley and Samet,⁶¹ in reviewing this study, have calculated that there was insufficient power to detect a correlation between lung cancer mortality and residential radon exposure, even had the true correlation been as high as 0.6 (assuming a desired power of 0.8).

Other countries

The review by Stidley and Samet noted above, also looked at 15 ecological studies of lung cancer and indoor radon from a number of countries, including the Canadian study described above. Contained in this review were eight comparison studies and seven ecological regression studies. Stidley and Samet noted that these studies had generated considerable controversy, partly because of the wide between-study variation in results. Seven of the studies had found a positive association between lung cancer and indoor radon, while two had found statistically significant inverse relationships between levels of indoor radon and lung cancer. The remaining six studies had found no association. They also noted that policy makers had placed some reliance on these studies for the purpose of determining appropriate policy direction with respect to indoor radon exposure.

Stidley and Samet concluded the inherent methodological problems associated with ecological studies meant that they should “receive little prominence in describing the public health threat posed by indoor radon, considering their interpretation as evidence of no cancer risk from indoor radon. In fact, further *ecological* studies of indoor radon and lung cancer are to be discouraged.”⁶¹ They showed that both modest levels of measurement error and misspecification of the risk model could bias

the results of ecological studies.⁶² Other authors reached similar conclusions. Samet et al. reported on the outcome of an international workshop on residential radon epidemiology held in 1989. The workshop concluded that analytical studies should be performed and ecological studies should not, unless warranted by “special situation or unique opportunities.”⁶³

Analytical studies

Canadian studies

At least two case-control studies of the relationship between residential radon exposure and lung cancer were conducted in Canada. The largest was a study by Létourneau et al.⁶⁴ conducted in Winnipeg, the community found (in a previous study by Létourneau) to have the highest average radon levels in residences.⁵⁹ Cases were identified through the Manitoba Cancer Treatment and Research Foundation and controls (age and sex matched) were identified at random through the Winnipeg phone directory. Seven hundred thirty-eight case-control pairs were identified between 1983 and 1990. During the initial interview of all subjects (or their proxies), all previous Winnipeg residences occupied by the subjects for periods greater than one year were ascertained. Attempts were made to monitor radon levels in each of the residences that subjects had occupied during their lifetime in the Winnipeg area. This study differed from other case-control studies which monitored only the current residence of the subjects. The authors were successful in monitoring 57 percent of all homes occupied. Measurements were available for nearly 80 percent of the exposures occurring in the window 5 to 15 years before diagnosis of lung cancer. In each of these homes, a radon monitor was placed in the bedroom and basement of the home. Data were collected on potential occupational confounders, education, smoking history and country of birth. These factors were considered predictors in the logistic regression analysis.

The authors did not find a statistically significant relationship between radon exposure and lung cancer. Several issues may have contributed to this finding. First, cases and controls differed significantly in

education level and country of birth. Even though the logistic regression models adjusted for these differences between cases and controls (e.g., smoking), some slight residual confounding may have remained. Second, there were several sources of measurement error: The test radon monitors were accurate within +/- 25%; 34% (4448 out of 13,257) of the measurements resulted in complete data; radon levels at the time of measurement may not reflect historic levels (e.g., in homes renovated); and exposure levels could be modified by factors not accounted for, such as sleeping with an open window.⁶⁵ Given that such measurement error would likely affect cases and controls equally, it could bias the odds ratio for radon towards the null value.

An earlier case-control study involved lung cancer cases who were diagnosed or died of their cancers between 1969 and 1979. Cases lived for at least seven years in Port Hope, Ontario prior to their diagnosis.⁶⁶ The study was undertaken because of concerns that rubble from the demolition of the radium laboratories of the Eldorado Gold Mines Limited facility, used as landfill, was causing high exposures to radon around residences in the community. Cases were identified through the Ontario Cancer Registry. There were 27 cases and 49 controls matched by sex and date of birth. Estimates of radon exposure were obtained from each house occupied by the subjects after 1933.

The authors noted a strong relationship between smoking history and radon exposure. In this instance, when exposure was dichotomized into “lived in a problem home” (i.e., a home with high radon levels) or “did not live in a problem home”, all the high exposure cases were smokers and none of the exposed controls were smokers. Despite finding odds ratios greater than 1.0, which approached statistical significance in their conditional logistic regression analysis, the authors concluded the levels of radon exposure in the “problem” homes were not associated with an increased risk to the occupants. The small sample size resulted in limited statistical power and made it impossible to control for the strong confounding effect of smoking.

In summary, the two Canadian case-control studies found no association between residential radon and lung cancer risk. Although the negative findings may be due partly to design limitations that affected statistical power, the Canadian studies are not unique in this regard,^{67,68} as described further below.

Other countries

Studies of the relationship between residential radon exposure and lung cancer have been conducted in a number of countries including the United States,⁶⁹ Sweden,⁷⁰⁻⁷² Finland,⁷³ England,⁷⁴ and China.⁷⁵ A case-control study of women in New Jersey reported a significant trend in risk with increasing exposure.⁶⁹ Risks were comparable to those obtained from miner cohorts. Trends were strongest among light cigarette smokers.⁶⁹

Two residential radon studies have been conducted in Sweden. One involved a total of 586 women and 774 men with lung cancer and 1,380 female and 1,467 male controls^{70,71}; the second, a total of 210 women with lung cancer and 191 hospital and 209 population controls.⁷² Both studies reported risk associations between radon exposure and lung cancer risk which were comparable to those obtained from miner studies. Although the Finnish study observed elevated risks, there was no apparent dose-response relationship and the increase in risk was not statistically significant.⁷³

A study in Devon and Cornwall, England was one of the largest case-control studies conducted to date, with 982 lung cancer cases and 3,185 hospital and population controls.⁷⁴ Radon exposures over a 30-year period were considered, with measurements obtained in 9,448 out of 13,027 (72.5 percent) of the subjects' homes. When analysis was restricted to the 2,121 subjects for whom complete exposure measurements were available, the ERR per 100 Bq/m³ was 0.14 (95% CI: 0.01-0.29).

A case-control study was conducted in Shenyang, an industrial city in northeastern China.⁷⁵ A total of 308 female lung cancer cases and 356 population controls were studied. No association between radon and lung cancer was observed regardless of cigarette-smoking status.

Meta and pooled analyses

Lagarde and colleagues conducted a pooled analysis of five Swedish case-control studies, restricted to never smokers, resulting in 258 lung cancer cases and 487 controls.⁷⁶ They reported odds ratios of 1.08 (95% CI: 0.8-1.5), 1.18 (95% CI: 0.9-1.6) and 1.44 (95% CI: 1.0-2.1) for radon concentrations of 50, 80 and 140 Bq/m³, respectively, relative to less than 50 Bq/m³. Overall, they observed an excess relative risk of 1.1 per 100 Bq/m³.

In response to recommendations made at the 1989 International Workshop on Radon Epidemiology,⁶³ Lubin undertook a meta-analysis of case-control studies to overcome the small sample size and lack of power of individual studies to detect an elevated risk associated with the low exposure levels that arise in residential settings. Lubin and Boice expected a relative risk of between 1.1 and 1.3 and estimated that the necessary sample size would be from 5,000 to 15,000 lung cancer cases.⁷⁷ The meta-analysis included case-control studies with 200 or more case subjects and measurements in one or more residences for all, or nearly all, subjects. Only eight studies in the published literature met these criteria, including the study performed in Winnipeg by Létourneau et al.⁶⁴

The resulting study contained 4,263 lung cancer cases and 6,612 controls. Lubin and Boice concluded the combined data were consistent with extrapolations from the miner data and that the combined relative risk for an increment in exposure of 150 Becquerels (Bq)/m³ was 1.14. (95% CI: 1.01-1.30). This compares to a model-based RR estimate of 1.13 (95% CI: 1.0-1.2) for miner data where the exposure is less than 50 WLM. In this analysis, it was assumed that a miner exposed to 25 WLM had approximately the same exposure as an individual living 25 years in a house with 231 Bq/m³ of radon. This meta-analysis provided further evidence in favour of a positive, but weak association between radon levels present in typical residences and lung cancer.

In 2005, two large pooled analyses were published: one of the North American case-control studies⁷⁸ and one of the European

case-control studies.⁷⁹ These two studies provide the most compelling evidence to date that residential radon exposure results in an increased risk of lung cancer. The study by Krewski et al.⁷⁸ was based on individual data from the seven North American case-control studies and included 3,662 cases and 4,966 controls. They observed an odds ratio of 1.11 (95% CI: 1.00-1.28) after exposure to radon at a concentration of 100 Bq/m³ in the exposure time window 5 to 30 years before the index date, which was almost identical to that estimated by extrapolating from the miner data (RR 1.12, 95% CI: 1.02-1.28).

The study by Darby et al.⁷⁹ was based on individual data from 13 case control studies from nine European countries. It included 7,148 cases of lung cancer and 14,208 controls. After correcting for the random uncertainties resulting from estimating radon concentrations, the risk of lung cancer was observed to increase by 16 percent per 100 Bq/m³ (95% CI: 5%-31%). The high degree of agreement between the pooled analyses by Krewski et al.⁷⁸ and Darby et al.⁷⁹ and the existence of dose-response relationships for both analyses are evidence that residential radon exposure is causally related to lung cancer.

Radon exposure and malignancies other than lung cancer

Although the primary route of exposure of human tissues to radon is by inhalation into the respiratory tract, this is not the only potential route of exposure. It is also possible for radon to be absorbed into the gastrointestinal tract through contaminated drinking water or food, however, this route of exposure is insignificant compared to inhalation since most radon will volatilize at the tap due to radon's high volatility.^{80,81} Ionizing radiation has also been linked to leukemia, although the relationship has been mainly with gamma radiation rather than the alpha particle radiation produced by radon progeny. A number of other studies have addressed whether other types of malignancy are related to radon.

Ecological studies have suggested that certain malignancies other than lung cancer may be associated with residential radon

exposure. Miller et al.⁸² assessed whether residential radon data from 19 cities in Canada were associated with leukemia incidence rates, as a follow-up to a previous report by Henshaw et al.⁸³ which detected a relationship. Whereas Henshaw et al. had imputed the average provincial residential radon exposures from the data for corresponding cities in those provinces, Miller et al. examined the incidence rates for the cities themselves and found no relationship to the average radon exposures in residences in those cities.

A study by Collman et al.⁸¹ compared childhood cancer rates with average ground water radon concentrations in counties in North Carolina, and found a relative risk of dying from leukemia of 1.33 (95% CI: 1.13-1.57) in the group of counties where radon levels were classified as high. However, data for 25 out of 75 counties had to be imputed because there were no direct measures of radon levels in those counties. A similar study in France⁸⁴ found an elevated risk of dying from acute myelogenous leukemia in adults (SMR 1.08, 95% CI: 1.02-1.15), but not acute lymphoblastic leukemia (SMR 0.96, 95% CI: 0.84-1.10). However, data on radon levels was only available for 41 of 95 of the French *départements* (counties) while it was assumed that levels were low in the remaining *départements*. Lack of data for a large percentage of the *départements* was a significant weakness of this study, which was also subject to the usual limitations of ecological studies.

If associations between non-lung cancers and radon exist, they would most likely be detectable in settings where the exposure to radon is greatest. Several of the mining cohort studies examined the potential for such associations. The Ontario study³² found no significantly elevated risk of any cancer other than lung cancer in the uranium miner cohort. There was also no evidence of an association with non-lung cancers in the Beaverlodge (Saskatchewan) cohort.⁴⁰ In the Newfoundland fluorspar miners, there was a borderline statistically significant excess of cancers of the buccal cavity and pharynx (SMR 2.74, 95% CI: 1.00-5.96).⁴¹ The dose-response could not be assessed because of the small number of cases (six observed cases) and also because

other factors may have been confounders (e.g., smoking and alcohol). It was thus not possible to conclude from the Newfoundland study that radon was the factor responsible for this excess cancer risk. In the Chinese tin miner cohort, there was a statistically significant excess of lymphomas (five observed cases, $p = 0.03$). Again, the small number of cases precluded detailed dose-response analysis, but when tertiles of radon exposure were used, the relative risk of lymphoma in the highest tertile group was 7.4 compared to the lowest tertile. In the Colorado Plateau cohort,⁴⁴ a statistically significant excess of “Other & unspecified site” tumours (SMR 1.6, 95% CI: 1.2-2.2) and “Benign & unspecified tumours” (SMR 2.4, 95% CI: 1.0-4.6) was found in the white members of the cohort. The meaning of these findings is unclear, but some of these tumours may have been lung cancers that were misclassified (e.g., the primary tumour was not found or could not be distinguished from metastatic disease). Neither of these excess rates was in evidence in the Navajo members of the same cohort.⁴⁵ In the West Bohemian uranium miner cohort,⁸⁴ there was a statistically significant excess of cancers of the liver (SMR 1.67, 95% CI: 1.16-2.52) and gallbladder and extrahepatic bile ducts (SMR 2.26, 95% CI: 1.16-3.94). The liver cancer rate was not correlated with cumulative radon exposure; thus the authors concluded that the excess of liver cancers was likely due to factors other than radon exposure. The biliary tree cancer rates were positively correlated with cumulative radon exposure, but the association was inconsistent with dosimetric evidence from other studies.⁸⁵

In an effort to increase statistical power to detect potential associations between radon and malignancies other than lung cancer, Darby et al.⁸⁶ pooled the data from 11 miner cohorts. These 11 cohort studies were the same as those employed by Lubin et al. in their analysis of lung cancer risk.⁵⁶ Darby et al. found a significant increase in leukemia deaths (SMR 1.93, 95% CI: 1.19-2.95) in miners who worked for less than ten years. They also found an increase in stomach cancer deaths (SMR 1.33, 95% CI: 1.16-1.52) and liver cancer deaths (SMR 1.73, 95% CI: 1.29-2.28); however, these were

not related to cumulative exposure, and the authors concluded that they were not likely due to radon exposure.

Darby et al. also noted statistically significant deficits in deaths related to cancers of the tongue and mouth, pharynx and colon, but there does not appear to be any rationale for considering these deficits to be due to radon exposure. The overall conclusion from this study was that exposure to radon did not pose a serious threat with respect to any cancer other than lung cancer.

Case-control studies also examined the potential for association between leukemia rates and residential radon exposure. Lubin et al.⁸⁷ performed a study of childhood acute lymphoblastic leukemia involving cases and controls from nine states in the USA. Cases were eligible if they were less than 15 years old at diagnosis. Radon levels were measured for 97 percent of the exposure period for 505 cases and 443 controls. No association between leukemia rates and even the highest radon exposure levels (> 147 Bq/m³) was found and the authors concluded that there was no evidence of an association. This study had similar limitations to case-control studies of the association between radon and lung cancer, namely the possibility for mis-specification of the risk model, the potential for errors in the exposure assessment and an insufficiently large sample size.⁶⁸

Health implications for Canadians

There is no convincing evidence that any cancers other than lung cancer are associated with exposure to radon. There is consistent evidence of a substantially elevated risk of lung cancer among Canadians exposed to radon in certain occupational settings, particularly among uranium miners who received radon doses significantly above background doses. The decrease in the number of miners engaged in uranium mining activities and the increasing awareness of the risk (which has resulted in personal exposure monitoring of these workers and government-regulated dose limits, in conjunction with improved ventilation in the mines) should

result in a decrease in the risk of lung cancer associated with radon. Given these changes and the relative few employed in the high risk occupations, workplace exposure to radon likely contributes very little to the overall risk to Canadians.

The Environmental Protection Association (EPA) used Lubin and Boice’s meta-analysis⁷⁷ to estimate that residential radon exposure results in between 7,000 and 30,000 lung cancer deaths per year in the United States. The UNSCEAR 2000 Report⁸⁸ also summarized the literature and noted the effect of errors in assessing exposure to indoor radon and concluded that greater statistical precision in estimating risk is required before conclusions are drawn about the magnitude of the health risk.

In the United States, the EPA has recommended that action be taken to reduce residential radon concentrations when they exceed 148 Bq/m³. The BEIR VI Committee has calculated that the contribution to the attributable risk of radon levels above this action point was 30 percent of lung cancer deaths. If radon mitigation efforts were completely effective at reducing high radon levels to below the recommended action level, then the total reduction in lung cancer mortality would be 3 to 4 percent (i.e., 30 percent of the 12-14 percent of lung cancers attributable to radon) in the United States. In Canada, the recommended action level was reduced from 800 to 200 Bq/m³ in 2006 and officially adopted in 2007. ICRP-65 recommends a radon action level between 200 and 600 Bq/m³.⁸⁹ Most countries have adopted an action level for new homes of 200 Bq/m³.⁸⁸ Based on a risk model developed by the EPA, radon has been estimated to be responsible for over fifteen hundred cases of lung cancer a year in Canada.⁹⁰ Brand has used the BEIR-VI analysis in a Canadian context to estimate the population attributable risk for lung cancer mortality associated with radon at 8% (95% CI: 4%-14%).⁹¹

In the case of radon, government-mandated remediation below these recommended levels is considered too difficult and costly when there are techniques available to homeowners to reduce radon concentrations. Based on its interpretation of the

available data, the EPA in the United States has begun to inform the US public about the potential risk of lung cancer due to radon in the residential setting. A guide has been produced to inform physicians about the risk of lung cancer from radon. In this guide, the EPA states the following:

While smoking remains the number one cause of lung cancer, radon presents a significant second risk factor. That is why, in addition to encouraging patients to stop smoking, it is important for physicians to inquire about and encourage patients to test for radon in their homes.

and:

Enough data exists now, however, to be able to say with certainty that thousands of preventable lung cancer deaths annually in the United States are attributable to indoor residential exposure to radon.⁵⁸

Health Canada has produced a similar guide for homeowners.⁵⁷ A number of techniques are available to homeowners to reduce radon concentrations in their homes. These techniques, which are of modest cost, can be effective in reducing radon levels to approximately 75 Bq/m³.⁵⁸ This is half the action level recommended by the EPA, indicating that the EPA recommendations are achievable.

The reduction of the Canadian-recommended action levels, taking into account the most recent evidence regarding the association between lung cancer and radon exposure in the residential setting, appears warranted.

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Ultraviolet radiation

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The major source of ultraviolet radiation is solar radiation or sunlight. However, exposure to artificial sources particularly through tanning salons is becoming more important in terms of human health effects, as use of these facilities by young people, has increased. The International Agency for Research on Cancer has noted that there is sufficient evidence from studies in animals and in man to establish ultraviolet radiation as a human carcinogen.

Skin cancer has been the most commonly studied cancer site with respect to UV radiation. The nature and timing of sun exposure appear to be important determinants of both the degree of risk and the type of skin cancer. Cutaneous malignant melanoma and basal cell cancer are much more strongly related to measures of intermittent ultraviolet exposure (particularly those of childhood or adolescence) than to measures of cumulative exposure. In contrast, squamous cell cancer is more strongly related to constant or cumulative sun exposure. Lip cancer is causally related to lifetime sun exposure.

It has been estimated that solar ultraviolet radiation accounts for approximately 93 percent of skin cancers and about half of lip cancers. This translates to approximately 4,500 life-threatening cancers (cutaneous malignant melanoma) per year in Canada, as well as 65,000 less serious cancers (basal cell cancer, squamous cell cancer and lip cancer). Appropriate clothing use, care not to sunburn and judicious use of sunscreens could prevent at least half of these and save approximately 450 lives per year. In addition, physician and public education programs can significantly increase the proportion of melanomas diagnosed early. Lesions that have not yet penetrated deeply are associated with a mortality rate of less than five percent.

Several recent studies suggest a possible inverse relationship between ultraviolet radiation exposure and risk of non-Hodgkin lymphoma, colon, breast and prostate

cancer, and investigators have speculated that this might be due to the higher serum levels of vitamin D stimulated by high lifetime sun exposure. Further, studies conducted within cohorts using stored pre-diagnostic serum suggest that those with high levels of vitamin D have lower incidence rates of a number of malignancies, particularly colon cancer. However, since serum vitamin D levels can be raised through the use of supplements without increasing risk for skin lip and other known UV-related cancers, changes to health policy with regard to exposure are not merited at this point. Further research is needed in this area.

Introduction

Optical radiation within the electromagnetic spectrum includes ultraviolet radiation (UVR), visible light and infrared radiation. UVR, as used in this review, is defined as that radiation between 100 and 400 nanometres (nm) in length (WHO 1994).¹ It is characterized further according to wave length into ultraviolet A (315–400nm), B (280–315nm) and C (100–280nm).

The major source of UVR is solar radiation or sunlight. Ultraviolet C (UV-C), from the sun, is virtually completely screened out by the Earth's atmosphere, and is thus a negligible source of adverse human health effects. Ultraviolet B (UV-B) is responsible for erythema (sunburn), and associated with an increased risk of skin cancer, and immunosuppression. However, solar UV-B is crucial in the synthesis of vitamin D, which some recent studies suggest may potentially reduce risk of colon, prostate and breast cancers. Ultraviolet A (UV-A) contributes to skin aging and has more recently been implicated, along with UV-B, in the development of skin cancers in animals and in immunosuppression in humans. Although the sun is the main source of UV-A exposure, use of UV-A-emitting lamps in sunbeds for recreational tanning has raised concern about artificial sources of human exposure.

The International Agency for Research on Cancer has noted that there is sufficient evidence from studies in animals and in man to establish UVR as a human carcinogen (IARC 1992).² For the most part, this review will focus on UVR as a single exposure without an attempt to separate the effects of the types noted above. This is because most of the human evidence concerning the health effects of UVR relates to reported sunlight exposure. When artificial sources of UVR are used in animal studies, distinguishing the separate effects of UV-A and UV-B is often possible. However, to date, this has not been possible in human epidemiological studies, most of which are retrospective and depend on subject recall. Animal studies will, in general, not be referred to in this review except where no alternative evidence is available.

Cancer and ultraviolet radiation

This review focuses initially on the positive relationship between UVR and the three major types of skin cancer: cutaneous malignant melanoma (CMM), basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). In addition, the potential relationship with cancer of the lip and with uveal (ocular) melanoma is discussed. Recent evidence has suggested a potential association between UVR and non-Hodgkin lymphoma. This hypothesis is examined, along with the hypothesis that solar exposure may reduce risk of colon, breast and prostate cancer through stimulation of increased serum vitamin D levels. Finally, all of the evidence is considered with a view to assessing the impact of UVR on the burden of cancer in Canada.

Cutaneous malignant melanoma

Solar ultraviolet radiation

The age-sex standardized incidence of CMM has increased markedly over the past 25 years in Canada (Gallagher et al., 1990; Gaudette and Gao, 1998)^{3,4} such that it represents significant health problem from a population health based perspective.

Studies have revealed that the major environmental risk factor is solar and artificial UV exposure and that the principal modifying factor of this exposure is individual susceptibility as indicated by host pigmentation and sun sensitivity.

Solar UVR exposure is estimated to account for about 93 percent of melanomas in Canada (Armstrong and Kricker, 1993).⁵ Early descriptive studies observed associations between the latitude of residence and melanoma incidence and mortality in Caucasian populations (Lancaster, 1956; Elwood et al., 1974; Fears et al., 1976).^{6,7,8} The association, however, was not as strong as might have been predicted were there a simple and direct relationship between total UVR exposure and melanoma incidence. This led investigators to hypothesize that the character and timing of exposure might be more relevant than total lifetime exposure in inducing CMM (Elwood and Hislop, 1982; Holman et al., 1983).^{9,10}

Over the following 15 years, more than 25 case-control and cohort studies addressed this and other hypotheses concerning solar ultraviolet radiation; these studies have been evaluated in the review of Elwood and Jopson (1997).¹¹ Of the 29 studies outlined in Table 1, 22 evaluated at least one measure of intermittent solar exposure, usually defined as recreational time spent in the sun. A statistically significant positive association between intermittent exposure and melanoma risk was seen in 16 of the investigations ($p < 0.05$). In contrast, chronic or constant solar exposure, usually defined as occupational in origin, was assessed in 20 studies, the majority demonstrating either no increased risk or a reduced risk in those with the highest levels. Total sun exposure was studied in 11 investigations, with an absence of an association in all but two (those of Grob et al.²⁸ and Rodenas et al.³⁹), which observed increased risk of melanoma among those with higher exposures. Both of these studies, however, were conducted among Mediterranean subjects which differ from Canadians as they are, on average in high sunlight areas and possibly with respect to other risk factors for melanoma. Therefore, the extrapolation of these

findings to the Canadian population is not straightforward.

With respect to other risk factors for melanoma, differences in the populations in which studies of sun exposure and melanoma are conducted can affect risk estimates because pigmentation factors render some individuals more susceptible to melanoma than others. Individuals with light skin, hair and eye colour were consistently found to be at elevated risk of CMM in virtually all case-control and cohort studies of this tumour in the early 1980s.¹²⁻⁴⁵ Furthermore, the propensity of the skin to burn—rather than tan—in the sun also consistently increases risk.^{20, 21,43-46} Finally, the presence of either freckling^{41,47} or acquired melanocytic nevi (skin moles) substantially increases risk,^{42-44,47,48} and at least one study reported a synergistic effect of these two factors.⁴⁵

Overall, the results indicate that intermittent solar exposure is associated with an increased risk of melanoma in light-skinned populations, while constant or occupational exposure is associated with either no increase or a decrease in risk. Total solar exposure appears not to be associated with increased or decreased risk, except in Mediterranean populations, in which darker skin type may modify its effect. A cautious approach must be taken in interpreting the essentially negative findings for cumulative sun exposure. Most studies have been conducted in highly developed Western countries where indoor work predominates, effectively limiting the degree of cumulative exposure most people can accrue. Thus an effect for cumulative exposure might be missed due to limited range of exposure in these studies.

While the evidence indicates that the character of solar exposure is important in CMM, other findings, particularly those carried out in Australia, indicate that timing of exposure may also be important. Khlat et al.⁴⁹ demonstrated that migrants arriving in Australia after the age of 15 from low sunlight areas, such as the UK, had substantially lower mortality from CMM than those who arrived at a younger age. Other studies demonstrate a substantially reduced risk for melanoma in individuals coming to

Australia after age nine, when compared to those who are native born, even after controlling for lifetime exposure.^{43,44} A US study showed that early life spent in high sunlight southern states conferred an increased adult melanoma risk even among subjects who had later moved to low sunlight states.⁵⁰ Results of these investigations suggest that childhood may be a particularly susceptible period in relation to later risk of CMM.

In summary, as melanoma rates are substantially higher in white populations in high sunlight areas⁵¹ than in low sunlight areas, ambient levels of solar irradiance are clearly important in accounting for melanoma incidence. However, the analytic studies indicate that character and timing of exposure are also important, particularly in accounting for risk at the individual level. Armstrong⁵² has succinctly summarized the available information and hypothesized that for a particular intermittent pattern of exposure to solar UV, melanoma risk increases monotonically with increasing amount of exposure, and (for a given amount of exposure) risk of melanoma increases monotonically as exposure becomes more intermittent.

Recently, several studies have suggested that there may be at least two alternative etiologic pathways to melanoma.⁵³⁻⁵⁵ These studies are potentially very important as they suggest that the relationship between host susceptibility factors (skin colour, sun-sensitivity, nevus density, freckling density) and melanoma—and perhaps even the degree of solar exposure necessary for evolution of frank malignancy—may differ between the pathways. If this proves to be the case, it is likely that risk ratios associated with both susceptibility factors and solar exposure may have been substantially “diluted” in past epidemiologic studies due to inappropriate aggregation of etiologically distinct lesions.

Finally, a comparatively small proportion of malignant melanomas are due to what has been called either the atypical (dysplastic) nevus syndrome or familial atypical multiple mole-melanoma syndrome. Initially this was thought to be a phenotypic expression of a germline mutation

TABLE 1
Summary of case-control studies on solar UV radiation exposure and cutaneous malignant melanoma

Place of study	Diagnosis years	Overall no. cases/controls	OR (95% CI) in highest sun exposure category			Reference
			Intermittent	Occupational	Total	
Norway	1974-75	78/131	2.4 (1.0-5.8)	1.4 (0.6-3.5)	–	Klepp & Magnes 1979 ¹²
UK	1971-76	111/342	1.5 (0.9-2.5)	–	–	Adam et al. 1981 ¹³
Scotland	1978-80	113/113	0.6 (0.2-1.2)	0.4 (0.1-0.7)	–	Mackie & Aitchison 1982 ¹⁴
USA	1978-79	111/107	2.5 (1.1-5.8)	–	–	Lew et al. 1983 ¹⁵
USA	1978-81	114/228	2.4 (1.2-5.0)	–	1.6 (1.0-2.6)	Rigel et al. 1983 ¹⁶
Canada	1979-81	595/595	1.7 (1.1-2.7)	0.9 (0.6-1.5)	1.2 (0.7-2.0)	Elwood et al. 1985 ¹⁷
USA	1974-80	404/521	–	0.7 (0.3-1.3)	0.6 (0.4-0.9)	Graham et al. 1985 ¹⁸
UK	1980-82	58/333	6.5 (not given)	–	–	Sorahan & Grimley 1985 ¹⁹
USA	1972-82	1,103/585	1.7 (1.2-2.3)	2.5 (1.4-4.4)	1.1 (0.8-1.6)	Dubin et al. 1986 ²⁰
UK	1981-84	83/83	–	1.7 (0.3-8.6)	–	Elwood et al. 1986 ²¹
Australia	1980-81	511/511	1.1 (0.7-1.8)	–	0.7 (0.4-1.1)	Holman et al. 1986 ²²
Australia	1979-80	183/183	1.9 (0.5-7.4)	–	2.3 (0.9-6.1)	Green et al. 1986 ²³
Italy	1983-85	103/205	0.9 (0.5-1.7)	–	0.6 (0.4-1.0)	Cristofolini et al. 1987 ²⁴
Italy	1984-86	208/416	–	2.1 (0.6-6.8)	–	Zanetti et al. 1988 ²⁵
Denmark	1982-85	474/926	1.8 (1.2-2.5)	0.7 (0.5-0.9)	–	Osterlind et al. 1988 ²⁶
Germany	1987	200/200	–	5.5 (1.2-25.3)	–	Garbe et al. 1989 ²⁷
France	1986-88	207/295	8.4 (3.6-19.7)	2.5 (1.2-5.1)	3.8 (2.2-6.5)	Grob et al. 1990 ²⁸
Sweden	1978-83	523/505	1.8 (1.2-2.6)	0.6 (0.4-1.0)	–	Beitner et al. 1990 ²⁹
USA	1979-82	289/527	1.5 (1.0-2.4)	1.8 (0.9-4.0)	1.7 (1.1-2.8)	Dubin et al. 1990 ³⁰
Italy	–	260/416	2.3 (1.4-3.8)	–	–	Zanetti et al. 1992 ³¹
USSR	–	–	3.4 (0.6-17.4)	–	–	Zaridze et al. 1992 ³²
USA	1977-79	324/415	2.0 (1.3-3.3)	0.7 (0.5-1.0)	–	Herzfeld et al. 1993 ³³
Pan-European	1991-94	420/447	6.1 (1.8-20.3)	0.3 (0.1-0.9)	–	Autier et al. 1994 ³⁴
Netherlands	–	128/168	2.4 (1.3-4.2)	–	–	Nelemans et al. 1994 ³⁵
USA	1984-87	256/273	–	0.6 (0.3-1.2)	0.9 (0.5-1.6)	White et al. 1994 ³⁶
Sweden	1988-90	400/640	1.2 (0.8-1.8)	0.8 (0.6-1.0)	–	Westerdahl et al. 1994 ³⁷
USA	1981-86	452/930	0.8 (0.6-1.1)	0.8 (0.5-1.5)	–	Holly et al. 1995 ³⁸
Spain	1988-93	105/138	4.9 (2.2-10.9)	3.7 (1.7-7.5)	5.4 (2.4-12.0)	Rodenas et al. 1996 ³⁹
USA	1987-89	548/494	H&N 2.6 (1.2-5.6)	0.5 (0.2-1.1)	–	Chen et al. 1996 ⁴⁰
			UL 2.4 (1.2-4.8)	0.6 (0.2-1.1)		
			LL 2.7 (1.2-5.8)	0.3 (0.1-0.9)		
			T 2.7 (1.6-4.5)	0.9 (0.6-1.3)		

Table 1 adapted from Elwood and Jopson; *Int J Cancer*, 1997;73:198-203.

OR = Odds ratio; 95%
 CI = 95% confidence intervals
 H&N = Head and Neck
 UL = Upper Limb
 LL = Lower Limb
 T = Trunk

predisposing to familial melanoma. More recently, a specific (CDKN2A) germline mutation on chromosome 9p21 has been found to be associated with melanoma in about 50 to 80 percent of families with very high incidence of melanoma.^{56,57} At the present time, these germline mutations are thought to be transmitted from one generation to another in an autosomal dominant pattern, with variable penetrance, and individuals with them appear to be at high risk for the disease. However, such mutations account for fewer than 10 percent of the melanomas, and as population-based rather than family-study-based data on the mutation becomes available, this estimate will undoubtedly decline further. Interestingly, the presence of CDKN2A mutations does not appear to materially affect the relationship between solar UV and melanoma risk in carriers.⁵⁸ Reported family history of melanoma in a first degree relative (without testing for CDKN2A mutation) is only associated with approximately a twofold elevated risk of melanoma.⁵⁹

Artificial ultraviolet radiation

A total of 14 studies have evaluated risk of melanoma in sunlamp and sunbed users,^{21,22,26,37,38,46,60-67} although the relatively minimal data presented in four of them preclude a proper interpretation of their results.^{21,22,46,67} Table 2 presents selected results from the ten studies with relatively complete data. Because most of the studies conducted to date have small numbers of exposed subjects, they have limited statistical power. This has resulted in unstable risk ratios, with wide confidence intervals surrounding the risk estimates. Because of this, a recent meta-analysis was conducted in an attempt to summarize current knowledge.⁶⁸ Ten studies provided estimates of risk for being exposed to sunbeds and sunlamps. Where possible, risk ratios adjusted for host susceptibility and sun exposure were used in the analysis. Compared to those with no exposure, those who had ever used sunlamps or sunbeds had a 25 percent increase in risk of CMM, which was statistically significant (95% CI: 1.05-1.49). Compared with subjects having no sunlamp or sunbed exposure, those with the “longest duration or highest frequency of exposure” had a relative risk of 1.61 (95% CI, 1.21-2.12). The analysis

suggests that, overall, the existing body of epidemiological work indicates that use of sunbeds and sunlamps does increase risk of CMM.

Results of the meta-analysis must be interpreted with caution because there is likely to be at least some residual confounding due to host factors. Furthermore, individuals who use sunbeds to tan are also likely to engage in concomitant sunbathing. If this exposure is not adequately controlled for in the analyses, it is possible that the increased risk attributed to sunbed use may be explained in whole or in part by solar exposures. Finally, recreational exposure to artificial UV prior to the early 1980s entailed substantial UV-B exposure, whereas later (largely commercial) exposure was predominantly to UV-A. Thus, an analysis combining these exposures could conceivably be aggregating qualitatively different exposures. However, it should be noted that risk ratios from later studies do not appear to differ materially from those seen in earlier studies.

More research is necessary in this field to answer unresolved issues surrounding the relationship between artificial UV and CMM. Though contrary to some popular advertising, the body of available evidence does not suggest that artificial tanning reduces risk of CMM.

Solar UV-A

Solar UVR that reaches the Earth’s surface comprises approximately 95% UV-A and 5% UV-B; UV-C is completely filtered out by the Earth’s atmosphere.² Recent studies using the Xiphophorus fish model have demonstrated that UV-A radiation is effective in inducing malignant melanoma in this species.⁶⁹ In particular, melanoma induction showed particular sensitivity at the 365 and 405 nm wavelengths. Such findings have led to the suggestion that UV-A radiation may also induce CMM in humans.⁷⁰ This has led other investigators to suggest that the advent of effective UV-B sunscreens in the 1960s, and their adoption for common use shortly thereafter, may have inadvertently fueled the increase in CMM incidence as a result of increased UV-A exposure.⁷¹ The authors propose that light-skinned individuals might expose

themselves to the sun for much longer periods than previously because the onset of erythema is delayed by sunscreen use. This makes possible substantially more UV-A exposure in melanoma-susceptible individuals. A randomized trial conducted by Autier et al. tested the hypothesis that use of higher sun protection factor (SPF) sunscreens encourages longer exposure.⁷² Study subjects were randomized to unlabelled SPF 10 or SPF 30 sunscreen prior to vacation with instruction to use the sunscreen as needed and record time in the sun. Both groups used similar amounts of sunscreen, recorded similar sunburn patterns and similar mean vacation days, but subjects randomized to the SPF 30 compound spent significantly more time in the sun each day than those randomized to the lower SPF sunscreen. Thus, though there is some empirical evidence to support the notion that sunscreen use increases time in the sun, the findings apply as strongly to UV-B as to UV-A. It should be noted that the increase in incidence of CMM began prior to the advent of sunscreens,⁷³ and that current incidence data suggest that age-standardized melanoma rates in young people are levelling off and perhaps beginning to decline.⁷⁴ This trend is happening in the face of increasing popularity of very high SPF sunscreens, which should be allowing greater UV-A (and UV-B) exposure than ever.

Non-melanocytic skin cancer

Solar ultraviolet radiation

Ecological data collected in the US in the 1970s on the relationship between solar UVR and the two major forms of non-melanocytic skin cancer (NMSC), namely basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), indicated an incidence gradient from north to south within the country among the white population. This gradient correlated well with indices of UVR obtained using Robertson-Berger meters situated close to the areas where the cancer incidence information was collected.⁷⁵ This close correlation reinforced the prevailing hypothesis that the two major forms of NMSC were directly related (in white individuals) to cumulative solar UV exposure. However, recent results from a number of well-conducted analytic studies

TABLE 2
Summary of case-control and cohort studies of sunlamp or sunbed use and cutaneous malignant melanoma

Place of study	Diagnosis years	No. of cases/controls	Exposure	Summary OR	Reference
Eastern Denmark	1982-85	474/926	Sunlamp and sunbed use	0.7 (0.5-1.0)	Osterlind et al. 1988 ²⁶
Scotland	1979-84	180/197	Sunlamp and sunbed use	2.9 (1.3-6.4)	Swerdlow et al. 1988 ⁶⁰
Southern Ontario, Canada	1984-90	583/608	Sunlamp and sunbed use	Males: 1.9 (1.2-3.0) Females: 1.5 (1.0-2.1)	Walter et al. 1990 ⁶¹
Germany	1984-87	856/705	Use of sunbeds	1.5 (0.9-2.4)	Garbe et al. 1993 ⁶³
Pan-European	1991-93	420/447	Sunlamp or sunbed use	Overall: lamps: 1.3 (0.8-2.0) Beds: 0.8 (0.6-1.2) Tanning: lamps: 1.8 (1.0-3.2) Beds: 1.0 (0.6-1.4)	Autier et al. 1994 ⁶²
Southern Sweden	1988-90	400/640	Sunlamp or sunbed use	Overall: 1.3 (0.9-1.8)	Westerdahl et al. 1994 ³⁷
California, USA	1981-86	452/930	Sunlamp use	0.9 (0.7-1.2)	Holly et al. 1995 ³⁸
Connecticut, USA	1987-89	624/512	Sunlamp use	1.13 (0.8-1.5)	Chen et al. 1998 ⁶⁴
South Sweden	1995-97	571/913	Sunbed use	1.2 (0.9-1.6)	Westerdahl et al. 2000 ⁶⁵
Sweden and Norway	1991-99	Total cohort 106,379	Sunbed and sunlamp use	1.55 (1.0-2.3)	Veierod et al. 2003 ⁶⁶

OR = Odds ratio

Odds ratios presented are adjusted for other known melanoma risk factors (susceptibility and sun exposure) where such adjustment was carried out in the study.

(Table 3) suggest that the relationship of SCC and BCC to UVR is as complex as that seen for CMM.

Most studies⁷⁶⁻⁸⁸ have used relatively simple questions to elicit information on solar exposure from subjects. Results from one study⁸⁴ are difficult to interpret as BCC and SCC were combined in the analysis. In addition, the Egyptian population used in the study differs from other investigations in terms of pigmentary risk characteristics.

Later studies were designed specifically to separate the contributions of intermittent and constant solar exposure to risk, and appear to show differences between BCC and SCC.⁸⁹⁻⁹³ Overall, the studies demonstrate little or no relationship between measures of intermittent recreational exposure and SCC, but significant associations with BCC. Indeed, the studies of Kricger et al.⁸⁹ and Gallagher et al.⁹⁰ both suggest a dose-response gradient in BCC risk with increasing exposure to recreational UVR, particularly in youth. For SCC, the weight of evidence appears to suggest that risk is related to measures of constant (occupational or cumulative) exposure. In the study of Gallagher et al.,⁹¹ this form of skin cancer is related to exposures in the ten years prior

to diagnosis, while the Rosso et al.⁹² and English et al.⁹³ studies indicate a relationship with longer-term occupational exposure.

While results of these studies require confirmation, it appears that cutaneous malignant melanoma and BCC share a number of similarities in their relationships with solar UVR. Both appear much more strongly related to measures of intermittent UV exposure, particularly in early life, than to measures of cumulative lifetime exposure. Squamous cell carcinoma appears to be different in that it owes more to constant or cumulative sun exposure than to intermittent exposure. In addition, there is as yet little evidence which has reported that sun exposure in childhood or youth is strongly related to this disease.

Artificial UV exposure

There have been few studies specifically addressing the potential relationship between sunbed and sunlamp use and risk of NMSC.^{76,94} The few investigations conducted to date are summarized in Table 4. Overall, they indicate little increased risk, with the exception of the study of Aubrey and MacGibbon.⁷⁶ However, the 13-fold increased risk of SCC seen in subjects using “long-tube sunlamps” is based

on small numbers of study subjects, and so must be interpreted with caution. Well-conducted analytic studies with quantitative exposure data and good control for susceptibility factors and concomitant sun exposure are urgently needed to clarify risk.

Cancer of the lip

Cancer of the lip is rare in Canada and comprised only about 0.2 percent of cancers in females and 1.3 percent in males during the period 1984-1988, although by 2003 the rate in females had dropped to 0.1 percent and for males to 0.4 percent.^{95,96} The decline among males is likely due to the reduced rates of smoking and the continuing reduction in outdoor occupations.^{96,97} Both male and female proportional declines are also likely influenced by increases in incidence at other cancer sites. Evaluation of incidence rates in this cancer is complicated by the fact that diagnoses are a mixture of neoplasms of the external lip and the oral cavity.² Descriptive studies show that lip cancer is more common in males than females and that incidence rates are higher in light- than dark-skinned populations living in the same geographic area.⁵¹ Evaluation of mortality and incidence data from Australia show that rates of lip cancer are

Table 3
Summary of case-control and cohort studies of solar UV radiation and non-melanocytic skin cancer

Place of study	Diagnosis years	Type of study	No. of cases	No. of comparison subjects	OR (95% CI) in highest sun exposure category			Reference
					Intermittent	Occupational	Total	
Canada	1977-78	Case-control	92	174	SCC: 4.6 (0.58-36.53)	SCC: 9.12 (0.99-84.47)		Aubrey & MacGibbon, 1985 ⁷⁶
Australia	1987	Cross sectional	42	2,095 total subjects		SCC & BCC: 1.76 (0.77-4.05)		Green et al. 1988 ⁷⁷
USA	1985-86	Cross sectional	33 BCC 35 SCC	808 subjects		BCC: 1.11 (0.5-2.44) SCC: 2.53 (1.18-5.40)		Strickland et al. 1989 ⁷⁸ Vitasa et al. 1990 ⁷⁹
Canada	1988	Case-control	538 BCC	738		BCC: 1.29 (1.12-1.46)		Hogan et al. 1989 ⁸⁰
Australia	1985-87	Cross sectional	66 BCC 21 SCC	1,770 total subjects	BCC: 0.6 (0.3-1.3) SCC: 3.9 (0.5-30.9)	BCC: 1.3 (0.6-2.8) SCC: 5.5 (1.1-28.2)		Green & Battistutta, 1990 ⁸¹
USA	1980-84	Cohort	771 BCC	73,366 total cohort			BCC ^c : ≈ 1.4 (calculated)	Hunter et al. 1990 ⁸²
USA	1982-90	Cohort	197 SCC	107,900 total cohort			SCC ^c : ≈ 1.4 (calculated)	Grodstein et al. 1995 ⁸³
Egypt	91	Case-control	136 BCC & SCC	145		BCC and SCC ^b : 7.7 (4.0-14.6)	BCC and SCC ^d : 6.1 (2.3-16.0)	Khwsy et al. 1994 ⁸⁴
Australia	1987	Case-control within a cohort	226 BCC	1,015	BCC: 3.86 (1.93-7.75)			Kricker et al. 1995 ⁸⁹
Canada	1983-84	Case-control	226 BCC SCC	406	BCC: 2.6 (1.1-6.5) ^e SCC: 1.6 (0.6-4.5) ^e	BCC: 1.4 (0.8-2.4) SCC ^a : 4.0 (1.2-13.1)	BCC: 1.3 (0.7-2.4) SCC: 1.0 (0.4-2.1)	Gallagher et al. 1995 ^{90,91}
Pan-European	1989-93	Case-control	1,549 BCC 228 SCC	1,795	BCC: 1.47 (1.18-1.83) SCC: 0.63 (0.39-1.03)	BCC: 0.84 (0.65-1.10) SCC: 1.60 (0.93-2.75)		Rosso et al. 1996 ⁹²
Australia	1987	Case-control within a cohort	132 SCC	1,031	SCC on usually exposed sites: 1.3 (0.57-2.90) SCC on usually non-exposed sites: 0.94 (0.36-2.60)	SCC on usually exposed sites: 1.3 (0.58-2.80) SCC on usually non-exposed sites: 1.8 (0.55-5.60)		English et al. 1998 ⁹³

OR = Odds ratio; 95% CI = 95% confidence intervals

^a Occupational sunlight in the 10- years prior to diagnosis

^b Outdoor vs. indoor occupation

^c Recreational sunlight exposure age 0-19

^d Heavy sun exposure vs. light exposure

^e Subjects who used sunscreen and had 8 or more hours per week of sunlight compared to those with < 8 hours/week of exposure.

^f Subjects who used sunscreen and had "regular time outdoors" compared to those without regular time outdoors.

TABLE 4
Summary of case-control or cross sectional studies of sunlamp & sunbed use and non-melanocytic skin cancer

Place of study	Diagnosis years	No. of cases/controls	Exposure	Summary OR in highest exposure category (95% CI)	Reference
Canada	1977-78	92/174	Sunlamp use	13.42 (1.38-130.48)	Aubrey & MacGibbon 1985 ⁷⁶
Ireland	Unknown	63 SCC & 58 BCC/121	Artificial sunlight	0.3 ns (calculated)	O'Loughlin et al. 1985 ⁸⁵
Ireland	1984-85	396 BCC & SCC /396	Sunlamp & sunbeds	0.7 ns (calculated)	Herity et al. 1989 ⁸⁶
Canada	1960s to 1980s	857/2,753	Medical phototherapy or sunbed use	1.33 (1.04-1.70)	Hogan et al. 1991 ⁸⁷
USA	1980-86	1,805	Sunbathing or sunlamp use	1.04 (0.67-1.63)	Karagas et al. 1992 ⁸⁸
Canada	1984-85	226 BCC & 180 SCC/406	Sunlamp use	BCC: 1.2 (0.7-2.2) SCC: 1.4 (0.7-2.7)	Bajdik et al. 1996 ⁹⁴

OR = Odds ratio; 95% CI = 95% confidence intervals

lower in migrants from low sunlight areas than they are in native-born Australians.^{98,99} This finding is suggestive of the pattern seen in malignant melanoma in Australia⁴⁹ and may indicate the importance of sun exposure in youth for lip cancer.

Several studies have indicated that outdoor workers, such as farmers¹⁰⁰⁻¹⁰² and fishermen,¹⁰³ have elevated risks for lip cancer relative to the general male population or other males. A case-control study conducted in Los Angeles to evaluate risk factors associated with the sex differences in lip cancer incidence showed higher risk in those with fair complexion and in smokers.¹⁰⁴ Increased risks were strongly related to lifetime solar exposure (Relative Risk [RR] highest quartile 13.5, 95% CI: 4.5-40.6) and to annual time spent outdoors. Among those with high lifetime sun exposure, the risk was twice as high in women using lip protection once per day or less than those using it at least twice per day. These findings suggest that the stronger association between UV and cancer incidence observed among men, relative to women, may be explained, in part, by the increased use of lip protection by women. In summary, lip cancer appears to be causally related to lifetime sun exposure.

Melanoma of the eye

Ocular melanoma is a rare condition with an incidence rate in Canada of about seven per million population.⁵¹ The rarity of this cancer has meant that few studies have been conducted and knowledge of the etiology is limited. Also, because subjects with

this cancer are widely dispersed, the few studies have usually been restricted to telephone or postal questionnaires, which are probably inferior to in-person interviews for assessing important host susceptibility factors for melanoma.

The first case-control study¹⁰⁵ evaluated cumulative solar exposure as well as intermittent and constant exposure, and reported no differences between cases and controls, although odds ratios were not presented in the paper and this study had limited statistical power (65 cases and 65 controls). The study did indicate that subjects with light skin and blue or grey eyes were at an elevated risk of uveal melanoma; similar findings were seen in later studies.¹⁰⁶⁻¹⁰⁸

Tucker et al.¹⁰⁶ found an elevated risk of ocular melanoma in subjects born in the southern US (and thus perhaps exposed to higher levels of UVR in youth) by comparison with those born in the north. The Tucker study found elevated odds ratios for subjects who reported gardening outdoors, but similar associations were not seen with other outdoor activities. No elevated risks for solar exposure were seen in Holly et al. as assessed by tendency to tan or sunburn and vacation and leisure-time activities.¹⁰⁷ Seddon et al.¹⁰⁸ compared 197 patients with ocular melanoma with 385 controls recruited through random digit dialling and found an elevated but non-statistically significant risk of ocular melanoma among subjects with the highest reported outdoor exposure, relative to those with the lowest.

More recent evidence for an association between ocular melanoma and UVR came from a study conducted in Australia. A national case-control study of ocular melanoma cases diagnosed between 1996 and mid-1998, with controls frequency matched by age and sex, demonstrated higher risks in subjects with grey, hazel or blue eyes.¹⁰⁹ An increased risk of the cancer was found with increasing quartile of sun exposure up to 40 years of age (RR in highest quartile = 1.8 ;95% CI: 1.1-2.8), after controlling for phenotype susceptibility factors.¹¹⁰ Interestingly, no indication of increased frequency of CDKN2A germline mutations was found in 62 ocular cases and their ethnically matched controls, suggesting that genetic predisposition is not the strong factor in ocular melanoma that it is in CMM.¹¹¹

In general, evidence for associations between solar UVR and ocular melanoma has been weak to date. As the incidence of this cancer has not increased during the period in which cutaneous melanoma incidence has risen sharply, it seems unlikely that ocular melanoma will become a major public health hazard. Further studies of the relationship with solar UVR are unlikely to be productive until better measures of past solar exposure become available.

Three studies on sunlamp and sunbed use¹⁰⁶⁻¹⁰⁸ have shown at least one measure of exposure to be related to increased risk of ocular melanoma; only two of these risk estimates are statistically significant. The exposure prevalence is very small, however, and these results should be interpreted

cautiously. More studies with better quantitative data on artificial UV exposure are necessary before firm conclusions about a causal relationship can be reached.

Non-Hodgkin lymphoma

Solar ultraviolet radiation

Non-Hodgkin lymphoma (NHL) is the fifth most important cancer in Canada in terms of incidence.⁹⁶ It is clear that the factors known to increase risk of NHL, including AIDS (Acquired Immune Deficiency Syndrome), can account for only a portion of the incidence rise¹¹²⁻¹¹³ seen over the past 20 to 30 years in this group of cancers.

Recently a number of investigators using descriptive data have suggested that sunlight exposure may be important in the etiology of NHL. This hypothesis is based on a number of lines of evidence. First, the increase in incidence of NHL roughly parallels the increases seen for CMM and NMSC.¹¹⁴⁻¹¹⁵ This suggests that the factors known to be responsible for the increases in skin cancers may also be involved in NHL. The most significant factor for both CMM and NMSC is sunlight exposure.^{17,22,26,46,89-93}

The second line of evidence comes from parallel gradients of risk for NHL, CMM and SCC with proximity to the equator. Within the UK¹¹⁶ there is an incidence gradient for NHL, with higher rates in the south similar to that seen with CMM. Mean daily duration of bright sunlight in southern UK is 50 percent greater than in the north.¹¹⁷ Rates of NHL among countries in the northern hemisphere differ markedly; those whose population resides below 40 degrees north latitude have rates approximately 50 percent higher than those above 50 degrees north latitude.¹¹⁸ Using tables of ambient solar irradiation, McMichael and Giles plotted incidence rates of NHL from 49 cancer registries against ambient solar UVR. A strong, statistically significant correlation was seen between ambient solar irradiation determined by latitude of population residence and age-standardized incidence of NHL and of CMM. This relationship was similar in both males and females. The authors point out that no gradient is seen within

some countries, such as Canada. However, as the majority of the Canadian population resides in close proximity to the country's southern boundary, this is not unexpected. A separate study showed no latitude gradient in the US for NHL,¹¹⁹ but this was based on mortality data only, as incidence data were not available for the whole country.

A further line of evidence originates in studies of second primary tumours arising in cohorts of both NHL and skin cancer patients. Adami et al.¹¹⁴ showed a significantly increased risk of SCC (RR 5.5) and CMM (RR 2.8) among patients with NHL. In addition, an increased risk of NHL was seen in patients with prior SCC. In contrast to these findings, no other second primary tumours appeared to be elevated among the NHL and SCC cohorts, suggesting a similar causal agent in the two tumours. The authors noted the possibility of surveillance bias in the cohorts; however, the lack of elevated risk for other cancers argues against this explanation.

A further study carried out in Switzerland showed a twofold risk of subsequent NHL among a cohort of 11,878 BCC patients.¹²⁰ Of interest is that significantly increased risks of similar magnitude were seen also for cancer of the lip, for SCC and for CMM, each of which (along with BCC) is known to be strongly related to sunlight exposure. No other cancer sites showed significantly increased incidence rates in the BCC cohort. It is possible that such increases in second primaries are due solely to an underlying immunosuppression among the cohorts. It has been shown that SCC and NHL are both more common in individuals who are immune compromised, such as kidney transplant patients and AIDS patients. However, as will be discussed, solar and artificial UVR have been demonstrated to cause immune suppression. This suppression has been suggested as one of the reasons, along with its ability to damage DNA, that UVR causes skin cancer. Furthermore, little evidence of an excess of CMM and cancer of the lip has been seen among patients immune compromised by renal transplantation or AIDS. This suggests that the independent effects of DNA damage and immune suppression from UV might

be at work in the excess of NHL seen in cohorts of skin cancer patients.

Studies of migrants are often helpful in assessing the importance of environmental factors, as exposure often dramatically changes by comparison with the country of origin. Thus, data comparing NHL rates in migrants from low sunlight areas (such as the UK) to high sunlight areas (such as Australia and New Zealand) and vice versa are instructive with the caveat that changes in sunlight are likely accompanied with changes in diet (or other lifestyle factors) which may be relevant to NHL. Cancer incidence data from Australia show that rates of NHL in migrants from the UK are similar to those of native-born Australians, and substantially higher than those of nationals remaining in the UK and Wales.¹²¹ The increase in risk for NHL in UK migrants is similar in magnitude to that seen for CMM. In UK migrants to New Zealand, a significant increased risk for NHL is seen in both males and females by comparison with their expected risk, based on rates in England and Wales.¹²² By contrast, New Zealand males and females migrating to the UK experienced reduced risks for NHL by comparison with their expected risk, based on rates seen in New Zealand.

Several studies have noted an increased risk of NHL among farmers.¹²³ Although there is some evidence that this might be due to agricultural chemical use, the data are not compelling. Farmers also receive high cumulative solar UV exposures. Similarly, American soldiers having served in Vietnam have been reported by some—but not all—studies to have elevated rates of NHL.¹²⁴⁻¹²⁵ Although it has been suggested that this is due to exposures to herbicides, high sunlight exposure in Vietnam may have played a role.

The mechanism by which UVR might increase risk of NHL is through systematic immune suppression. There is a substantial body of evidence that suggests that UVR causes significant changes in human immune status. Chronic high levels of UV-B exposure have been reported to be immunosuppressive through induction of suppressor T-cells.¹²⁶ Hersey et al.¹²⁷ have also reported that exposure of human volun-

teers to UV-A radiation for 30 minutes per day over a twelve-day period provoked a reduction in natural killer cell activity, with an accompanying decline in the number of such circulating cells. It is also known that T-lymphocytes are substantially more sensitive to the cell killing effects of UV-B than are fibroblasts.¹²⁸ This indicates that, even at relatively low levels, an effect might be seen from UV exposure on the cells critical to human immune function. Granstein¹²⁹ and Murphy et al.¹³⁰ have also noted that fairly low doses of UVR result in depletion of epidermal Langerhans' cells and in reduced levels of activity. Langerhans' cells are important participants in the immune process as they present antigens to antibody producing cells in the body. Finally, there is animal evidence indicating that UVR produces suppressive effects on the immune systems of mice and impairs their ability to reject antigenic transplanted UV-related tumours,¹³¹⁻¹³² including melanoma.¹³³ The evidence suggesting that UV-A might be nearly as effective as UV-B in inducing immune suppression could be particularly important, as use of UV-A sunbeds for tanning in Europe has increased rapidly in recent years, particularly among young people. It has been suggested that this could be related to the increases in NHL seen in Europe in young persons.¹³⁴

Notwithstanding data from descriptive studies suggesting that sunlight exposure may be positively related to NHL, the evidence from carefully conducted case-control studies to date does not support this. A recently reported study in Australia found an inverse relationship between sun exposure and NHL.¹³⁵ Similar results were seen in a Scandinavian study.¹³⁶ After adjustment for potential confounders, a case-control study conducted in Sweden and Denmark also showed a reduced risk of NHL with increasing frequency of sun vacations abroad, and episodes of sunbathing at age 20 and 5 to 10 years prior to interview. A similar—though non-statistically significant association—was also detected for Hodgkin lymphoma. These results suggest that the increased frequency of skin cancer in those with prior NHL, and vice-versa, may not be related to UVR exposure, and also heighten the need for more studies of NHL,

Hodgkin lymphoma and solar and artificial UV radiation.

Solar UVR and cancers of the colon, breast, ovary and prostate

Several review articles^{137,138} examining primarily laboratory evidence, and also some epidemiological findings, have suggested that sunlight exposure may exert a protective effect against a number of cancers including colon, prostate, breast and perhaps other female cancers. The suggested mechanism of action is that the active metabolite of vitamin D (1,25(OH)₂D) inhibits proliferation and induces differentiation of cells that carry vitamin D receptors. This hypothesis is not new; in 1980, an ecological correlation study examining latitude of residence and colon cancer mortality found lower rates with declining latitude in North America.¹³⁹

The role of solar UV-B in stimulating vitamin D synthesis is thought to be a potential mechanism by which sunlight might affect incidence of these internal cancers. Although some vitamin D is taken in food, principally through consumption of fish, eggs and vitamin-D-enriched milk, most vitamin D is synthesized from 7-dehydrocholesterol in the skin under the influence of UV-B radiation in sunlight.¹⁴⁰ It is then hydroxylated to 25(OH)D in the liver, and further, into biologically active 1,25(OH)₂D in the kidney. As noted above, this metabolite acts like a hormone and is taken up by many organs in the body. Receptors for vitamin D are present in breast and prostate tissue.¹⁴⁰ Furthermore, there is evidence that proliferation of cultured human prostate cancer,^{141,142} breast cancer,^{143,144} and colon cancer cells^{145,146} are inhibited by Vitamin D. Finally, *in vivo* animal studies appear to show vitamin D induced inhibition of carcinogen induced colon¹⁴⁷ and mammary tumours¹⁴³ in rats.

Colon cancer

Garland and Garland¹³⁹ noted that colon cancer death rates were lower in areas of the US with high solar UV levels than in low sunlight areas. They hypothesized that

this finding might be due to sunlight's ability to stimulate increased serum levels of vitamin D. A more detailed ecological correlation study which used incidence rates and also attempted some control for duration of residence in an area prior to diagnosis also found that risk of colon cancer appeared to be lower in high sunlight areas of the US.¹⁴⁸ Bostick et al.,¹⁴⁹ in an analysis of dietary intake among older women with colon cancer, found a modest protective effect for dietary calcium and vitamin D.

Intake of dietary vitamin D and calcium has been associated with lower risk of colon cancer and adenomatous polyps in a number of studies.¹⁵⁰⁻¹⁵² However, in at least one of these studies, vitamin D consumption is highly correlated with multivitamin use and the attendant concern that the effect attributed to vitamin D may actually be due to another vitamin.¹⁵²

Several cohort studies have shown a reduced risk of colon cancer in subjects with high serum vitamin D levels.¹⁵³⁻¹⁵⁸ A further investigation demonstrated a modest protective effect for high serum vitamin D, but only in certain sites in the colon.¹⁵⁹

Not all studies of colon cancer and vitamin D have been positive. Several^{160,161} (including cohort studies) have shown either no protective effect or suggestion of an effect which is not strong enough to be statistically significant.¹⁶²

At the present time there is strong suggestive evidence that vitamin D, perhaps in conjunction with calcium, may reduce the risk of colon cancer and its precursor lesion, adenomatous polyps. Most of this evidence is based on studies of dietary intake of the vitamin. There is little direct evidence showing that increased sunlight exposure reduces risk. Any evidence comes from ecologic correlation studies, a relatively weaker form than that which analytic studies might provide.

Breast and ovarian cancer

Gorham et al.¹⁶³ examined mortality rates for breast cancer in the USSR and found the highest rates in the regions with the lowest sunlight levels. The relationship appeared

to persist after an attempt to control for socio-economic factors, but no control was possible for ethnic and dietary factors. The association could have been due to other factors. Studies by Garland et al.¹⁶⁴ and Freedman et al.¹⁶⁵ also suggested that mortality from breast cancer is lower in areas of the world with more sun exposure. However, data from the Nurses' Health study did not find a geographic gradient for breast cancer.¹⁶⁶ Again, these studies are of the ecologic correlation variety and no actual measurements of sunlight exposure were made.

Analysis of data from the US National Health and Nutrition Examination Survey (NHANES) suggested that sunshine exposure may reduce risk of breast cancer (RR in highest sun exposure group relative to the lowest was 0.54, 95% CI: 0.28-1.02).¹⁶⁷ The authors suggested that high serum levels of vitamin D, mediated through higher levels of sun exposure, might be responsible for this reduced risk. A further investigation carried out in Scandinavia suggested that women diagnosed with breast cancer in the summer months had longer survival than those diagnosed in winter.¹⁶⁸ The authors suggested that this might be due to a beneficial effect of sunlight.

Case-control data from North Carolina showed significantly lower serum levels of 1,25 dihydroxy vitamin D in breast cancer cases than in controls.¹⁶⁹ More recently, studies of dietary vitamin D have demonstrated that women with a high intake had lower risks of breast density¹⁷⁰ and breast cancer.¹⁷¹ Neither of these examined exposure to UV radiation as a factor in vitamin D levels among the women.

Several studies of mortality from ovarian cancer^{165,172} have demonstrated lower rates in high sunlight areas. The evidence for a protective effect of sunlight exposure in breast or ovarian cancer is, at present, modest. Furthermore, there is only scant evidence that either dietary intake of vitamin D, or serum levels of this vitamin, are associated with either cancer.

Prostate cancer

Several geographic studies of prostate cancer mortality in the US indicated decreased mortality in the southern US, consistent with an effect of sunlight exposure.^{165,173} The authors hypothesized that the effect might be due to the effect of UVR on vitamin D production. Schwartz and Hulka noted an increased risk of prostate cancer in men with higher serum levels of vitamin D binding protein.¹⁷⁴ A study of pre-diagnostic serum levels of vitamin D found a higher risk of prostate cancer in men with low levels of 1,25 dihydroxy vitamin D, although there was no difference for levels of 25 dihydroxy vitamin D.¹⁷⁵ One further investigation showed similar results (Ahonen et al. 2000).¹⁷⁶ Several other studies have shown no association between serum levels of vitamin D or its metabolites and subsequent risk of prostate cancer.¹⁷⁷⁻¹⁸¹ The Scandinavian study noted earlier found a better prognosis in men diagnosed with prostate cancer in summer than in winter.¹⁶⁸ A study of vitamin D receptor polymorphisms, vitamin D levels and prostate cancer among US physicians found little effect of different variants of the *BsmI* and *TaqI* polymorphisms on risk of prostate cancer.¹⁸²

Two different investigations^{183,184} conducted by John et al. have suggested a reduced risk of prostate cancer as sun exposure increases. The first, conducted using data from the NHANES I study, showed that inhabiting a more southerly located region of the US (rather than a northern one) might reduce risk of the disease.¹⁸³ The second was a case-control study in which the ratio of skin reflectance on a sun-exposed site of the body (i.e., forehead), compared to that on a non-exposed site (i.e., upper underarm), served as a measure of sun exposure.¹⁸⁴ However, it is possible that this metric is actually a better indicator of ability to tan vs burn in the sun, rather than a measure of solar exposure *per se*. A number of other sun exposure measures in the same study, showed little or no association with risk.

In summary, the results of studies linking sun exposure to subsequent risk of colon, prostate, breast and ovarian cancer have

not yet demonstrated a convincing relationship between exposure and internal cancers. However, taken together, they do suggest a possible protective effect, at least for colorectal cancer, perhaps through the stimulation of higher serum levels of vitamin D. Many of the studies are descriptive or, if analytic, may suffer from incomplete control for confounders. The results from a recently published randomized clinical trial suggest that interventions designed to increase serum levels of vitamin D and calcium among postmenopausal women in order to reduce osteoporosis, might also reduce their risk of developing cancer (Lappe et al, 2007).¹⁸⁵ However, it should be noted that the follow-up of the women in the trial was very short, providing insufficient study power to assess individual cancers. Furthermore, there was no intervention arm dedicated to vitamin D alone, and so it is difficult to determine the effects of the vitamin in the absence of supplemental calcium. Finally, the reduced incidence of cancer was achieved without increasing exposure to solar or artificial UV, and so it appears clear that the benefits might be realized without increasing risk of UV related diseases. More research is needed, and it is clearly inappropriate at this point in time to suggest that more solar exposure, particularly in fair-skinned populations, is a rational cancer prevention strategy.

Impact of UVR on cancer incidence and mortality in Canada

Attributable fraction

The impact of UVR-related cancer in Canada can be estimated through reference to incidence and mortality data. The major cancer types known to be related to solar or artificial UVR are CMM and NMSC, as well as cancer of the lip. It was estimated that in 2007, 4,600 new cases of melanoma would be diagnosed.⁹⁶ In 2003 there were about 350 new cases of lip cancer.⁹⁶ In addition, it was estimated that about 69,000 new cases of basal cell, squamous cell and other non-melanocytic skin lesions would be diagnosed. Armstrong and Kricke⁵ have estimated

that about 93 percent of CMM in Canada can be attributed to solar UVR. It is likely that the figure for SCC and BCC would be very similar.

Deriving an estimate of the burden of skin cancers caused by artificial UVR, in particular that from sunbed and sunlamp use, is more difficult. Although a recent meta-analysis has shown a positive association between sunbed exposure and CMM, the odds ratios are relatively low for most users.⁶⁸ Among those in the highest use categories, the risk ratios found in the meta-analysis are similar to those seen for reported sun exposure. However, with probable imperfect control for concomitant solar exposure, it is possible that at least some of the elevated risk in frequent users is due to outdoor sunbathing for tanning purposes. Marrett¹⁸⁶ has estimated the population attributable risk for CMM due to sunlamp and sunbed use at between 6 and 15 percent if true relative risk is about 1.2, which is compatible with the aggregated data seen in the meta-analysis. Thus, if sunlamp and sunbed exposure is causally related to CMM, then combined with solar exposure, most of the CMM incidence seen today in this country can be attributed to one form or another of UVR.

The studies carried out to date do not allow an estimate to be made of the proportion of non-melanocytic skin cancer attributable to sunbed and sunlamp use.

The proportion of lip cancer attributable to sunlight exposure is difficult to estimate, as other factors such as pipe and cigarette smoking are also etiologically significant. However, the study of Pogoda et al.¹⁰⁴ suggests that the use of lip covering (lipstick) among women more than once per day results in a 60 percent reduction in risk of the disease. It seems likely, then, that some 50 percent of the incident cases, probably in both sexes, are attributable to solar exposure. No studies have yet addressed the issue of artificial UV exposure and lip cancer risk, but the attributable fraction must be very small.

The original hypothesis that sunlight exposure might contribute to an increased incidence of non-Hodgkin lymphoma is of

concern. However, the analytic studies conducted to date^{135,136} appear to show a reduced—rather than increased—risk with high exposure. Further studies of a putative relationship are in the analysis phase and until the nature of the relationship is firmly established, no estimate can be made of the impact of UVR on the incidence or mortality of this disease.

Similarly, it is not possible to estimate the role of sunlight in the prevention of solid, internal cancers since a causal relationship has not been convincingly demonstrated. Further analytic studies are needed to illuminate the relationship between solar UV exposure, circulating vitamin D levels, and colon, prostate, and breast cancer.

In summary, some 4,500 life-threatening cancers per year are thought to be directly causally related to UVR, as well as some 64,000 less serious (basal and squamous cell) skin cancers and cancers of the lip. Melanoma of the eye, although very rare, is likely related to UVR, though its impact on the combined burden of cancer caused by UV radiation in Canada is probably negligible.

Primary prevention

Stern et al.¹⁸⁷ estimated that consistent regular use of sunscreens in childhood (up to 18 years of age) might reduce non-melanocytic skin cancer incidence by 78 percent. This estimate is certainly optimistic for several reasons: first, sunscreens have not been shown to reduce incidence of BCC (or cutaneous melanoma) in humans, although they do appear to be effective in preventing squamous cell carcinoma of the skin.¹⁸⁸ Furthermore, the reduction is based on an estimated 80 percent of lifetime sunlight exposure occurring in childhood, which appears to be an unacceptably high estimate.¹⁸⁹ Nevertheless, with appropriate clothing use, care not to sunburn and judicious use of sunscreens, it is likely that 50 percent of these tumours are preventable. A similar figure is likely possible for CMM. Lip cancer incidence in females is only one-fifth that in males, likely due to lower levels of chronic UV

exposure, but also to use of lip protection (lipstick and other UV-screening lip balms). In addition, females smoke less than males and female pipe-smoking is virtually non-existent. It is likely that some 30-40 percent of male lip cancers are preventable as occupational solar exposure declines in men, although this is an estimate only.

Mortality

Deaths from non-melanoma skin cancers are rare, and official mortality statistics are likely to overestimate deaths from NMSC by nearly 60% (Lewis and Weinstock 2004)¹⁹⁰ due to mistakes in completion of death registrations, or errors in cause of death coding. It is likely that no more than 100 deaths from SCC occur annually in Canada. In addition, there is evidence that many of the genuine NMSC deaths occur among individuals with comorbid psychiatric conditions,¹⁹⁰ perhaps associated with extreme delay in seeking medical care for their lesions. It is unlikely that public health campaigns designed to reduce mortality from skin cancer would affect these deaths. Mortality from lip cancer is also low, probably not exceeding 20 deaths per year. Recent cancer mortality estimates suggest that some 900 deaths will occur from CMM each year in Canada.⁹⁶ In total, then, probably about 850 to 870 deaths per year can reliably be attributed to UVR.

Secondary prevention

Most studies of CMM prognosis suggest that in lesions which are less than 0.76 mm in depth, mortality is only about five percent.¹⁹¹ Physician and public education programs have been shown to significantly reduce the proportion of melanomas which are deeply penetrating at diagnosis.¹⁹² Although declines in mortality from melanoma are being seen especially among the young in Canada,⁴ it is difficult to attribute the decline to early detection or education programs. A randomized clinical trial of early detection is necessary to evaluate whether routine screening for CMM is cost effective, and such a trial is beginning in Australia, a high incidence area. Even though Marrett et al.⁴⁷ have shown that nearly 70 percent of melanomas could, in theory, be detected by screening only about 30 percent of the population in Canada, it is not clear that lay persons at high risk

would be able to self-select for entry into a surveillance program. Even if subjects could self-select appropriately, screening 30 percent of the population of Canada on a continuing basis would be prohibitively expensive. Thus, the magnitude of melanoma mortality reduction possible with some form of self- or physician-conducted screening is not clear. As noted above, mortality from BCC and SCC is low in Canada and screening for these lesions would prevent few deaths.

Mortality reductions from lip cancer early detection programs implemented by dentists and oral hygiene practitioners are likely to be low. Given the costs involved, programs to detect ocular melanomas early would not produce worthwhile mortality reductions.

In summary, with our present state of knowledge, primary prevention manoeuvres aimed at more rational UV exposure are likely to be most effective in reducing the cancer burden from UVR in Canada. At the same time, more intensive research is needed to determine whether the incidence rates of other malignancies such as cancer of the colon, prostate, breast and ovary, as well as non-Hodgkin lymphoma are related, inversely or otherwise, to UV exposure.

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Electric and magnetic fields at power frequencies

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Exposures to electric and magnetic fields are among the most ubiquitous exposures that the Canadian population experiences. Sources of electric and magnetic field exposures may be occupational or residential and include proximity to certain types of electrical equipment, transmission and distribution power lines as well as appliance use. The early studies of children tended toward a consistent association between risks for leukemia and brain cancer and residential proximity to power lines having high wire configuration.

More recent studies—and studies which have attempted to improve upon the measurement of exposure by using calculated fields, point-in-time or personal monitoring—have been inconsistent, with some suggesting increased risk and others not. Occupational exposures have suggested an increase in risk for leukemia, and to a lesser extent brain cancer and Non-Hodgkin lymphoma. However, studies of residential exposures and cancer in adults generally have suggested no effect. Laboratory work has been unable to demonstrate a biological mechanism which might explain the epidemiological findings.

In spite of extensive efforts over the past 20 years and many expert reviews, it has been difficult to reach consensus regarding the carcinogenic effects of electric and magnetic fields. Exposure assessment has proven to be complex, and agreement on the relevant exposure metric has not yet been obtained. There is justification to question whether point-in-time measures in homes are appropriate indices of the relevant etiological exposure, as they fail to account for changes over time, peak exposures or time-varying fields. Nevertheless, it is probably desirable to err on the side of caution in not placing too much weight on the inconsistencies. The IARC has classified EMF as a “possible carcinogen” which refers to the circumstances where there is limited evidence of carcinogenicity in humans and inadequate evidence in experimental animals. The IARC review indicated limited

evidence for the carcinogenicity of extremely low-frequency magnetic fields in relation to childhood leukemia at high level exposure in the residential environment (average residential magnetic field strength $>0.4 \mu\text{T}$). Even higher levels of exposure in the occupational environment may increase the risk of leukemia in adults.

Introduction

Exposures to extremely low frequency electric and magnetic fields (ELF EMF) are among the most ubiquitous exposures to non-ionizing radiation that the Canadian population experiences. In 1979, it was first suggested that residential exposure to ELF EMF might lead to increased cancer risk in children.¹ Since then, a number of studies have examined possible relationships between exposure to a range of electric and magnetic field sources and cancer. High voltage transmission lines and distribution network lines, as well as appliance use, are among the field sources considered in these studies. Studies have been conducted on children and adults in the general population and among workers where high exposure to electric and/or magnetic fields seemed likely. Children may also be exposed in schools or day-care centres.

For the general public, residential exposures seem to be the most contributory and are the type most often considered in studies. As such, we will focus on these as the prime source of environmental exposures. However, as occupational exposures are generally higher than residential exposures, consideration of studies of occupational exposures may be helpful.

General considerations relating to exposure assessment

At power frequencies (50 or 60 Hertz), there is no constant quantitative relationship between electric field strength and magnetic flux density, and it is therefore necessary to measure these components

separately. Electric field strength is measured in volts per metre (V/m) and depends upon the voltage in the circuit. Electric fields are easily perturbed and thus stable and reliable measures of personal exposures to electric fields are difficult to obtain. The attenuation of electric fields is so dominant that penetration of the body is minimal; however, these fields do induce currents in the body.

Magnetic flux density is a measure of magnetic field strength per unit area and is quantified by units of tesla (T) or gauss. In contrast to electric fields, power frequency magnetic fields easily penetrate the body and, in general, are not easily shielded. In residential settings, however, the electric and magnetic fields vary temporally and spatially, making the measurement of human exposure difficult and complex.

The ability of epidemiological research to assess the relationship between cancer risk and exposure to electric and magnetic fields is dependent upon the quality of the exposure assessment. Further, in case-control studies in the residential environment where cases have been ascertained retrospectively, measurements of electric and magnetic fields are inevitably taken after the diagnosis of the case and the corresponding time period for the controls. If there has been no major change in the electrical service to the home or in the way the subject spends time in the various rooms in the home and in the external environment, measurements of residential exposures may reflect (to a reasonable extent) the exposure of the subject in the time period relevant to the development of the cancer. However, if the subject has moved, measurements in the current residence may bear no resemblance to the relevant exposures.² Few case-control studies have satisfactorily addressed these issues.

Attempts have been made in various ways to develop indices of exposure to ELF EMF that are intended to reflect long-term

exposure. The extent to which these efforts have been successful is not clear. It would seem that, at best, these indices reflect a correlate of exposure, or a confounder in the strict epidemiological sense. This is particularly true for wire codes, considered in more detail later in this discussion.³

In the occupational environment, there are additional complexities. Job titles have been used in many studies to infer exposure. More recently, job exposure matrices have been developed, accompanied by measurements of specified tasks, with the objective of more accurately reflecting actual exposures. However, even with improved estimation of occupational exposure, total exposure of the worker to ELF EMF is not taken into account. In such studies, it is implicitly assumed that the effect of the residential exposures is small and that what is being estimated is the risk from the occupational exposure alone.

Hence, for most studies, there has been an element of misclassification. To the extent that this misclassification is non-differential, elevated risks probably represent an underestimation of the true risk. Thus, in the absence of a systematic bias, if ELF EMF exposures are indeed carcinogenic, it is likely that, as the precision of measurement of ELF EMF increases, the estimated risks from ELF EMF exposure will also increase. However, if the proportion of cancer incidence attributable to ELF EMF is small and the risk only detectable at relatively high levels of exposure, then a study conducted under circumstances where the proportion of the study population exposed to high levels of ELF EMF is low is likely to demonstrate no association, regardless of the precision of ELF EMF measurement.

The earliest studies of ELF EMF exposures and cancer used exposure assessment methods which were indirect. Exposure was estimated either through categorization of the type of electrical wiring serving the residence, or wire codes, or through static measurements (usually of magnetic fields) within rooms most often used by subjects. The availability of personal monitors that could be worn by an individual has considerably facilitated estimates of individual

exposure both to magnetic and, in some instances, electric fields. Developmental work for one such device was conducted by Hydro Quebec, Canada. The device was then adapted and became available commercially as the Positron™ monitor, used in the Canada/France study of electrical utility workers^{4,5} and in three case-control studies of childhood cancer and/or leukemia.^{6,8}

Determination of the most relevant exposure metric has been hampered by the lack of a biological model suggesting how ELF EMFs may operate in the carcinogenic process. It has been suggested by some that ELF EMF may operate as a promoter. For adults, the length of the induction period for cancer may be very long, such that for residential exposures it may be impractical to attempt reliable estimation over many years. The same difficulty applies to occupational exposures, but the task in these situations may be less problematic than for residential if good historical estimates of exposure can be made. For children's cancers, many of these difficulties are less, as the induction period must be relatively short.

The following review considers exposure circumstance (residential or occupational) by subject (children or adults) with attention paid to the way in which ELF EMF measurements were made. Studies are described in chronological order.

Residential studies

Residential exposures and cancer in children

Wertheimer and Leeper¹ reported a statistically significant two- to threefold increase in leukemia mortality in Denver, Colorado among children in residential proximity to wiring of high current configuration. Exposure to magnetic fields was assessed indirectly according to what has come to be known as the "Wertheimer-Leeper wire code". This code refers to a categorization of electrical wiring of power lines close to residences according to the number of conductors and their diameters, location of transformers and service drops, as well as the distance of the conductors from the home. Increased risk of childhood cancer was observed for those children residing in homes with higher current configurations.

Factors such as social class, traffic density and type of neighbourhood (urban versus rural), which the authors thought might be related to either the risk of leukemia or magnetic field exposure, were taken into account.

Fulton et al.⁹ attempted to replicate the study by Wertheimer and Leeper¹ in Rhode Island with respect to childhood leukemia. No association was found, but there was some indication that the replication of measurement methodology was not close.

Subsequent studies accomplished some refinement of the wire code by including more comprehensive measures of the distance from the power lines or electrical installations and taking into account line loading. Power lines must be within approximately 100 metres for their electric and magnetic field strengths to predominate over those generated in the homes by household wiring and appliances. Unfortunately, these studies did not use identical "sources" of electric and magnetic fields from which distances were measured, making direct comparisons difficult.

In a case-control study of childhood cancers in Sweden, all cancers and cancers of the nervous system were found to be associated with proximity to 200 kV (kilovolt) transmission lines and with measured residential magnetic field measurements greater than 0.3 μ T (micro-Tesla).¹⁰ No excess risk was observed for childhood leukemia, but a statistically significant excess of brain cancer was found. ELF EMF exposure was considered for both birth residence and residence at the time of diagnosis. Controls appeared to be more residentially stable than the cases in this study, but it was not possible to assess how this might have biased the results, if at all. Exposures to magnetic fields were assessed according to distance to electrical conductors and from calculations of magnetic fields from the source. Potential confounders were not considered in the analysis of this association.

In a case-control study of incident childhood cancers in Denver, Colorado, Savitz et al.¹¹ introduced further improvements in exposure assessment of magnetic fields by

carrying out point-in-time or spot measurements inside the child's residence, as well as wire coding. Cases were children diagnosed before the age of 15 years, and controls, matched by age and sex, were selected through random-digit dialling. Of the 70 percent of eligible cases who were interviewed (compared to 80 percent of the eligible controls), only 36 percent had measures of magnetic fields, whereas measurements were available for 74 percent of the controls. Wire codes denoting high current configurations were correlated with higher measured magnetic fields within the home, while wire codes associated with higher magnetic fields were more common among case than control homes. Odds ratios for total cancers, leukemia and brain cancer showed an association with wire code but not with the direct measures of magnetic fields inside the home. The authors suggested that this might be due to the imprecise manner by which a current and point-in-time measurement predicts past exposure. They reasoned that wire codes are more stable over time and thus might "better approximate historical field levels". The authors commented that any trends or excesses observed showed a clearer pattern for leukemia than for other childhood cancers.

Myers et al.¹² studied childhood cancers in Yorkshire, England diagnosed between 1970 and 1979. No association between childhood cancer and proximity to overhead power lines for a child's residence at birth or for exposure to magnetic fields, as calculated on the basis of line-network maps and load records, was observed. Few addresses for cases or controls had background levels of calculated magnetic fields exceeding 0.01 μT .

London et al.¹³ used three exposure assessment methods to improve upon the measurement of ELF EMF in their case-control study of childhood leukemia carried out in Los Angeles County, California: 24-hour magnetic field measurements in the child's bedroom, spot measurements of electric and magnetic fields, and wiring configuration as defined by Wertheimer and Leeper.¹ A non-significant elevated odds ratio (OR) was observed for the association between 24-hour magnetic field

measurements and leukemia (OR 1.69, 95% Confidence Interval [CI]: 0.71-4.00 for exposure in the 90th to 100th percentile [0.268 μT or more]). A statistically significant association (OR 2.15, 95% CI: 1.08-4.28) was observed for leukemia risk and exposure according to the Wertheimer-Leeper¹ very high current configuration relative to the very low current and underground configuration combined. It was only possible to obtain ELF EMF measurements for about half of the eligible cases, and possible biases, such as residential stability and housing characteristics, were not taken into account. Although the association of leukemia risk with wire code was similar to that reported by Savitz et al.,¹¹ the mean magnetic field measurements associated with wire code in Los Angeles were lower than those observed in Denver. This, together with the unexplained seemingly wide discrepancy between 24-hour and spot measurements in the London et al.¹³ study, adds to the question of what wire codes actually mean.

Feychting and Ahlbom¹⁴ in Sweden attempted to improve estimates of historical magnetic field exposures at the time of diagnosis by using power line load data. With this calculated estimate of magnetic field exposure, significant associations with leukemia risk were observed with the highest level (0.3 μT) of exposure (OR 3.8, 95% CI: 1.4-9.3). Elevated odds ratios for leukemia were also found for those living within 50 metres of a power line. However, no associations were observed with contemporary exposures, whether measured or calculated—findings consistent with those of Savitz et al.¹¹ and London et al.¹³ The authors suggested that their calculated historical fields were reasonably good predictors of past exposure and reasoned that the "lack of an association with spot measurements is consistent with the assumption that fields assessed through contemporary, short-term measurements are poor predictors of past exposure".

In Denmark, Olsen et al.¹⁵ reported significant associations between all major types of childhood cancer combined and exposure to magnetic fields of $>0.4\mu\text{T}$ from high voltage installations.

A pooled analysis of these two studies confirmed the findings of the components, showing an increased risk of childhood leukemia (OR 5.1, 95% CI: 2.1-12.6) in relation to magnetic field levels of $>0.5 \mu\text{T}$.¹⁶

In a Finnish cohort study investigating cancer risk, Verkasalo et al.¹⁷ found no evidence of an increased risk for leukemia or for all cancers in children living close to overhead power lines. An elevated odds ratio for nervous system tumours for boys was observed with magnetic fields $>0.2\mu\text{T}$. However, the small numbers and the fact that one boy had three primary tumours of the nervous system necessitates that the results be qualified.

Coghill et al.¹⁸ conducted a small case-control study of childhood leukemia in England (56 cases and 56 controls) in which the cases were solicited largely by advertising and the controls were selected by the parents of the case. Electric and magnetic fields were measured in the child's bedroom. There was no association with magnetic field exposure, but risk estimates for electric field exposure of 20 volts per metre or more were associated with a significantly increased risk of 4.69 (95% CI: 1.17-27.78).

A case-control study of childhood leukemia in Germany was designed to test several etiological hypotheses.¹⁹ An elevated but non-significant association between high-level exposure ($>0.2 \mu\text{T}$) and risk of developing leukemia was found, based on 24-hour measurements of magnetic fields in the bedroom of the residence where the child had lived the longest and spot measurements in residences in which the child had been living for more than one year before diagnosis. The increased risk was based on only four leukemia cases and only 1.5 percent of the study population was exposed to magnetic fields $>0.2 \mu\text{T}$.¹⁹

A nested case-control study assessing cancer risk among children and proximity to high voltage power lines in Norway found no association with leukemia or brain cancer but did find an excess risk for "other cancer sites" in relation to residences within 50 metres from these lines. However,

small numbers limited the conclusions that could be drawn from the study.²⁰

A large case-control study conducted in parts of the mid-western and mid-Atlantic United States evaluated risk of acute lymphoblastic leukemia in relation to several types of measurements.²¹ These included wiring configuration and 24-hour measurements of magnetic fields in the child's bedroom, and magnetic field point-in-time measures in three to four other rooms and just outside the front door of the child's residence. The measurements covered 95 percent of the defined reference period for 77 percent of the subjects. Quartiles of exposure to magnetic fields were defined *a priori*. Slightly over 200 cases were eligible for the analyses of summary time-weighted averages of magnetic fields in the home, although the study enrolled substantially more and 45 percent of these subjects were exposed to magnetic field levels of $<0.065 \mu\text{T}$. Subdivisions of the upper exposure quartile showed that one level of exposure (0.40-0.49 μT) was associated with a significant increased risk in both the unmatched (OR 3.28, 95% CI: 1.15-9.89) and matched (OR 6.41, 95% CI: 1.30-31.73) analyses. For the highest level of exposure ($>0.5 \mu\text{T}$), similar elevations were not observed either for the unmatched (OR 1.41, 95% CI: 0.49-4.09) or the matched (OR 1.01, 95% CI: 0.26-3.99) analyses. The authors concluded there was lack of support for a relationship with measured magnetic field exposures and the risk of leukemia. Linet et al.²¹ also found no evidence of association of leukemia with wire code. Random-digit dialing was used for the selection of controls according to the first eight digits of the telephone number. Depending upon how telephone numbers are assigned within the areas studied, it is possible that this matching by neighbourhood, and hence potentially by wire code, constitutes overmatching and reduced the ability to observe a possible association with wire code.

A cohort study carried out in Taiwan in children younger than 15 years of age at diagnosis showed an elevated leukemia risk (standardized incidence ratio (SIR) 2.43, 95% CI: 0.98-5.01) for those living less than 100 metres from high voltage

transmission lines. The risk was more pronounced and achieved statistical significance (SIR 4.70, 95% CI: 1.3-12.1) among children aged five to nine years at diagnosis.²²

Dockerty et al.⁶ reported a study of electromagnetic field exposures and childhood cancers in New Zealand. For the leukemia cases and controls, Positron™ monitors were used in a stationary position to estimate the exposure of children to electric and magnetic fields in the child's bedroom and in the daytime room used most often by the child two years prior to diagnosis. For the 40 case-control leukemia pairs that lived in the houses monitored with the dosimeter, the OR for exposure in the child's bedroom of $>0.2 \mu\text{T}$ was 15.5 (95% CI: 1.1-224) (based on five cases and one control), while that for comparable exposure in the daytime room was 5.2 (95% CI: 0.9-30.8) (based on seven cases and three controls). No association was seen for tertiles of exposure. There was a suggestion of an elevated risk for the highest categories of electric field exposure, but all lower CIs were below 1.0.

Dockerty et al.²³ were prompted to re-analyse their data using a combination of measurements and different cut-points in order to facilitate comparisons with the large UK case-control study of childhood leukemia.²⁴ Only 40 case-control pairs had measurements which were potentially relevant to the etiological period. The re-analysis of the time-weighted averages of magnetic field measurements in the child's bedroom and living room showed a non-significant association between increased leukemia risk (OR 3.3, 95% CI: 0.5-23.7) and exposures of $0.2 \mu\text{T}$ or more when adjustment was made for potential confounding variables. Small numbers limited the interpretation of this analysis, as did lack of details pertaining to exposure assessment and differences in the methods used in this and the UK study.

A study conducted in British Columbia, Alberta, Saskatchewan, Manitoba and Montreal, Quebec evaluating childhood leukemia risk used personal monitoring as part of the exposure assessment.⁸ In this study involving 399 case-control pairs,

exposure assessment included 48-hour personal ELF EMF measurement, wire coding and magnetic field measurements for subjects' residences from conception to diagnosis/reference date, and a 24-hour magnetic field bedroom measurement. Personal exposure to magnetic fields was not related to leukemia risk (OR 0.95, 95% CI: 0.72-1.26 per $0.2 \mu\text{T}$ incremental rise in exposure). There was no evidence of increased risk from exposure to elevated levels of electric fields. For magnetic fields measured either in the current or previous residences, there were some indications of increased risk for some of the potential associations examined. For example, subjects who lived in the same residence at least two years before the diagnosis date had an OR for exposures above $0.2 \mu\text{T}$ of 1.64 (95% CI: 0.89-3.00). Further, there was a non-significant elevation of risk for magnetic field exposure measured at the front door of residences in the highest exposure group (90th percentile, OR 1.59, 95% CI: 0.86-2.93). There was no association with wire code (correction issued after publication of report).

The risk of developing childhood leukemia in relation to electric and magnetic field (EMF) exposures was also evaluated in a population-based case-control study of 201 cases and 406 controls carried out in southern Ontario.^{7,25} The mean proportion of the period of inquiry covered by all measured residences was 81 percent for cases and 88 percent for controls, respectively. The corresponding percentages relating to the child's current residence were 71 and 77.

Wire codes were generally not a strong predictor of childhood leukemia. For measured residences with the longest occupancy and according to the highest proportion of time spent at residences with high current configuration, there was no association with childhood leukemia risk. However, for children under six years of age, there was a suggestion of an elevated risk for a very high current configuration wire code in the residence they had occupied the longest (OR 2.88, 95% CI: 0.57-14.50).

Time-weighted averages of point-in-time measurements of magnetic fields around

the perimeter of residences and inside the home, the child's bedroom and two other most frequently used rooms were associated with some elevations in leukemia risk.²⁵ There was, however, no evidence of increasing risk with increasing exposure, irrespective of the location at which the measurement was taken. Residences occupied earliest in the etiological period and for some part of the prenatal period with high wire code configurations were associated with a significantly increased risk of leukemia in children diagnosed before the age of 6 years (OR 3.45, 95% CI: 1.14-10.45). Point-in-time measurements of magnetic fields in residences occupied during the first two years of life and during the prenatal period were also associated with significant elevations in leukemia risk for children diagnosed at a younger age (OR 2.50, 95% CI: 1.14-5.49).

For 88 cases and 133 controls, the residence at the time of interview was relevant to the period of inquiry and these subjects wore a personal monitor, Positron™.⁷ For electric fields measured by personal monitoring, there was no evidence of an increased risk of childhood leukemia. Indeed, the risk of leukemia decreased with increasing exposure to electric fields. For magnetic field exposures as measured by personal monitoring, there was evidence of significant associations with childhood leukemia. The risk of developing leukemia increased in magnitude and in statistical significance after adjustment for potential confounders (≥ 0.14 μT , OR 4.5, 95% CI: 1.3-15.9). Leukemia risk was more pronounced for children diagnosed at younger than six years of age and for those with acute lymphoblastic leukemia, with estimates of risk ranging from 3.7 to 5.7.

Magnetic field exposures in schools were also evaluated in the study by Green²⁶ and were on average much lower than those found in residential environments. Among school-age children (five years and older) there was no evidence that exposures to magnetic fields at school were associated with an increased risk of leukemia.

One of the largest case-control studies of childhood leukemia was reported in 1999.²⁴ For a component of this study (2226 matched

pairs) magnetic field measurements were made in homes occupied by children diagnosed with leukemia and their control 12 months before diagnosis. The time period of inquiry was limited to 12 months preceding diagnosis, based on the assumption that magnetic fields can only act as a promoter. No account was taken of previous residences or lifetime exposure. Twenty-four- or forty-eight-hour magnetic field measurements were taken in the child's bedroom and in the main family room. No overall association between these estimates of magnetic field exposures and the risk of acute lymphoblastic leukemia, all leukemias, cancers of the central nervous system or other malignancies was found. However, more than 90 percent of the subjects were in the referent group, which was defined by exposures of less than 0.1 μT . For exposures of 0.4 μT or more, the risk for acute lymphoblastic and all leukemia was non-significantly elevated (OR 1.68, 95% CI: 0.40-7.10). Thus, notwithstanding the large number of study subjects, few were in the highest level of exposure. The authors acknowledged that the study had low statistical power to examine associations at higher exposure levels and that a question "may still remain about the effect of exposures higher than 0.4 μT ".

Two pooled analyses of the risk for childhood leukemia were published in 2000. Ahlbom et al. found an OR of approximately 2 for children with exposures greater than or equal 0.4 μT , and the Greenland pooled analyses found an OR of 1.7 among children with exposures greater than or equal 0.3 μT .^{27,28}

Among subsequent studies, the observation that children with Down syndrome have a 20-fold higher risk of leukemia prompted a case-control study of 42 children with both acute leukemia and Down syndrome as cases and 124 healthy children with Down syndrome as controls.²⁹ The odds ratio for direct measurements of magnetic fields exposures greater than or equal 0.6 μT was 3.7 (95% CI: 1.05-13.1). The authors suggested the possibility of a role for magnetic fields in the etiology of leukemia among this genetically susceptible subgroup of children. In a study conducted in Japan, the odds ratios for children

whose bedrooms had magnetic field levels of 0.4 μT or higher compared with the reference category (below 0.1 μT) was 2.6 (95% CI: 0.76-8.6) for acute lymphoblastic leukemia (ALL) plus acute myelocytic leukemia (AML) and 4.7 (1.15-19.0) for ALL only.³⁰

In a study in the North of England of parental occupation, an occupational exposure matrix was used to assign individuals to exposure groups. There was an increased risk of leukemia reported among the offspring of men employed in occupations likely to be associated with EMF or radiation exposures (OR 1.31, 95% CI: 1.02-1.69).³¹

Residential exposures and cancer in adults

Compared to children, there are fewer residential studies relating to adults. Wertheimer and Leeper³² attempted to replicate and improve upon the methodology used in their original study of childhood cancers in an adult population in Denver, Colorado. They found statistically significant associations for all cancer mortality, cancers of the nervous system, uterus and breast and for lymphomas with increased exposure to magnetic fields assessed by wiring configuration. A major weakness of this study related to the fact that those carrying out the exposure assessment were not blind to the case-control status of the subject.

A retrospective population cohort study was undertaken by McDowall et al.³³ in East Anglia, England, examining cancer mortality for all ages in relation to distance from overhead power lines (30 metres) and from electrical installations (50 metres). The only statistically significant finding was an approximately twofold increase in risk of lung cancer for females, with a dose-response relationship evident for distance from electrical installations.

Severson et al.³⁴ investigated population registry-based incidence of acute non-lymphoblastic leukemia (ANLL) in adults in western Washington State in relation to wire codes comparable to those defined by Wertheimer and Leeper.¹ The codes were assessed for the residence closest to the reference date and the longest residence three to ten years before the reference date. Spot measurements of magnetic fields were

also made in several rooms in the home. There was no evidence of significantly increased risk with any magnetic field measurement. High wiring configuration was associated with a decreased risk of ANLL.

Coleman et al.³⁵ used distance between residence and overhead power lines and electrical installations, as well as a measure of the calculated magnetic field over a three-year period, to evaluate adult leukemia incidence in southeast England. A non-significant elevation in risk of leukemia in relation to residential exposure to ELF EMF from power lines and transformer substations was found. However, the authors cautioned that the study had limited statistical power (less than 80 percent) to detect even a threefold excess in risk in relation to proximity to overhead power lines.

Youngson et al.³⁶ studied hematological malignancies in northwest England and Yorkshire using controls discharged from hospital. Exposures were assessed according to distance from overhead power lines and calculated magnetic fields based on current load. No statistically significant associations were observed, although excess risk was seen for myeloid leukemia.

A retrospective cohort study design was used to compare observed and expected deaths among residents who had lived five years or more in a section of Maastricht, Holland which had two 150 kV power lines and one transformer substation.³⁷ Exposure was defined according to distance from power lines or substation; exposed were those living at distances less than 100 metres with associated measured magnetic fields of 0.1-1.1 μ T; the referent was defined as distances greater than 100 metres with magnetic field exposures of 0.02-0.15 μ T. The standardized mortality ratios (SMR) showed no associations between exposure as defined and those cancers with previously reported relationships with ELF EMF.

Feychting and Ahlbom³⁸ evaluated excess risk of myeloid leukemia in adults in relation to residential magnetic fields, assessed according to distance from power lines. Magnetic fields generated by power lines

were calculated and archival information on line current was used to make historical corrections. Excess leukemia risk was observed for cumulative exposure of 2.0 μ T-years or more during the 15 years preceding diagnosis, and distance of 50 metres or less from the lines.

A study of residential exposure and adult cancers (leukemia, brain and female breast cancer) in Taiwan³⁹ showed a statistically significant increased risk of leukemia with measured magnetic fields greater than 0.2 μ T (OR 1.4, 95% CI: 1.0-1.9) and with residential proximity (at time of diagnosis) of less than 50 metres to the nearest transmission line (OR 2.0, 95% CI: 1.4-2.9). No evidence of risk was observed for the two other cancers studied.

A study from Finland found no evidence of increased risk of leukemia in adults, although an excess of multiple myeloma in men and colon cancer in women was observed.⁴⁰ Exposure was based on calculations of the average annual magnetic fields, similar to that used for the childhood study.¹⁷ Some elevated ORs were observed in the upper two exposure categories in a Norwegian study of 1068 hematological cancers, but the results are based on small numbers and no firm conclusions can be drawn.⁴¹ Analysis of total leukemia using 0.4 μ T as the upper residential cut-off point gave an OR of 1.6 (95% CI: 0.6-3.8), nine cases. Analysis of linear trend using exposure in the 10 years before diagnosis in the case showed a borderline statistically significant result for chronic lymphatic leukemia (CLL) and all hematological cancers. In a similar Norwegian study of breast cancer with 1830 cases and 3658 controls, women with residential exposure greater than or equal 0.05 μ T had an odds ratio of 1.58 (95% CI: 1.30-1.92) when compared with unexposed women, but there was no association observed for occupation.⁴² A population-based case-control study of breast cancer in Seattle, Washington that included 813 women 20-74 years of age also reported no association of residential magnetic field with breast cancer.⁴³

Exposure to electrical appliances in the home

Electric and magnetic field exposures associated with household appliances can be high because of the close personal proximity with use. As an example, the magnetic flux density of a hair dryer is 6 to 2000 μ T at a distance of three centimetres from the hair dryer, whereas at a distance of 30 centimetres this range is <0.01 to 7 μ T.^{44,45} Because magnetic fields are greatly attenuated with distance, electric blankets, electric razors, hair dryers, and water beds are candidate "appliances" for evaluation of potential risk because of their close proximity to the body during use.^{13,34,46,47} Savitz et al.⁴⁷ found a non-significant association (OR 1.7) for childhood leukemia risk and a significant risk for brain cancer (OR 2.5) associated with prenatal electric blanket use. A non-significant leukemia risk was found with postnatal exposure to bedside electric clocks. The authors cautioned against over-interpretation of these results in light of the small numbers and non-response rate. In the study by London et al.¹³ examining childhood leukemia, significant risk (OR 2.82) at the 95% level was found with the regular (at least once a week) use of electric hair dryers and (OR 1.49) with black and white television use. In the Dockerty et al.⁶ study in New Zealand, appliance use exposure by the mother in pregnancy or directly by the child was evaluated for all childhood cancers. There was no increase in risk for many of the appliance exposures. For electric blanket use by the child before diagnosis, adjusted odds ratios were 2.2 (95% CI: 0.7-6.4) for leukemia, 1.6 (95% CI: 0.4-7.1) for central nervous system cancers and 2.4 (95% CI: 1.0-6.1) for other solid cancers. In the study of Green et al.²⁶ a preliminary analysis of childhood leukemia in southern Ontario in relation to the use of a number of different appliances common to the residential environment was uninformative.

Occupational exposures and cancer

Early reports of associations between cancer risk and electric and magnetic fields were based primarily on proportional mortality studies using job titles as surrogate

indices of exposure to electric and magnetic fields. These studies were followed by case-control and cohort studies using similar indirect estimates of exposure to high levels of electrical and magnetic fields. Collectively, these studies suggested that “electrical occupations” were associated with increased risks of leukemia and/or brain cancer.⁴⁸⁻⁶⁰

Subsequent occupational studies were still restricted in exposure assessment by the use of job titles to infer exposures to electric and magnetic fields.⁶¹⁻⁶⁵ A case-control study of non-CLL leukemia in a primarily retired population of American Telephone and Telegraph workers found non-significant increased risks.⁶⁶ There were similar findings in a study of Norwegian workers.⁶⁷

Floderus et al.⁶⁸ carried out a population-based case-control study of leukemia incidence and brain cancer in Sweden. Measurements of magnetic fields were derived from a personal monitor worn for a representative day in the work environment, with a focus on those jobs or tasks held the longest during the ten-year period before diagnosis. Adjustments were made for potential confounders such as benzene, ionizing radiation, pesticides, solvents and smoking. A dose-response relationship was observed for all leukemia and for chronic lymphocytic leukemia, with statistical significance attained at the highest exposure levels. There was no association with acute myelogenous leukemia. Elevated risks were also found for brain cancer and statistical significance was attained, but not in the highest exposure level.

Sahl et al.⁶⁹ examined leukemia, brain cancer and lymphoma mortality among workers in a US electric power utility in relation to measured magnetic field exposures and also to employment in electrical occupations defined as “exposed” *a priori*. Using both a cohort and case-control approach, no excess risk of any cancer site under study was observed, although the small numbers place limitations on the interpretation and significance of this study.

Theriault et al.⁴ studied cancer incidence in electric utility workers from Canada and France using a nested case-control study

design. Current workers, selected according to job title, wore Positron™ monitors which measured electric and magnetic fields. Using these measurements and a work history, a job-exposure matrix was created and applied to cases and controls in each of the participating utilities. The investigators also attempted to control for possible occupational confounders. A statistically significant association was observed for acute non-lymphocytic leukemia and specifically for acute myelogenous leukemia. The excess risk was most pronounced in the Ontario Hydro cohort but also was apparent in the Hydro Québec cohort, where all cases of acute myeloid leukemia (N=6) were confined to the exposed group and, as a result, the reported odds ratio was undefined.

Savitz and Loomis⁷⁰ reported on the mortality experience of five US utilities. Personal monitors were worn, but yielded only a time-weighted average exposure to the magnetic field per worker. An association was observed with leukemia for electricians (OR 2.5, 95% CI: 1.08-5.76) having 20 or more years of employment, and a statistically significant excess of brain cancer mortality (OR 2.3, 95% CI: 1.15-4.56) was associated with magnetic field levels of >4.3 μ T-years. The findings relating to brain cancer showed a significant trend of increasing risk with increasing exposure to magnetic fields.

In the study of electric utility workers in Ontario, Miller et al.⁵ raised the possibility that electric fields might be more important than magnetic fields with respect to occupational exposures and leukemia risk. An odds ratio for all leukemia of 4.5 (95% CI: 1.01-19.7) was reported for electric field levels >345 volts per metre (V/m) years. Further, there was evidence of an interaction between electric and magnetic fields (OR 11.3, 95% CI: 1.52-84.3) for electric field exposure >345 V/m years and magnetic field exposure >7.1 μ T-years, with the electric field component being dominant in the contribution of excess risk. An association between lung cancer and exposure to both electric and magnetic fields also was suggested.

Guenel et al.⁷¹ also reported findings suggesting that exposures to electric fields might be important in the occupational environment. Among French electric utility workers, increased odds ratios for brain tumours were observed which were statistically significant at the highest exposure level (OR 3.08, 95% CI: 1.08-8.74) and for those with employment of 25 years or more. There was no evidence of increased risk of leukemia with electric field exposure.

Kheifets et al.⁷² attempted to evaluate leukemia risk and occupational electric field exposure in Los Angeles County, California. No association was found.

Although in the Canada-France study no association between lung cancer and time-weighted averages of magnetic fields was noted,⁴ an association was reported between lung cancer and exposure to pulsed electromagnetic fields (PEMF) in the combined Hydro Québec and Electricité de France data.⁷³

To date, only one study has considered both occupational and residential exposures to electric and magnetic fields.⁷⁴ Modest increases in risk were observed for leukemia and exposure (0.2 μ T) in the residential (OR 1.7, 95% CI: 1.1-2.7) and occupational environments (OR 1.3, 95% CI: 0.8-2.2). Exposure to magnetic fields of 0.2 μ T or more in both the residential and occupational environments was associated with risk of acute myeloid leukemia (OR 3.7, 95% CI: 1.5-9.4). Central nervous system tumours showed no association with magnetic field exposure.

Kheifets et al.⁷⁵ conducted a comparative analysis of the recent occupational studies. They concluded that there was evidence of a weak association between magnetic field exposure and risks of leukemia and brain tumours. They were unable to evaluate electric field exposure.

If some aspect of electric or magnetic field exposure unique to the workplace increases cancer risk, then the use of cumulative time-weighted average (TWA) estimates of exposure may dilute the true risk. The evaluation of other indices of magnetic fields has been done explicitly in some

studies.^{13,66,68} Other work has assessed cancer risk by using cumulative electric and magnetic field exposures, based on the geometric and arithmetic mean field strength. The arithmetic mean is more sensitive to skewed data and is better suited for modelling threshold effects, whereas the geometric mean, which is closely related to the median of the exposure distribution, minimizes the influence of outliers. However, results from further analyses of the Ontario Hydro study population indicated that the use of the arithmetic and geometric means does not adequately characterize the variability of either electric or magnetic field exposures.⁷⁶ Therefore, further analyses have evaluated the association between other indices of electric and magnetic fields and cancer in the Ontario Hydro cohort. Both duration of employment and average annual exposure to electric fields were independently associated with an increased risk of leukemia.⁷⁷ The analyses supported the hypothesis that exposure above an electric field threshold is the relevant aspect of field strength to predict leukemia risk.

An Australian study with 694 cases and controls investigated the risk of non-Hodgkin lymphoma (NHL) using a job-exposure matrix (JEM) to assess exposure to occupational magnetic fields at the power frequencies of 50/60 Hz.⁷⁸ For the total work history, the odds ratio (OR) for workers in the upper quartile of exposure was 1.48 (95% CI: 1.02 to 2.16) compared to the referent (p-value for trend was 0.006), providing weak support for the hypothesis. A similar Australian study of 414 histologically confirmed cases of glioma did not indicate support for a role of ELF EMF.⁷⁹ Also, a case-control study in Germany of testicular cancer with 269 incidence cases and standardized face-to-face interviews indicated ELF EMF was not a risk factor for this cancer type.⁸⁰

Two recent studies of occupational exposure and female breast cancer have reported negative findings and one a positive finding. While the residential component of a Norwegian study of female breast cancer observed an association as noted above, there was no association observed for occupation as assessed individually by an

expert panel.⁴² In addition, the findings of a Swedish study of occupation and breast cancer using 20,400 cases identified from the cancer registry do not support the hypothesis that magnetic fields influence the risk of developing the disease.⁸¹ The exposure was assessed by linkage to a job-exposure matrix based on personal magnetic field measurements. A study in the Montreal region was undertaken with 608 postmenopausal breast cancer cases and 667 controls. Industrial hygienists assigned to each job an average duration of exposure to ELF EMF at four levels of intensity. Adjusted for other risk factors, an OR of 1.13 (95% CI: 0.94-1.35) for lifetime occupational exposure to ELF EMF at medium or high intensities was reported (greater than or equal 0.5 μ T) and risks were larger for exposures before age 35.⁸²

Experimental studies

Biological plausibility is one of several criteria used to judge causality. To date, it has not been possible to demonstrate a biological mechanism whereby exposure to electric or magnetic fields causes cancer. Notwithstanding the lack of evidence from laboratory research, it needs to be remembered that the carcinogenic potential of some exposures has been suggested initially by epidemiological research, only to be corroborated much later by experimental studies.⁸³

Discussion

In spite of extensive efforts over a period of 20 years and many expert reviews,^{44,83-87} it has been difficult to reach consensus regarding the carcinogenic effects of electric and magnetic fields. One of the difficulties has been different approaches to the measurement of ELF EMF and different epidemiological methods used to assess the association.⁸⁸ While there have been notable improvements in methods relating to case ascertainment and accounting for other factors, exposure assessment has proven to be complex and agreement on the relevant exposure metric has not yet been obtained.

Studies to date have suffered from lack of specificity with respect to exposure. It is by

no means certain that all epidemiology studies have measured the right parameters for ELF EMF exposures. While consistency of reported risks by certain metrics of ELF EMF is the most compelling argument suggesting a causal role for ELF EMF, biological plausibility is weak. Laboratory work has failed to demonstrate a biological mechanism which might explain the epidemiological findings. As a result, there have been few clues about the relevant exposure metric, if any, to apply to epidemiological investigations.

The early studies of children tended toward a consistent association between risks for leukemia and brain cancer and both residential proximity to power lines and high wire configuration. More recent studies have tended not to confirm this association. Because of this and the observation that the earlier studies that used point-in-time “measures” of magnetic fields showed either an acutely attenuated risk or no risk, some have concluded that the association should not be regarded as causal. There are, however, several reasons to question whether point-in-time measures in homes are appropriate indices of the relevant etiological exposure, as they fail to account for changes over time, peak exposures or time varying fields.

While several studies have shown measured magnetic fields do increase with higher wire configuration, the disparate associations of these two “measures” observed with leukemia risk have led to the speculation that wire code may be a surrogate for the true etiological agent. Research directed at a better understanding of the correlates with wire code, such as traffic and housing density is underway.⁸⁹ Many of these potential correlates are related to socio-economic status. It has been proposed that wire configuration is more stable and, as such, may be superior to point-in-time measurements as an indicator of integrated exposure over time.⁸⁸ However, wire codes have been tested in relatively few urban environments, and there is a need to gather more information to determine if the presumed meaning of wire code changes with the geographic location/jurisdiction.

Measures of exposure-as-distance-from-electrical-installations almost certainly suffer from substantial misclassification, especially if it is not possible to take the exposure directly experienced by the subject in the house into account. The Scandinavian studies of children and adults attempted to incorporate historical corrections with distance to better estimate lifetime exposures, and several of these studies support increased risk, especially of childhood leukemia, if the residence is within 50 metres of a power line. Kaune et al.⁹⁰ suggested that a significant increase in leukemia risk is seen with exposure calculated from historical line-load data, but not with current measurements. The authors found that the correlation between the current measured value of magnetic field and the calculated magnetic field using historical line-loading data diminished to zero as the historical data extended back more than five years. This argues that studies using contemporary measurements of magnetic fields may not capture the relevant exposure if the etiological period extends back many years.

In addition to the difficulties in interpretation posed by the different methods of ELF EMF exposure assessment, potential selection and information biases may exist in several of the published childhood cancer residential studies, and it is not possible to determine how this might have influenced the results. Some studies have imposed a residency requirement on the controls.^{10,11} This has led to the criticism that the controls might be more residentially stable than cases, a situation which in turn might be associated with other lifestyle or socio-economic characteristics that may confound the relationship between leukemia risk and magnetic field exposures.⁹¹ By studying defined areas of Columbus, Ohio, Jones et al.⁹¹ found that “high wire codes were associated with homes in which the residents were mobile and low wire codes were associated with homes occupied by stable residents”.

Differential non-participation of controls as function of socio-economic status was proposed by Gurney et al.⁹² as a possible explanation of the association between wire codes and childhood cancer. Their

study in Washington state found that non-participants were more likely to have lower income, which was in turn found to be associated with very high wire configuration. The studies by Savitz et al.¹¹ and London et al.¹³ have the potential for this non-response bias.

A similar concern might be raised over the method of control selection used in the study by Green et al.^{7,25} (telephone-based sampling from lists obtained at one time period). The selection of controls was not concurrent with the cases and bias might have resulted from the controls being more stable than the cases. Cases and controls in the Green et al.^{7,25} study did differ significantly with respect to residential mobility, a factor which is potentially related to socio-economic status. There was an inverse relationship between number of residences and family income, with lower income families moving more often. Residential mobility was also an influential variable in all the multivariate models; children who moved more frequently had higher risks of leukemia. Although both the Green et al.^{7,25} and McBride et al.⁸ studies detected an association between mobility and leukemia risk, the results of the two studies differed; after taking mobility into account, the Green et al. study^{7,25} detected a significantly positive association between residential exposures to magnetic fields and leukemia, whereas the McBride et al. study⁸ did not.

The paper by Borugian et al. underscores the relevance of socio-economic status as a risk factor for childhood leukemia.⁹³ A slightly lower relative risk of childhood leukemia was observed in the poorest quintile compared with the richest (RR = 0.87; 95% CI: 0.80–0.95). The lower risk in the poorest quintile was restricted to acute lymphoid leukemia (0.86; 0.78–0.95).

To assess the possibility of bias from the selection of non-concurrent controls in the Green et al.^{7,25} study, risk estimates for outside point-in-time measures of magnetic fields were calculated for those diagnosed at less than six years of age by including only controls who had lived in one residence. These risk estimates were attenuated relative to analyses where no mobility

restriction was applied to the control population. However, when risk estimates were calculated including only controls that lived in more than one residence, they were higher than those calculated with no mobility restriction applied to the controls. These results suggest that, if it had been possible to include more mobile controls, the risk estimates might have increased. Thus the results from the study may underestimate rather than overestimate the risk of leukemia. Green et al.⁷ also examined non-participating cases and controls with respect to wire code of the most current residence and found no differences. Although non-participating subjects were more mobile than participating subjects, there were no differences observed between cases and controls.

The disparate findings in the two Canadian studies^{7,8,25} are currently unexplained. There were substantial similarities, but also differences between these two studies. For example, the investigators met regularly with the sponsors’ representatives as the studies proceeded and attempts were made to ensure similarity in the data collected. Thus, although the questionnaires were not identical, they were exchanged and attempts were made to ensure that similar data were collected on potential confounders. The ELF EMF measurement protocols were not identical either. Yet in both studies, personal monitoring using the Positron™ monitor was performed for subjects living in a residence relevant to the period of enquiry and measurements were made of magnetic fields in previous residences. Further, the distribution of exposures to electric and magnetic fields seemed similar; in both studies, the 75th percentile for magnetic field exposures was approximately 0.15 μ T.

However, there were major differences in the way the data from the personal monitor were used in the analysis. First, a mean of the measurements over a 48-hour period was computed to estimate exposure in relevant current residences in the McBride et al.⁸ study. Given that the majority of cases were ascertained prospectively, it is possible that many of them had not yet resumed their normal activity levels after diagnosis and treatment. Further, the mean

includes exposures outside home, i.e., at school and in other circumstances, and these may not represent etiological exposures as relevant as those at home. In contrast, in the Green et al.⁷ study, with retrospective assessment of cases, sufficient time had occurred for the cases to resume normal activity. Further, the exposures as measured in the current residence, school and other environments were analysed independently. Indeed, the exposures in other environments were not considered, as they were deemed not to represent etiologically relevant exposures. Second, in the McBride et al.⁸ study, personal exposures in previous residences were constructed using regression analyses which used wire codes and the available magnetic field exposures in such residences. This process probably involved substantial misclassification; the correlation was relatively low between exposures actually measured in residences using the personal monitor and those estimated. For this reason, this approach was not attempted in the Green et al.²⁵ study. Rather, an attempt was made to develop integrated estimates of exposure from the actual measurements made in the relevant residences. Third, although the McBride et al.⁸ study was closely pair-matched by age, the matching was dissolved for the analysis, and age was controlled using only strata substantially larger than those used for matching. This process was said to have been adopted in order to avoid too much loss of data, but it seems likely to have introduced uncontrolled confounding by age. This was avoided in the Green et al.^{7,25} study by preserving the individual matched design in the analyses.

There is a parallel between the largely negative findings of the McBride et al.⁸ study and the study of Linet et al.²¹ Both were conducted in areas away from very large conurbations and largely in the west of North America, except for the Montreal component of the McBride et al.⁸ study. It would be of interest to determine if there is greater similarity between the findings from Montreal and the Green et al.^{7,25} study conducted in the greater Toronto region of southern Ontario, than between the findings from western Canada and the United States.

The largely negative study in the UK, based as it is on substantial numbers of case-control pairs, might also be regarded as strong evidence against the hypothesis that exposure to magnetic fields in the home increases the risk of childhood leukemia. However, as pointed out by Repacholi and Ahlbom,⁹⁴ the exposures in the UK may be criticized for being restricted to time-weighted averages and, because of the 220-volt service to the homes, are much lower than those in North America. Thus, there were only four cases and three controls exposed to 0.2 μ T and above. The power of this study was, therefore, substantially lower than that of either of the Canadian studies. Further, there has to be concern over the exposure estimates used. They were restricted to the year before diagnosis for the cases and to a corresponding period for the controls—a period that was, in fact, not regarded as being relevant to the defined etiological period for cases and controls older than two years in the Green et al.^{7,25} or Linet et al.²¹ studies. There was also no attempt in the UK study to derive estimates of exposure for earlier time periods or previous residences.

The studies of residential exposures and cancer in adults generally suggest no effect. However, in most studies, measurements have been confined to one residence (current) for which representativeness of lifetime exposure cannot be assumed. While this issue of studying only one residence is also applicable to studies of children,² except for the more recent studies, it would seem to be even more important with respect to adults who have many more years for exposure opportunities to electric and magnetic fields and to known or suspected carcinogens both occupationally and residentially.

In a recent review of adult cancers, Li et al.⁹⁵ calculated the statistical power of these studies to detect a doubling of risk with “high” levels of residential exposure. That only four studies^{14,33,35,36} had power over 80 percent to detect such levels of risk led the authors to conclude that “inadequate statistical power is more of a concern than bias in explaining the inconsistencies across studies”. The studies where no leukemia

risk was demonstrated had a very small proportion of the population exposed to magnetic field levels of 0.2 μ T or more, however that measurement was derived.

The studies of electric and magnetic field exposures and cancer risk in workers present the generic advantages of studying occupationally exposed groups. The exposures of workers often can be more accurately measured without bias, as a result of records collected and retained for independent purposes and prior to the onset of disease. However, exposures with respect to electric and magnetic fields in the work environment are very different from exposures usually found in residential settings. Occupational exposures are typically higher and reflect wider ranges than those found in homes, and generalization from occupational to residential environments is not appropriate given the current state of knowledge. Moreover, exposures in a residential setting are comparatively uniform, whereas workers may move in and out of high fields throughout their workday or week. It is possible that measuring exposures in the workplace allows for better distinction between exposure ranges and, as a result, high exposures are more accurately characterized and an association detected.

Occupational studies have tended to show an effect with exposure when a distinction was possible by histological type, with acute myelogenous leukemia showing stronger associations, though a few show associations with chronic lymphocytic leukemia. Such types are rare in children, with the dominant type being acute lymphoblastic leukemia. Higher risks have also been observed with cancer incidence than with cancer mortality.

Particularly, but not exclusively, for adults, historical corrections may be important. Most occupational studies have used current exposures applied to current job titles. Recent studies have attempted to apply a correction factor to account for changes over time; however, there is no way by which the validity of the correction can be assessed and, as a result, current measurements are used to estimate exposures as much as 50 years ago.

Delpizzo⁹⁶ highlighted the susceptibility to misclassification by the use of job titles as a surrogate of exposure. Miller et al.⁵ found that failure to consider work location in addition to job title, and *a priori* selection of job titles according to “presumed” exposure to magnetic fields can attenuate risk estimates.

The recent finding from further analyses of the Ontario Hydro study, that exposure to electric fields over certain thresholds is the greatest predictor of risk of leukemia,⁷⁷ supports the need for more extensive work on alternative dose metrics. It is unfortunate that the measuring instrument used in the largest US occupational cohort⁷⁰ did not measure electric fields, while the detail obtained on magnetic field exposure does not permit exploration of thresholds. More evidence on the precise circumstances that increase risk in electric utilities cannot therefore be expected from the United States until new studies are mounted.

Studies of exposures in workers are not generalizable to the members of the public, particularly children. Electric field exposures in the occupational environment are several orders of magnitude higher and show far greater variation than those observed in residential settings or settings typically inhabited by children. The risk of adult leukemia associated with electric fields, as reported by Miller et al.,⁵ is related to the level of exposure and its duration. However, exposure levels equivalent to those in the occupational environment are not achievable through usual childhood activities.

In spite of the uncertainties described, it is probably desirable to err on the side of caution in not placing too much weight on the inconsistencies. The IARC has classified EMF as a “possible carcinogen” which refers to the circumstances where there is limited evidence of carcinogenicity in humans and inadequate evidence in experimental animals. The IARC review indicated limited evidence for the carcinogenicity of extremely low-frequency magnetic fields in relation to childhood leukemia at high level exposure in the residential environment (average residential magnetic field strength $>0.4 \mu\text{T}$).⁹⁷ Even higher levels of

exposure in the occupational environment may increase the risk of leukemia in adults.

The National Institute of Environmental Health Sciences in the United States concluded that although the overall evidence is weak, EMF cannot be recognized as entirely safe and as such should be regarded as a possible human carcinogen. This conclusion is based on “limited evidence of an increased risk for childhood leukemia with residential exposure and an increased occurrence of chronic lymphoblastic leukemia associated with occupational exposures”.⁸⁶ The National Radiological Protection Board in the United Kingdom concluded that there is some epidemiologic evidence that prolonged exposure to higher levels of power frequency magnetic fields is associated with a small increased risk of leukemia in children.⁹⁸

Adoption of regulations by governments for ELF EMF exposure from power lines is not widespread. However the California Department of Education (CDE) provides an example of an official body which has established guidance notwithstanding the uncertainty of the scientific evidence. The CDE has made recommendations regarding school site power transmission line setbacks (California Code of Regulations, Title 5, Section 14010⁹⁹).

The CDE guidance for overhead transmission line easement setbacks as measured from the edge of easement of overhead transmission lines to the usable portions of the school site are: 100 feet for 50-133 kV line (interpreted by CDE up to $<200 \text{ kV}$); 150 feet for 220-230 kV line; 350 feet for 500-550 kV line.⁹⁹

This guidance was developed in consultation with international experts on the health effects of electric and magnetic fields (EMF), state agencies such as the Department of Health Services, the Division of the State Architect, and the California Public Utilities Commission, electric utilities, school districts, consultants, and private citizens with an interest in the topic.⁹⁹

The CDE recognizes other hazards need to be considered when locating a school, such as major roads or long distance busing of

students. In certain instances, the setback distance can be measured from the transmission line (at ground level) instead of from the edge of easement, and setback distances have been reduced for underground transmission lines.

Summary

1. The current evidence relating to averaged magnetic field exposures greater than $0.4 \mu\text{T}$ and leukemia in children suggests, but does not prove, a causal relationship.
2. Studies of workers occupationally exposed to high levels of electric and magnetic fields also suggests an association between high level ELF EMF exposure and an increased risk of cancer, specifically acute non-lymphocytic leukemia.
3. There is inadequate evidence that residential exposures to electric or magnetic fields are associated with increased cancer risks for adults.

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