INSIGHT ON CANCER

environmental exposures and cancer

HIGHLIGHTS

- **Evidence supports an association of one or more cancers with environmental exposure to:**
  - **air pollution**
  - **arsenic**
  - **asbestos**
  - **water disinfection by-products**
  - **extremely low frequency electromagnetic fields**
  - **solar radiation**
  - **radon**

- **Commentators discuss prevention and policy issues related to environmental exposures**

Insight on Cancer is a series of joint Cancer Care Ontario and Canadian Cancer Society (Ontario Division) publications, designed to provide up-to-date information for health professionals and policy-makers about cancer and cancer risk factors in the province.

insight on cancer
volume four
june 2005

Canadian Cancer Society | Société canadienne du cancer
www.cancer.ca

cancer care ontario | action cancer ontario
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ACKNOWLEDGEMENTS

The authors acknowledge Jennifer Frood for contributions made during the early development of this report.

Thanks to Eva D'souza, Lori-Ann Larmand, and Gayle Morrison for providing technical support, and to Christine Naugler for assistance with editing this document.

Thanks also to the many reviewers who provided valuable comments on a draft of this report:
Ruhee Chaudhry, Donald Cole, Ken Johnson, Robert Kyle, Heather Logan, Ronald Macfarlane, Verna Mai, Loraine Marrett, Anthony Miller, Patti Payne, Jim Purdham, Herveen Sachdeva, Larry Stoffman, Terrence Sullivan, and Loren Vanderlinden.

Published and distributed by the Canadian Cancer Society (Ontario Division). This *Insight on Cancer* was written by staff of Cancer Care Ontario's Division of Preventive Oncology:

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FOREWORD

by Terrence Sullivan
President & CEO
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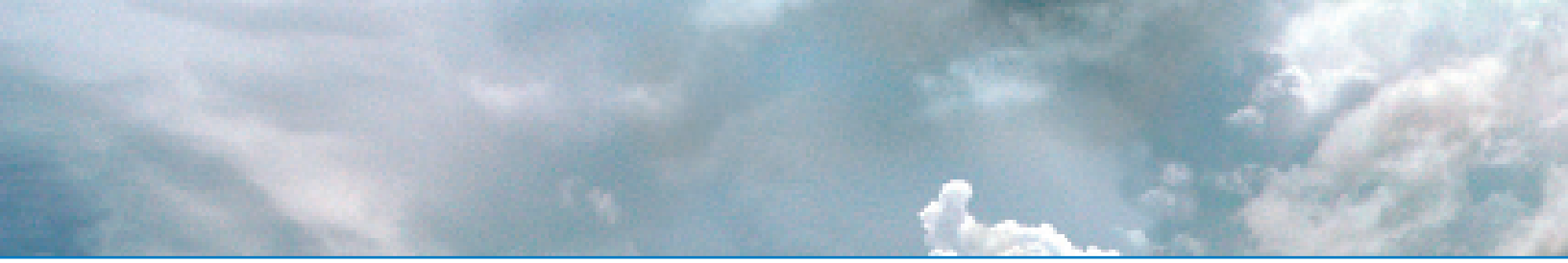
Cancer Care Ontario is pleased to present this *Insight on Cancer*, which reviews published and official reports relating to selected environmental exposures and the risk of cancer. In 2001, Ontario hosted an expert panel which identified candidate environmental exposures that might warrant special attention going forward. These exposures were considered for this *Insight*. Although the primary focus is on environmental exposures in the general population, in many cases, as Dr. Miller's commentary points out, the strongest evidence comes from occupational exposures and therefore those have been considered, along with relevant toxicology data.

The environmental causes of cancer is a field where claims are many and the evidence must be harnessed carefully to support both the development of social consensus and public decision-making. In the last two years, contrasting reports from Canadian policy groups have made claims ranging from the absence of any strong evidence linking environment carcinogens and human health (1) to claims that a significant fraction of the "epidemic" of cancer can be tied to industrial exposures and environmental causes (2). The existence of such extremes in claims underlies simultaneously the need for a strong base of evidence in making policy decisions about cancer risks and the inadequacy of the evidence on which to make decisions. Indeed, a number of jurisdictions are now approaching environmental regulation in a fashion which balances the evidence present in the scientific literature with a kind of juried consensus of stakeholder views on what might be acceptable to the population. It was with this in mind that we invited commentaries from our three capable colleagues Larry Stoffman, Tony Miller, and Don Wigle.

A leader in occupational/environmental health and safety with the United Food and Commercial Workers, Mr. Stoffman is chairing the National Environmental and Occupational Cancer Committee for the Canadian Strategy for Cancer Control through its Primary Prevention Committee. Dr. Tony Miller is a distinguished cancer epidemiologist with a career of achievement in cancer research and significant international consultation work. Dr. Miller is also playing a role with the Canadian Strategy for Cancer Control in the development of targets for cancer control. Dr. Don Wigle spent much of his earlier career as a scientist with Health Canada informing federal policy and has authored an important collection of publications on environment and health issues.

Environmental and occupational regulation of exposure rests with distinct federal and provincial authorities who work with the force of law in their regulatory initiatives. Cancer Care Ontario as a surveillance and cancer control agency has no regulatory authority, but has a special role to play in identifying potential risks for cancer, the surveillance and publication of those risks, supporting research on those risks, and advising government. Governments may choose to go beyond existing evidence and be guided by a range of principles which recognize the protective measures needed in the face of



serious harm, even if some cause-and-effect relationships are not fully established scientifically. Indeed, this is the tradition of public health, a tradition which in Canada, through the Supreme Court, has given municipalities the authority to ban pesticides (3). While the predominant international trade regime has tended to support unencumbered trade, the recent World Trade Organization (WTO) decision supporting the government of France in its decision to ban asbestos importation has been upheld. Based on public health concerns, the asbestos ban represents a significant breakthrough in an otherwise consistent pattern of decisions supporting trade liberalization by the WTO (4). The government of Canada has yet to show the same commitment to banning asbestos production and importation. Close to 100 workers will die in Ontario this year of historical mesothelioma exposure.

The Toronto Cancer Prevention Coalition, a significant initiative at the municipal level, has focused on policy in several areas related to municipal activities, including occupational and environmental carcinogens, and has recommended the adoption of the following principles:

- The **precautionary principle,** which states that, when an activity poses potential harm to human health or to the environment, precautionary measures to reduce exposure should be taken even if some cause-and-effect relationships are not fully established scientifically.

- The **weight of evidence** approach, taking into account the combined results of many kinds of research to reach a conclusion about the need for action.

- **Pollution prevention**, acknowledging that it is less expensive and more effective to prevent environmental and human health damage than to manage or cure it.

- **Just transition**, which allows workers and communities to choose economic security and a healthy environment for themselves, and which suggests that the cost of transition should not be borne disproportionately by workers in affected industries.

- **Communities' right to know** about environmental risks and to participate in making the decisions affecting their health.

Cancer Care Ontario acknowledges these principles and recognizes that reducing environmental exposures is an important component of a comprehensive cancer control strategy. Indeed, on the right to know principle, Don Wigle argues that Ontario should have access to pre-market evaluations conducted by Health Canada as well as related Canadian information on toxins and environmental standards. In the release of Cancer 2020, Cancer Care Ontario called for research, surveillance, and action in both the areas of occupational and environmental exposures. Cancer Care Ontario has, in the last three years, developed a focus on occupational cancer surveillance.

Prevention measures aimed at reducing cancer risks may have further benefits, since environmental exposures increase risks of diseases other than cancers. Against those benefits must be weighed the potential economic impact of discontinuing use (for example, chemical pesticides used to improve farm yields in Ontario), the potential risks of eliminating potentially carcinogenic products that are instrumental in preventing other diseases (such as chlorination by-products preventing waterborne infections, unless less hazardous but equally effective compounds can be substituted). I believe that this *Insight on Cancer* offers useful to-date information from a series of perspectives on environmental risks for cancer.

Cancer Care Ontario will continue to play a role on the surveillance and research on the risks for cancer sketched in this *Insight*. Together with our colleagues across Canada, we will work towards a better understanding of the environmental contribution to those cancers on the rise, including non-Hodgkin lymphoma and thyroid cancer, among others. As we better understand where causal links exist, we will be better able to reduce or eliminate these substances in the interests of prevention.

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COMMENTARY

by Anthony B. Miller
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When good data became available on the differences in incidence of cancer internationally, the amount of cancer attributable to "environmental" factors, that is factors external to man, was estimated by Higginson (1) to be about 80%. This estimate has often been misunderstood by the public, who have tended to assume that the majority of cancers is caused by "them", i.e. by government and industrial action. Gradually it has been appreciated that most of the causes of the 80% are lifestyle factors, especially smoking, poor diet, alcohol (especially with smoking), obesity, lack of exercise, and exposure to sunlight, i.e. factors largely within our individual control. However, three causes remain: infections (perhaps causing 15% of cancers in the world but less in Canada), occupational exposure to carcinogens, and exposure to carcinogens in the general environment, the latter the subject of this Commentary and this *Insight on Cancer* by Cancer Care Ontario which it accompanies.

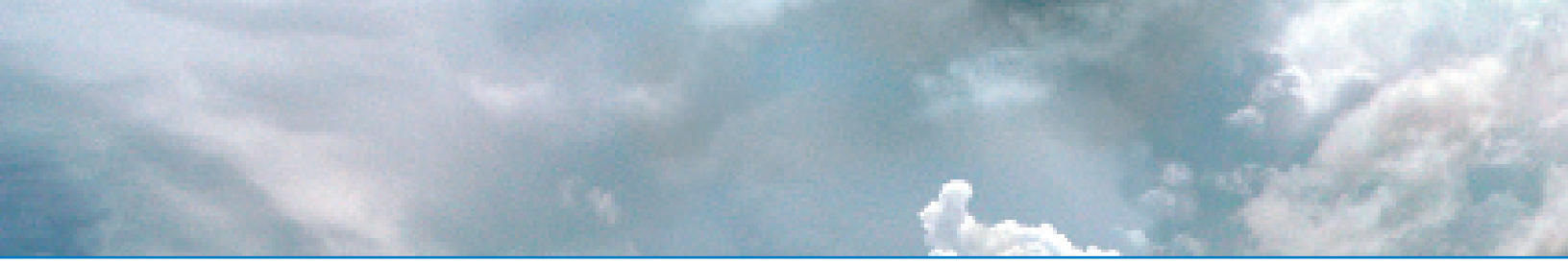
The Committee on Environmental Epidemiology of the U.S. National Research Council (2) pointed out the difficulty in studying the effect of environmental exposures, because they are so widely distributed, and exposure tends to be uniform. The Ontario Task Force on the Primary Prevention of Cancer (3) also considered these exposures and their possible effects, and recommended a number of strategies to ameliorate those effects. This *Insight on Cancer* by Cancer Care Ontario goes further, and is an important addition to the increasing number of monographs making recommendations for control of environmental exposures. Table 3 is useful, and although there could be some disagreement on the categorization of some of the exposures listed (e.g., the pesticides), in general this is a good summary of the evidence to date derived, as the accompanying text discusses, largely from non-environmental sources, largely because of the difficulties in measuring weak exposures.

The document considers in some detail eight exposures: air pollution, polycyclic aromatic hydrocarbons, metals, asbestos, water disinfection by-products, radiation, pesticides, and endocrine disruptors. This list encompasses the exposures of concern for which there are data. It is of interest that when Tomatis et al. (4) considered the environmental determinants of cancer, they simply listed the chemicals that had by then been considered in the International Agency for Research on Cancer Monographs programme on the evaluation of carcinogenic risks to humans. Nearly all exposures were occupational in origin, and their influence in causing general environmental exposure was not considered. The Committee on Environmental Epidemiology (2) went much further. They reviewed the knowledge then available on hazardous wastes in air, water, soil and food, and biological markers of such exposures. The concentration on hazardous wastes derived from the charge to the committee that they review the evidence on hazards to humans on exposures from hazardous waste sites, which inevitably meant assessing routes of

human exposure to gases and effluents from such sites. Such questions come up from time to time in Canada, and within the last decade, in relation to a large site in Ontario. Unfortunately, the evidence that relates to human risk from some sites is often poor, even when exposure comes from such a well recognised potential hazard as the Love Canal, considered by the committee in some detail. In contrast, the Ontario Task Force on the Primary Prevention of Cancer (3) was sufficiently concerned about environmental exposures from persistent toxic (bioaccumulating) chemicals, pesticides in the food supply, radioactivity and motor/fuel vehicle emissions, that they made a number of recommendations to government designed to reduce human exposures, even though there might not be proof, in the scientific sense, of hazards to humans. In that respect they went far towards the precautionary principle, in suggesting that the standards applied to suspected carcinogens would be based on a balance of probabilities, and that new chemicals should require proof beyond all reasonable doubt that they were not carcinogenic before they were introduced. I shall return to consideration of the implications of applying such standards later in this commentary.

One of the major concerns over assessing whether environmental exposure to carcinogens increases cancer risk relates to the validity of extrapolating data from animal or even human studies to estimate risk at the low levels of exposure usually encountered in the general environment. In the radiation area, controversies have usually centred upon whether a linear extrapolation from measured effects at high doses underestimates the risks at low. But even here, there have been suggestions that the risks from low level exposures are far less than the linear extrapolation would suggest. The main reason for this is that in our evolution, we had to develop mechanisms to repair damage to DNA caused by cosmic radiation, and these natural defence mechanisms have to be overwhelmed for the carcinogenic process to be initiated. There is some evidence for this suggestion. In our study of breast cancer following multiple fluoroscopies, for example, we could not detect risk at the lower levels of exposure, and the dose-response curve when extrapolated down seemed to reach the abscissa at well above zero exposure (5). In this *Insight on Cancer* it is pointed out that a similar mechanism applies to exposure to chromium. However, even if this protective mechanism applies to a few exposures, there is no reason to believe it applies to low levels of exposures from chemicals that are new, and could not have been encountered during our evolution.

The precautionary principle, as defined by the Canadian Cancer Society, is "When an activity raises threats of harm to human health, precautionary measures should be taken even if some cause-and-effect relationships are not fully established scientifically". The potential penalties from not following this principle are that cancers that could be prevented are not; but if it is followed and in fact there is no hazard to human health, unnecessary costs will be incurred. The latter, economic, argument has often won the day, and still affects the reaction of the Governments of Canada and Quebec to the use of asbestos. Also, when the report of the Task Force on Primary Prevention of Cancer was released, the provincial government had changed, and the report was largely ignored. However, the government has changed again, and perhaps this time, the sensible recommendations of this *Insight on Cancer* as they affect cancer control will not be ignored.



Perhaps the implications of this somewhat historical commentary as they relate to cancer control in Ontario, and the responsibility of Cancer Care Ontario in this regard, will lead to more action than in the past, especially as parallel initiatives within the Canadian Strategy for Cancer Control are being developed. This *Insight on Cancer* emphasises that more research, on both exposure determination and risk, is required. This will hopefully guide future priorities, especially with regard to the cancers that are increasing, for which the cause is uncertain, namely thyroid cancer and non-Hodgkin lymphoma. But in the meantime, there is no excuse for not attempting to apply the knowledge we now have, both on lifestyles and carcinogens in the environment, if we are to have any important impact upon cancer in the next 20–30 years.

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COMMENTARY

by Larry Stoffman
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National Committee on Environmental & Occupational Exposures
Canadian Strategy for Cancer Control

The National Committee on Environmental and Occupational Exposures (NCEOE), established under the Primary Prevention Action Group (PPAG) of the Canadian Strategy for Cancer Control, recently concluded a best practices review (1). Twenty-three recommendations reached by consensus (NCEOE and PPAG) targeted needed action in the following key areas:

- Primary prevention of the environmental and occupational exposures needs to become a priority issue within provincial cancer control agencies/programs.

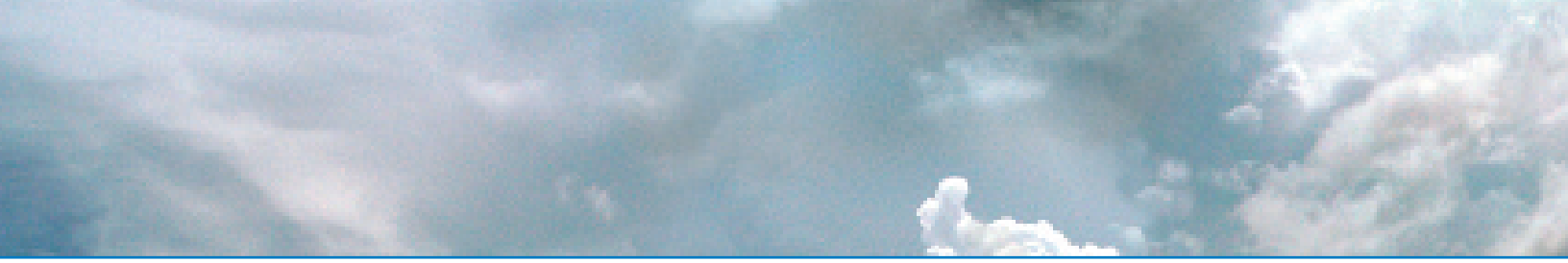
- Disclosure of the presence, use and release of classified carcinogens is a necessary prerequisite to primary prevention in workplaces, the environment and the home.

- Further legislative, regulatory and policy development are required in primary prevention.

This *Insight on Cancer* begins to address some of the important issues Canadian policy-makers need to act on concerning environmental exposure to classified human carcinogens. While there continues to be debate over the contribution of environmental exposures to the overall cancer burden, the most important point is that among exposed people environmental and occupational carcinogens may contribute significantly to the risk of cancer and that these exposures are preventable. The report overview notes that it is extremely difficult to find unequivocal evidence regarding the associations between environmental exposures and cancer. Data collection is underdeveloped with respect to low level exposures. It is therefore prudent and necessary to account for occupational evidence of carcinogenicity with respect to public environmental exposures to classified human carcinogens, and in particular to take action to protect more vulnerable population groups from environmental exposures to these same classified human carcinogens. There are increasing concerns regarding increased incidence rates for certain cancer sites (non-Hodgkin lymphoma [NHL], for example) that may be linked to certain environmental exposures.

This *Insight on Cancer* has recommended personal measures that may be taken to reduce exposures. Public policy recommendations are, however, missing. Some may argue that this is premature as there lacks "sufficient" evidence. However, the reverse can and must be argued. Public policy in primary prevention is driven by limited data, and the necessity for precautionary measures. The precautionary principle forms the basis for policy addressing environment and human health:

Whenever reliable scientific evidence is available that a substance may have an adverse impact on human health and the environment but there is still scientific uncertainty about the precise nature or the magnitude



of the potential damage, decision-making must be based on precaution in order to prevent damage to human health and the environment (2).

Initiatives to eliminate environmental tobacco smoke (ETS) from public and occupational environments are a welcome example of the application of this principle to public and environmental health policy.

In Canada, our federal Canadian Environmental Protection Act (CEPA) cites this same principle, although there are many significant gaps in our policy and practice when it comes to implementation. Instead of asking what level of harm is acceptable, a precautionary approach asks: How much contamination can be avoided? What are the alternatives to this product or activity, and are they safer?

In each of the eight areas of environmental exposure this Cancer Care Ontario *Insight on Cancer* begins to address, the necessity and opportunity for policy development and regulatory action becomes apparent. Space does not allow for a proper articulation of the many issues raised; however, a brief overview is possible.

Air pollution

There are a number of classified human carcinogens as common components of air pollution. Many of these are addressed in later chapters. Both the levels and nature of exposure need to be addressed. While some important initiatives have been taken under CEPA toxic rules, (notably restrictions on benzene and SO_2 content in diesel and gas), emission controls in both transport and point sources need to be much more stringent and enforceable. The 2010 targeted standard for $PM_{2.5}$ (30 $\mu g/m^3$) is too high (this is higher than the highest concentration in the Harvard study). In fact, our National Pollutant Release Inventory collects data on the highest source releases of carcinogens, and this data needs to be linked to required pollution prevention programs and environmental community surveillance. Presently, for the most part, it is not.

Polycyclic aromatic hydrocarbons (PAH)

Diesel emissions are among the most significant sources of environmental PAH. These emissions can be significantly reduced through emission control. These emissions contain a number of International Agency for Research on Cancer (IARC) class 1 carcinogens, and CEPA toxics. The California standard needs to be reviewed for adoption in Canada. Emissions in urban environments and port cities need to be monitored, and publicly disclosed.

Metals

Arsenic compounds should be restricted from use as wood preservatives. Chromated copper arsenate

(CCA) treated lumber should be removed from playgrounds and not used in domestic environments. The European Union took this action in 2003 (3).

The removal of leaded gasoline marked a significant step in pollution control; however, environmental monitoring of lead and lead based compounds in communities adjacent to industrial sources needs to be strengthened and publicly disclosed.

Most Canadian jurisdictions do not require public disclosure of metals in drinking water. All IARC classified (1 and 2A) human carcinogens need to be monitored and disclosed. Canada lags behind U.S. water quality disclosure rules (1).

Asbestos

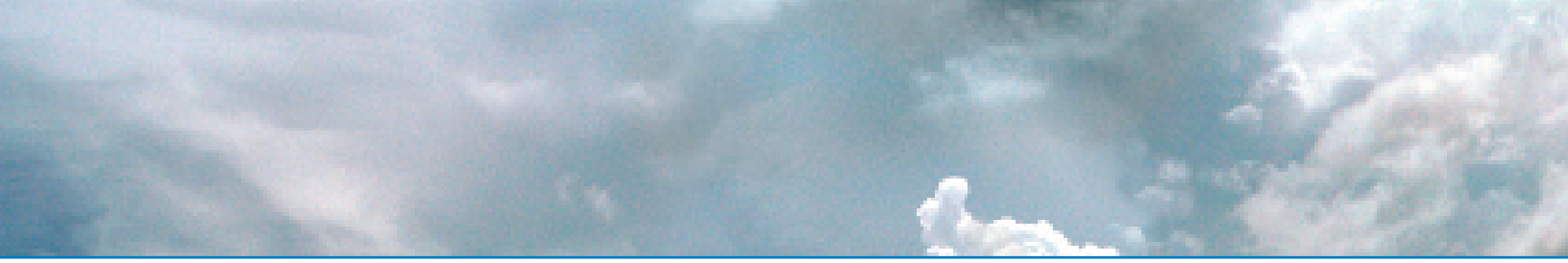
While asbestos use is strictly controlled in most workplaces, exposures still occur in both workplaces and the community. Asbestos exposures in asbestos mining communities have led to significantly increased incidence of asbestos related cancers. We are in the midst of an epidemic of work related mesothelioma cases, which, due to long latency periods, is yet to peak (4). Canada's promotion and sale of asbestos worldwide compromises our ability to be taken seriously regarding cancer prevention, and exports environmental exposure and cancers to those countries with the least resources to control them. Transition programs for asbestos mining communities are needed and the sale and use of this potent carcinogen should be banned.

Water disinfection by-products

There is consensus that it is possible or probable that there is a significant risk to Canadians from exposure to classified 2A carcinogens in disinfection by-products. There are important policy implications from this, yet little is being done to address this. The issue is not whether to disinfect or not, but rather the active promotion of safer disinfection methods. We have seen that water filtration techniques and ozone treatment can be effective means of doing this. Again, the best example appears to come from the European Union, although several Canadian companies are leaders in the development of these alternative technologies. There need to be federal initiatives to assist municipalities with infrastructure costs. There need to be municipal initiatives, including public education, referenda, and proposed tax measures to fund safer disinfection systems, and homeowner subsidies for in-home filtration. Drinking water standards need to include full disclosure of monitored levels of disinfection by-products.

Radiation

Radon monitoring in communities with higher environmental exposures is required, and grants available for renovations and upgrades.



The data on childhood leukemias and extremely low frequency electromagnetic field (ELF EMF) exposures greater than 4 milligauss require precaution and policy initiatives. National Institute of Environmental Health Sciences (U.S.) data (5) indicate that a significant number of homes may exceed this level, and a wide range of exposures from common personal appliances. Low ELF EMF products are available, ranging from computer monitors to hair dryers and electric blankets. Required emission labeling of such products would ensure an informed public was capable of choosing lower emitting devices.

Pesticides

As with other environmental carcinogens, vulnerable populations, particularly children, may be most at risk. Domestic use of cosmetic pesticides is the largest source of exposure for this group. In addition, the general public are not fitted with proper protective equipment when applying such products, and their exposures may therefore be relatively high. Chlorophenoxy pesticides such as 2,4-D have been classified as possible human carcinogens (IARC) and there is significant data showing elevated risk of NHL. While this *Insight on Cancer* cites conflicting data, not to act on the basis of the important if limited evidence we have would be a policy choice itself, rooted in imprudence and placing public health at risk. The Pest Management Regulatory Agency review of registered pesticides is long overdue; however, significant resources and independent reviews are required. In addition, many pesticide formulations carry toxic (some carcinogenic) non-active ingredients that are generally not disclosed. While this lack of public disclosure is being addressed in workplace legislation, domestic-use pesticides have to date been exempt. Canada is a signatory to an international agreement established to harmonize information disclosure requirements in chemicals policy, which calls for each authority to use its discretion with respect to consumer product disclosure and labeling. Canada needs to set an example and respect the public right to know, particularly with respect to pesticide formulations and carcinogens. Due to concern over both carcinogenicity and other important developmental health effects, many municipalities have taken steps to curtail or ban the use of cosmetic pesticides. Independent polling done for the Canadian Association of Physicians for the Environment recently confirm an overwhelming support for such action in the cities of Edmonton and Ottawa (71-83% want precautionary measures taken) (6). Quebec-proposed legislation restricting the use and sale of cosmetic pesticides is an example of public policy both heeding public concern and acting on the evidence we have of potential for significant harm.

Endocrine disruptors

While non-cancer endpoints (developmental effects) are driving concern and regulation of many endocrine disruptors, this *Insight on Cancer* cites some of the research concerning increased rates of endocrine-related cancers and exposure to endocrine disruptors such as dieldrin and phthalates. A number of jurisdictions have taken steps to eliminate endocrine disruptors in consumer product formulations. For example, the European Union has banned the use of phthalates in cosmetics and nonyl

phenols in cleaning products (7). Canada needs to require proper consumer labeling alerting the public to the presence of endocrine disruptors. Canada needs to monitor the growing evidence of adverse health effects and endocrine disruptor exposure and, in particular, implement policy and regulatory action that addresses this growing public health concern.

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COMMENTARY

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This *Insight on Cancer* provides an excellent overview of research findings to date on the relationships between human cancer and environmental exposures. Given the relative paucity of epidemiologic research conducted to date, I believe that future research will provide a much richer understanding of the many potential cancer-environment relationships and their relative importance. Only a few of the many possible cancer-environment relationships are supported by a substantial body of adequately designed epidemiologic studies. Consider for a moment the potential causal relationships between preconceptual maternal or paternal, prenatal maternal, childhood and adult exposures to multiple environmental hazards and their potential lifetime cancer outcomes. Then add further potential causal factors including dose, dose patterns and genetic susceptibility traits. Clearly, what we currently understand about cancer-environment relationships can only be a glimpse at the total actual relationships.

Persons with new cancer diagnoses annually in Ontario could populate a new city the size of Barrie. How many of their cancers are caused by preventable environmental exposures? This *Insight on Cancer* notes the Harvard estimate of about 5% but wisely does not endorse this figure, calling instead for a continuing review of evidence, a prerequisite for effective decision making. Among the cancer-environment issues touched on in this *Insight on Cancer*, these strike me as particularly important:

- The relative paucity of robust epidemiologic studies of the etiologic role of preconceptual parental, prenatal maternal and early-life exposures in childhood and adult cancers.

- The promise of strengthening environmental epidemiology by incorporating biomarkers of exposure and susceptibility; to this one might add biomarkers of early cancer developmental states (preclinical).

- The implicit need for substantial, dedicated long-term funding to address methodologic issues in cancer-environment studies while addressing the many knowledge gaps in this field.

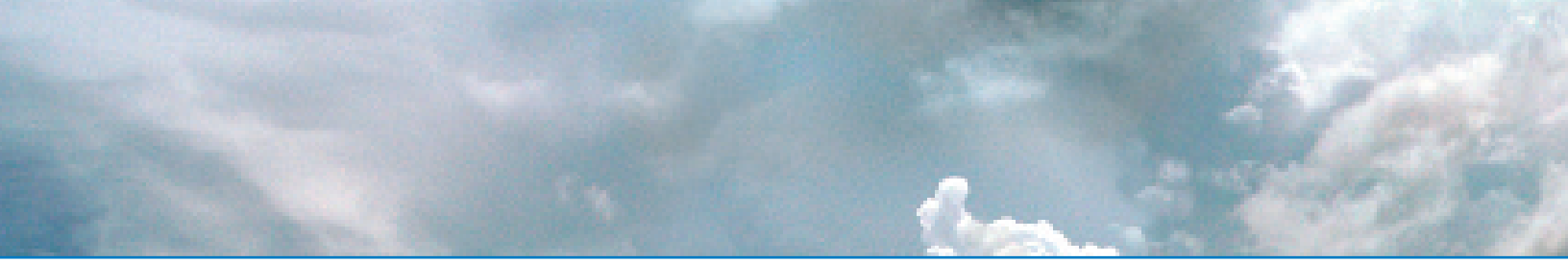
This *Insight on Cancer* discusses important limitations of epidemiologic studies but some readers may misinterpret these caveats. For instance, the statement that biases can produce false positive or false negative associations in epidemiologic studies is true but how often does this actually happen? My impression is that there have been remarkably few cancer-environment associations found in reasonably well designed case-control or cohort studies and later proven to arise from bias. The early report of an association between coffee consumption and bladder cancer (1) was later considered to be a false

positive result caused by confounding from smoking. Although smoking is a potential confounder for this association, a recent pooled analysis of European case-control studies of bladder cancer among non-smokers found a statistically significant excess risk among subjects who consumed at least ten cups daily (OR=1.8, CI 1.0-3.3) (2).

Although this *Insight on Cancer* states that health risks associated with pesticide exposure are more likely to be associated with toxicities other than carcinogenicity, this should not be interpreted to mean that pesticides pose no significant cancer risks. As of the late 1990's, there were about 900 pesticide active ingredients licensed for use in the United States (3). These included about 165 known, probable or possible human carcinogens (4). Limited epidemiologic evidence supports associations between childhood brain cancer, leukemia, Wilm's tumour, neuroblastoma and Ewing's sarcoma of bone and parental occupational pesticide exposure (5,6,7,8). A recent review noted increasing evidence for associations between childhood leukemia and lymphoma and paternal occupational pesticide exposure (9). A large case-control study in Montreal found exposure-risk relationships between childhood acute lymphatic leukemia and maternal prenatal use of pesticides in or around the home, especially among the subset of cases with the m1 or m2 polymorphisms of *CYP1A1* (10). Such findings underscore the need for expanded research to better define the roles and relative importance of preconceptual and prenatal parental exposures to specific pesticides or categories of closely related pesticides and interactions with susceptibility biomarkers. Only very large epidemiologic studies (or pooled analyses of multiple coordinated studies) will have the statistical power to analyze risk relationships at the level of detail required.

This *Insight on Cancer* calls for more research on the role of pesticide exposure in children and immunologically compromised individuals. Given evidence that most childhood leukemias are initiated *in utero* (11), preconceptual paternal and periconceptual maternal pesticide exposures may be most relevant for this disease. This *Insight on Cancer* notes the fact that the U.S. EPA and Health Canada are reviewing the carcinogenicity of 2,4-D. It is disturbing that adequate independent carcinogenicity testing of 2,4-D has not been completed as of 2005 even though this has been the most intensely used herbicide since its introduction during the 1940's. Moreover, a carcinogenicity study completed in 1986 found increased numbers of brain astrocytomas in the most exposed group of male rats with a statistically significant dose-response trend; EPA initially categorized 2,4-D as a possible human carcinogen but results of this study have since been discounted after substantial *post hoc* analysis and debate (12). This *Insight on Cancer* also notes that the Pest Management Regulatory Agency of Health Canada reviews pesticides before registering them for use. However, the toxicity test results reviewed by Health Canada come from studies conducted by or for industry. To the best of my knowledge, little or no truly independent toxicity testing of new pesticides occurs *before* registration. Moreover, only a small fraction of pesticides and consumer products have been subjected to independent carcinogenicity testing since commercialization. Unlike the USA and Germany (13,14), Canada has conducted almost no biomonitoring of human population exposure levels to pesticides and other environmental hazards[1] .

[1]The only such national measurement ever conducted in Canada was the measurement of blood lead levels during the 1978-1979 Canada Health Survey.



This *Insight on Cancer* calls for large international collaborations to better define lung cancer risk from residential radon exposure. A recent pooled analysis of all seven North American residential radon studies found a pooled odds ratio of 1.11 (CI 1.00-1.28) for exposure to an average of 100 Bq/m^3 during a period from 5 to 30 years before diagnosis (15). The pooled data set included alpha-track detector data on average long-term residential radon concentrations for 3662 cases and 4966 controls. This gives some idea of the level of investment needed to improve existing knowledge of this relationship, e.g., a very large coordinated multicentre case-control study of lung cancer based on a shared protocol and excellent long-term radon exposure assessment, reflective of all residences occupied since childhood. Given the difficulty of actually achieving such exposure assessment, research is needed to assess potential biomarkers of long-term radon exposure including chromosomal abnormalities (including inter-chromosomal abnormalities) in peripheral lymphocytes (16,17).

Also noted in this *Insight on Cancer* is the growing evidence that outdoor air pollution increases the risk of lung cancer (18). I endorse the report's recommendations for improving future studies of cancer and outdoor air pollution. Needed improvements include biomarkers of exposure and susceptibility and monitoring of urban air polycyclic aromatic hydrocarbons (PAH) and ultrafine particulate levels. The report notes the lack of Canadian standards for PAH emissions from diesel engines. Given that diesel engines are the major source of fine particulate matter containing PAH and other known carcinogens, and mindful of Canada's commitment to the Kyoto accord, provincial and federal policies and regulations are urgently needed to reduce diesel emissions. Why then, one might ask, do Ontario's cities continue to buy diesel-powered buses for schools and urban transit? The obvious answer is short-term cost savings but this ignores the short-term and long-term costs of the cancers and cardiovascular and respiratory diseases caused by outdoor air pollution (not to mention the likely impact of air pollution on preterm births and intrauterine growth restriction).

In discussing the role of PAH in cancer, this *Insight on Cancer* notes the potential role of dietary sources. Other potential dietary mutagens and/or carcinogens of environmental origin include aflatoxins and other mycotoxins (19). Although not environmental contaminants in the normal sense, heterocyclic amines are produced during cooking of meat/fish and are highly mutagenic and carcinogenic. PhIP[2] , a major heterocyclic amine in the human diet, causes breast, colon and prostate tumours in rats (20) and hepatomas in monkeys (21). Human volunteer studies have shown that ingested heterocyclic amines are absorbed and they or their metabolites are excreted in urine (22). Other potential dietary carcinogens include nitrosamines formed during meat curing with nitrite and during cooking of such products. In endorsing this *Insight on Cancer's* recommendation to expand research into environmental PAH exposure and cancer, I suggest that the scope encompass other important dietary carcinogens and cooking methods. Expanded use of exposure biomarkers in diet-cancer studies is needed as is continued use of well-designed questionnaires, e.g., as in studies of colorectal cancer, meat cooking characteristics and exposure biomarkers (23,24,25).

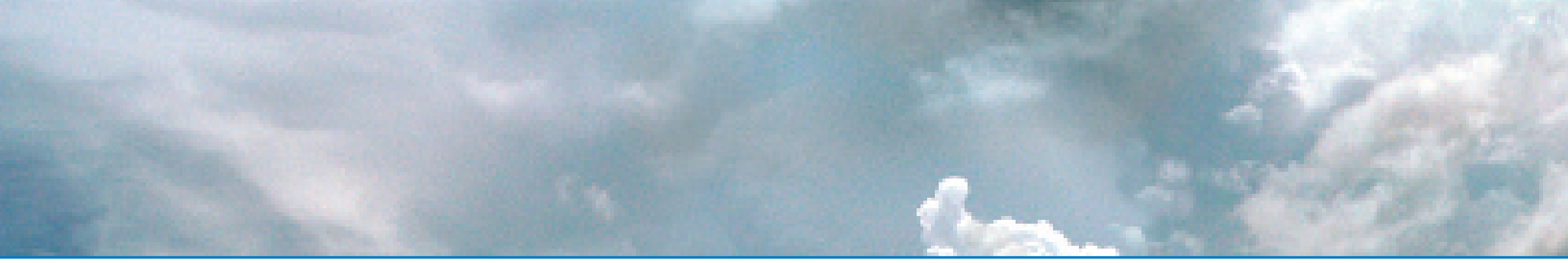
[2]2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine

This *Insight on Cancer's* chapter on asbestos covers the science well but does not mention Canada's role in opposing international asbestos bans. All 25 member countries of the European Union have banned asbestos, the five-year phase-out period having ended January 1, 2005. Through the World Trade Organization, Canada challenged an asbestos ban in France in 1999. In 2003, Canada joined Russia and other asbestos-producing countries to block a United Nations proposal to ban importation of chrysotile asbestos, the type produced in Quebec (26). In the same year, a federal department (Natural Resources Canada) granted $775,000 over three years to the Asbestos Institute, the lobby for promoting asbestos sales in countries like India, Japan and Brazil (26). The actual or virtual banning of asbestos in many developed countries means that over 70% of global asbestos production is now used in Eastern Europe, Latin America and Asia (27). A recent review noted incontrovertible evidence that chrysotile asbestos causes lung, laryngeal and certain gastrointestinal cancers and malignant mesothelioma as well as asbestosis, accompanied by risks that increase with cumulative lifetime exposure and time since first exposure (28). The authors concluded that safer substitute materials are available, controlled use of asbestos is not possible and health risks of asbestos are not acceptable in developed or developing countries. Until Canada bans asbestos uses completely, Ontario, as Canada's most populous and industrialized province, should consider acting unilaterally.

The chapter on water disinfection by-products (DBPs) notes the growing evidence for an association with human bladder cancer. Some DBPs are known to be fetotoxic, teratogenic or carcinogenic in experimental animals. There is limited epidemiologic evidence that DBPs may also cause fetal deaths, intrauterine growth restriction and neural tube birth defects in humans (29,30,31). Despite such evidence, Canada has lagged behind the United States in taking action to protect human health from DBPs. Canada's national drinking water guideline for trihalomethanes (a subset of four DBPs) remains at 100 μg/L compared to 80 μg/L in the USA. Even the U.S. standard may require substantial reduction, given the evidence of increased bladder cancer risks among men using drinking water with trihalomethane levels above 50 μg/L (OR=1.44, CI 1.20-1.73) (32) and increased risks of late fetal deaths among women exposed to levels above 60 μg/dL during late pregnancy (OR=1.11, CI 1.00-1.23) (33).

The chapter on radiation notes that the action level for residential radon levels is 800 Bq/m^3 in Canada and that this is higher than those in several other countries, e.g., the USA action level is 148 Bq/m^3. The estimated lifetime excess lung cancer risk from chronic exposure at the U.S. action level is 2.3% for the entire population (34); the excess risk at the Canadian action level would thus be about 12%. This is far higher than usual definitions of acceptable lifetime excess risk and calls into question the appropriateness of the Canadian guideline.

In its response to a document on federal health protection legislative renewal (35), the Canada Health Coalition recommended that Health Canada allow full public access to the information upon which federal regulators base their approval of a product or technology, including laboratory, animal and clinical studies as well as the reviewers' assessments of these studies and the rationale for their decisions



(36). The Coalition also endorsed Justice Krever's recommendations that Health Canada must develop its own expertise and not rely on that of the regulated and not lose sight of the principle that it regulates only in the public interest and not in the interest of the regulated (37). The Ontario government, and indeed the general public, should have unfettered access to premarket evaluations conducted by Health Canada and to meetings and reports related to the setting of guidelines or standards for environmental contaminants (and other hazards) in air, water, foods and other consumer products. After all, these are products to which the public and future generations will be exposed.

The Royal Society of Canada noted that the precautionary principle is essentially a rule about how to manage risks when one does not have fully reliable knowledge about the identity, character or magnitude of those risks. The principle assumes that there is often the possibility of error in the assessment of risks, and the higher the potential for this error, the greater the precaution it prescribes in proceeding with actions that place certain values at risk (38). In his report on the safety of the Canadian blood supply, Justice Horace Krever restated the precautionary principle to mean that, where there is reasonable evidence of an impending threat to public health, it is inappropriate to require proof of causation beyond a reasonable doubt before taking steps to avert the threat. The challenge then is to identify "reasonable evidence" and this *Insight on Cancer* is an important step in this direction. Ontario will be well served by a continuing commitment to this goal supported by appropriate policies, regulations and investments in population-based cancer research and systems to track population health and exposure status.

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OVERVIEW

In 2004, an estimated 54,600 Ontarians were diagnosed with cancer, and 25,000 died from the disease (1). As the population grows and ages, the occurrence of cancer will continue to increase. Understanding the modifiable causes of cancer may lead to meaningful prevention strategies.

Published estimates vary as to the relative importance of the physical environment for explaining the total cancer burden (2,3,4,5). Some of this variation depends on the definition of the physical environment. When focused on environmental pollution, ionizing/ultraviolet radiation, and food additives/contaminants, an often-quoted estimate of the total cancer burden is less than 5% (3). Because we are nevertheless all exposed, in varying degrees, to natural and manufactured chemical and physical hazards in the air, water, and soil, review of the evidence is warranted. The central issue facing those involved in cancer prevention is determining the amount and strength of evidence required before action is taken to reduce or eliminate exposure (6, 7).

Cancer Care Ontario hosted an expert workshop in 2001 to identify priority environmental exposures in Ontario (8). Those discussed in this document are:

1. Air pollution
2. Polycyclic aromatic hydrocarbons
3. Metals
4. Asbestos
5. Water disinfection by-products
6. Radiation
7. Pesticides
8. Endocrine disruptors

For clarity we review each environmental topic independently, but we acknowledge that many of these exposures occur in combination. Involuntary smoking, although identified as a priority environmental exposure in Ontario, is excluded because workshop recommendations were mainly to support existing initiatives on surveillance and tobacco control in the workplace. Air pollution is included because the workshop identified polycyclic aromatic hydrocarbons (PAH) as a priority exposure with an addendum that other outdoor air pollutants and combustion by-products were also of importance.

This *Insight on Cancer* summarizes, for health professionals and policy-makers, the scientific evidence relating these environmental exposures to cancer risk. Readers interested in a more detailed scientific discussion or in continuing assessments by expert panels may find the references helpful.

Methods

Review articles regarding cancer risk were identified using the National Center for Biotechnology Information PubMed search engine, with key terms and synonyms associated with the environmental exposures. These were supplemented with more recent original papers, also located through PubMed. Peer-reviewed literature published through 2003 was considered for this review. In addition to the peer-reviewed literature, we obtained the most recent summary reports from Canadian and international agencies: Health Canada, Environment Canada, the Canadian Cancer Society, the International Agency for Research on Cancer (IARC), the U.S. Environmental Protection Agency (EPA), the U.S. National Toxicology Program (NTP), the U.S. Agency for Toxic Substances and Disease Registry (ATSDR), and such other topic-specific bodies as the UK National Radiological Protection Board.

The main emphasis in this document is on the evidence for exposure in the general environment and cancer risk in the general population. Where appropriate, we present exposure carcinogenicity according to the IARC (Table 1) and the U.S. EPA (Table 2) classification systems, while recognizing that these agencies base their assessments primarily on toxicological and occupational data rather than general environmental exposures. Each chapter deals with one group of exposures and discusses exposure assessment difficulties, future research needs, and current control measures. Bold type in the text indicates that a definition may be found in the Glossary.

Limitations of the evidence reviewed

The limitations of both epidemiologic and toxicologic data complicate the assessment of environmental exposures and cancer risk.

Toxicologic evidence. Toxicologic studies with animals have provided evidence of the **carcinogenicity** of some chemical and physical agents. Animal testing is often based on a maximum tolerated dose; about half of such extreme dose studies have reported a carcinogenic response in rats or mice (11). Cancer risk in humans, who are mainly exposed to these carcinogens at very low doses, cannot be simply and accurately extrapolated from high-exposure animal data. Additional complications include uncertainty as to the validity of toxicologic data derived from out-of-date methods and of applying results across species (7), and the difficulty of devising suitable laboratory animal models (12).

Occupational evidence. Occupational studies are often used to identify the carcinogenicity of chemical or physical agents. These studies commonly use groups of workers chronically exposed at high levels to a given agent or mixture of agents. Members of the general population are rarely exposed at such high levels. Identifying workplace carcinogens and preventing further worker exposure is, however, an essential workplace health and safety issue, and offers insight on the potential importance of similar exposures in the general environment. A real association between a particular agent and cancer that might be missed in a general population study is more likely to be observed in an occupational study, with its greater variation in exposure levels and more accurate classification of exposure intensity, type, and duration.

General population studies. Failure to observe an association between an environmental exposure and cancer in observational epidemiologic research among the general population may occur for a number of reasons:

- there may be no association (which is unlikely if evidence from animal studies and the workplace indicates a relationship);
- the exposure may not be associated with cancer at the low levels generally found in the environment; or,
- the risk associated with low levels of exposure may not be detectable in studies of reasonable size, and thus preclude observation of a true association.

Exposure assessment. Part of the challenge in conducting environmental studies comes from difficulties in measuring the actual environmental exposure. Methodologic issues facing epidemiologists who attempt to characterize environmental exposure are:

- *Multiple routes of exposure.* Environmental exposure to pesticides can occur, for example, through the air,

on surfaces, and in foods and drinking water. Failure to account for different routes of exposure can lead to misclassification of the exposure levels assigned to individuals, and detailed personal exposure measurement is difficult.

- *Complex mixtures of chemicals.* Studies relating water disinfection by-products to cancer have been restricted to particular trihalomethanes, whereas the chemicals measured may not be the only potentially carcinogenic by-products of chlorination (13). Air pollution is another complex mixture, which includes sulphur and nitrogen oxides, and particles of different sizes.

- *Individual vs. group level measurements.* Although the most accurate approach is to measure exposure on an individual level, this is not always practical. In many studies, exposure is measured by using proximity to a point source of a pollutant or by applying exposure estimates from a few samples in an area to all local residents. In studies on air pollution this has resulted in applying measures of air quality to individuals who live many kilometres away from the sampling station (14). Since the cost of personal exposure measurement generally is prohibitive, often the only practical solution is to increase the density of sampling stations to improve the precision of exposure estimates. This would not, however, necessarily account for exposures that occur in the home and/or workplace environments.

- *External vs. internal dose.* Measurement of external exposure may not accurately reflect the true level of internal dose, although many studies assume that

Table 1. Carcinogenicity defined by the International Agency for Research on Cancer (9)

Group	Classification	Definition
1	Carcinogenic to humans	Sufficient evidence of carcinogenicity in humans
2A	Probably carcinogenic to humans	Limited evidence in humans, and sufficient evidence in experimental animals
2B	Possibly carcinogenic to humans	Limited evidence in humans, and less than sufficient in experimental animals or Inadequate evidence in humans and sufficient evidence in experimental animals
3	Not classifiable as to carcinogenicity to humans	Inadequate evidence in humans and inadequate or limited evidence in experimental animals
4	Probably not carcinogenic to humans	Evidence suggests a lack of carcinogenicity in humans and in experimental animals

Table 2. Carcinogenicity defined by the U.S. Environmental Protection Agency, 1986 guidelines (10)

Group	Classification	Definition
A	Human carcinogen	There is sufficient evidence from epidemiologic studies to support a causal association between exposure to the agents and cancer
B1	Probable human carcinogen	There is limited evidence of carcinogenicity from epidemiologic studies
B2	Probable human carcinogen	There is sufficient evidence from animal studies and there is inadequate evidence or no data from epidemiologic studies
C	Possible human carcinogen	There is limited evidence of carcinogenicity in animals in the absence of human data
D	Not classifiable as to human carcinogenicity	There is inadequate human and animal evidence of carcinogenicity or there are no data available
E	Evidence of non-carcinogenicity for humans	There is no evidence for carcinogenicity in at least two adequate animal tests in different species or in both adequate epidemiologic and animal studies

these are equivalent. For example, **bioavailability** of PAH may vary depending on whether the route of exposure is through ingestion or inhalation (15). In addition, metabolic breakdown of specific substances generally varies among individuals, which reduces the correlation between internal and external dose.

- *Past vs. present exposures.* Because cancer has a long **latent period,** past or long-term exposure may be of primary interest. Although this can be addressed through constructing cohorts with lengthy follow-up periods, the cost and time required for such studies are major drawbacks. **Case-control studies** are more common; in these studies, efforts must be made to reconstruct exposure history. Further, evidence for carcinogenicity from environmental exposures that occur during developmentally critical periods is currently lacking, and requires even more detailed case-control and **cohort studies.**

- *Measurement at low levels of exposure.* If quantitative estimates of exposure are desired, instruments must be sensitive enough to distinguish small differences in exposure to environmental factors. These must also be cost effective for use in epidemiologic investigations. An alternative is to find populations where an exposure gradient is assured: for example, using closeness to a point source of pollution, such as an industrial smokestack. The assumption must be made, however, that other sources of the exposure are negligible, and few environmental exposures can be studied effectively in this manner.

In the absence of studies of the risk associated with low exposure concentrations, researchers sometimes extrapolate from the evidence of risk at high concentrations. This requires making assumptions about the **dose-response** relationship. If the relationship is linear (e.g. the risk of cancer increases directly with increased exposure) then it is possible that there is no level of exposure that can be considered safe. One example of a carcinogen for which this assumption has been made is arsenic in drinking water (16). Conversely, if there is a threshold above which risk commences, then exposure at levels below that threshold would not increase risk. This is the assumption, for example, made in the case of chromium [VI], which at low levels of exposure can be reduced to compounds not known to be carcinogenic (17,18).

Biomarkers hold some promise in reducing the misclassification of exposure in environmental epidemiology. Markers of internal and biologically effective dose may improve exposure classification for individuals. They may also elucidate different steps in the carcinogenic process (19). Useful biomarkers have not yet been found for most of the environmental factors discussed here. An exception is PAH, where exposure has been measured with DNA **adducts** or urinary **metabolites**. An important limitation with biomarkers is that many reflect recent exposures, and would not necessarily reflect exposures in the more distant past (20).

Bias. Epidemiologic studies are susceptible to certain biases which can either obscure the relationship between a given risk factor and disease or indicate the presence of an association when none exists. Bias can result from **confounding** by known risk factors inadequately measured, or by unknown risk factors. These biases can be reduced by conducting well-planned and thorough studies, but may not be completely eliminated.

Certain biases are specific to study design. While case-control studies are cost efficient, they rely on recall of past exposures to environmental factors. If

questionnaires are used, differential recall errors by individuals with cancer relative to healthy people without cancer can bias results. Cohort studies are expensive and require long periods of time to observe cancer outcomes. While not susceptible to recall bias, these studies risk bias from differential loss to follow-up over their long time course (21). This can be reduced if an unbiased system of ascertainment of outcome is possible (e.g., linkage to cancer registries). While the long duration period can be avoided with historical cohort studies, these must then rely on estimated exposure data, which may not be as accurate or as detailed as concurrent measures. For example, estimates of exposure type might be determined from occupational title; similarly, estimates of total cumulative exposure might be estimated from duration of employment (or of residence, in a general population study). Information on confounders, such as cigarette smoking, is more difficult to ascertain in such historical studies.

Exposure levels. The identification of appropriate comparison groups is a further challenge. To identify an association between cancer risk and a putative environmental carcinogen, different exposure levels among members of a given population are needed. If cancer is more common among those people with higher exposure levels than those with lower exposure levels, evidence for an association may be inferred. Since the exposure levels of many environmental agents are similar among population groups, differential levels of exposure are sometimes rare, thereby making accurate estimates of association not possible (7). Many environmental exposures occur in very low doses, and little is known about the risks associated with very low background levels of exposure.

Conclusions

It is difficult to establish that environmental exposures to chemical and physical agents cause cancer. Any summary of published research is affected by the difficulties in conducting large-scale studies that might provide evidence for more definitive conclusions about particular exposures and cancer causation.

A number of environmental factors reviewed here have been classified as carcinogenic by organizations such as the IARC and the U.S. EPA. Evidence supporting carcinogenicity in humans, however, comes largely from studies of occupational groups with high exposure. Such studies indicate that lung cancer risk is increased by some exposures; these are arsenic, cadmium, chromium [VI], beryllium, nickel, asbestos, and radon. Chromium [VI] and nickel are also associated with nasal cancer. Asbestos exposure is also associated with increased risk of mesothelioma, and PAH have been associated with increased risk of both lung and bladder cancer.

Although all the agents considered in this report are released into the environment, the strength of evidence for an association between exposure to them and risk of cancer in the general population varies (Table 3). Several of the agents have evidence supporting an association with at least one type of cancer. These include, for example, arsenic exposure, where exposure through drinking water with high concentrations is consistently associated with skin, lung, and bladder cancers (22); asbestos exposure, where a substantially increased risk of mesothelioma has been reported among those with high environmental exposure (23); and radon exposure, which has been linked to lung cancer in residential studies (24).

Among the other environmental factors reviewed here, only solar radiation is a conclusively established risk

factor for cancer at levels generally found in the environment. **Squamous cell cancer** risk rises with increasing UVR exposure, and risk of **basal cell cancer** and **melanoma** increases with intermittent exposure (25). Studies on air pollution have pointed to an association between components of air quality, such as fine **particulate matter**, and risk of lung cancer. These studies, which also reported a relationship between greater exposure to fine particulate matter and cardiopulmonary and all-cause mortality (26,27), have figured importantly in the U.S. EPA's proposal of National Ambient Air Quality Standards for fine $PM_{2.5}$ (28). While evidence suggests associations with cancer for some of the other environmental exposures reviewed here, for many there is little supporting evidence of cancer risk at common environmental exposure levels.

It is likely that not all factors currently under investigation increase cancer risk. Many of the exposures nevertheless require further investigation to increase our understanding of their relationship, or lack thereof, with cancer in the general population.

Future research

The methodologic difficulties surrounding investigations into environmental exposures, and the combination of costs and lack of funding, have resulted in a number of environmental exposures being inadequately investigated. Multiple exposure routes for PAH have hindered efforts in investigating environmental PAH exposure and cancer risk, and research efforts are needed to better characterize exposure. The long-term effects of low-level environmental exposures of some metals are unknown and require investigation.

Exposure of the general population to pesticides has also been poorly researched, and priorities include studies of exposure in children and immuno-compromised individuals.

Many compounds have known or suspected **endocrine** disruption properties. Few studies have examined endocrine disruptors and their relation to endometrial, testicular or prostate cancer. A number of studies have examined exposure to dichlorodiphenyltrichloroethane (DDT), polychlorinated biphenyls (PCB), and their metabolites (29,30,31) and breast cancer, although further studies targeting exposure during critical development periods are required, as are studies of other endocrine disruptors.

Some environmental exposures have received a great deal of attention from the research community. Several studies have examined the relationship between air pollution and lung cancer, and large cohorts have been followed for several years (32). Future studies should include the quantitative assessment of fine particulate matter ($PM_{2.5}$) and better measurement of potential confounders such as occupational exposures. Future epidemiologic studies of EMF should address the specific methodologic issues (including patterns and sources) related to measuring these exposures. Longer follow-up periods from several cohorts may provide sufficient data to assess the relationship between cancers of the brain and the head and neck and radiofrequency fields. Large international collaborations should permit better assessment of lung cancer risk from residential radon exposure.

In conclusion, many environmental exposures remain inadequately investigated. Large epidemiologic studies with detailed and long-term exposure measurement are required to assess the cancer risk related to these exposures. Although the relationship of some environmental exposures with cancer risk has been well-investigated, further research is required and improved exposure measurement is a priority.

Table 3. Summary of environmental exposures and cancer risk

Strength of evidence	Exposure	Comments
The evidence supports an association with at least one cancer.	Air pollution	There is some evidence of a relationship between lung cancer and air pollution. (There are insufficient data to assess a relationship with any other cancer.)
	Arsenic in drinking water	Increased risk at high concentrations has been established for cancers of the skin, lung, and bladder, although dose response relationships are still unclear. It is not known if there is a safe level of exposure. (The evidence relating to cancers of the kidney, liver, and colon is inconsistent.)
	Asbestos	The relationship with mesothelioma, originally established through occupational studies, has been confirmed in environmental studies where there is high exposure. (The evidence relating to lung cancer and environmental exposure is less consistent.)
	Water disinfection by-products	Chlorinated drinking water has been associated with an increased risk of bladder cancer. (Less consistent are the findings for cancers of the colon and rectum.)
	Extremely low frequency electromagnetic fields	There is evidence of an association between childhood leukemia and high-intensity fields. (The evidence does not support an association with any adult cancers.)
	Solar radiation	The associated exposure measure varies with different skin cancers: increased UVR exposure for squamous cell cancer, intermittent exposure for basal cell carcinoma and melanoma. The relationship with lip cancer, established in occupational studies, has been replicated in one environmental study. There is evidence that ocular melanoma risk is associated with total sun exposure. (Findings for sunlamps/beds and skin cancers are inconsistent.)
	Radon	The relationship with lung cancer, established in occupational studies, is supported by the weight of evidence in residential studies. There may be no safe minimum exposure. (The evidence does not support an association between environmental exposure and leukemia or childhood cancers.)
There is inconsistent evidence of an association.	Endocrine disruptors, some pesticides	Although there is some evidence of an association between environmental exposure to TDCC and PCB and breast cancer, findings have been inconsistent. (Studies of the association between endometrial cancer and organochlorides have been negative. Findings for 2,4-D and malathion are generally negative.)
Data are insufficient to assess the association.	Metals, PAH	The relationship with cancer for several metals and their compounds, and for PAH, has been reported in occupational studies. Studies of these exposures in the environment (specifically the oral route of exposure to metals) have not been of sufficient quality to assess the risk. Required are more precise exposure measurements, control for confounding factors, and adequate numbers of cases and/or years of follow-up.
	Radiofrequency fields	Despite some studies which found increased risks of brain cancer, leukemia and lymphoma among occupational groups, there is no evidence for the presence or absence of risk. Cell phone studies are now underway.

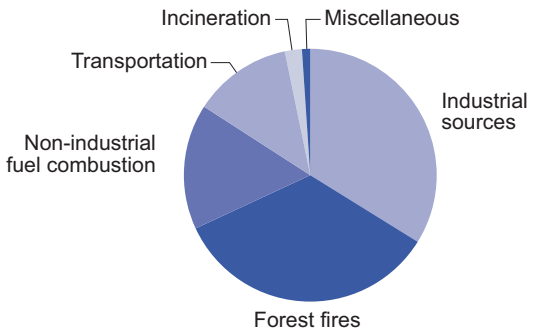
CHAPTER 1. AIR POLLUTION

Air pollution is the presence in the air of substances that can affect the health of humans, plants or animals, or that can cause damage to property and the environment (33). Both natural and human sources contribute to air pollution, with the main contribution coming from everyday human activity (34). Air pollution is a mixture of substances: volatile organic compounds (VOCs), nitrogen oxides (NOx), ground level ozone (O_3), sulphur dioxide (SO_2), carbon monoxide (CO), airborne particulate matter (PM), and other contaminants (34).

Volatile organic compounds are a group of carbon-containing compounds that are present in the atmosphere at very low levels (34). There are thousands of chemicals, both natural and synthetic, considered to be VOCs. Some VOCs are **carcinogenic**, such as formaldehyde and benzene, while others are irritants. Nitrogen dioxide (NO_2), produced by combustion, is a principal member of the NOx family (33). Ground level ozone occurs naturally, but is also formed when VOCs and NOx react in sunlight and stagnant air (34). SO_2 is largely produced by coal-fired power generating stations and **non-ferrous ore** smelters (33). CO is an odourless and colourless gas produced by fuel combustion mainly from automobiles (34). Exposure to the gas can have severe acute effects, including death.

Particulate matter (PM) is composed of small solids and liquids that are released into the air from a variety of sources (35). Total suspended particulate matter refers to the sum total of all particulate matter floating in the air (34). These particles may range in size from 0.005 to 100 micrometers (μm) in diameter. Particles that are 10 μm or less are capable of entering the lungs and are categorized into two groups: coarse ($PM_{2.5-10}$) and fine ($PM_{2.5}$), where the subscript refers to the particle size, in micrometers (μm) (34). Of the coarse and fine sub-groups, $PM_{2.5}$ is of greater health concern because it is capable of penetrating more deeply into the small airways of the lungs (27). $PM_{2.5}$ is primarily formed from combustion processes, either directly or through precursor gases such as SO_2, NOx, VOCs, and ammonia (33). $PM_{2.5}$ is mainly composed of ammonium, sulphate, carbon compounds, and metals (e.g., lead and cadmium) (36). Figure 1 shows the relative contribution of various emission sources to the direct formation of $PM_{2.5}$. The relative contributions, however, vary by geographic region and by season.

Figure 1. Emission sources contributing to the direct formation (i.e., not including formation by precursor gases) of $PM_{2.5}$ in Canada (35)



industrial: e.g., coal industry, pulp and paper industry, non-ferrous mining and smelting, wood industry

non-industrial fuel combustion: commercial and residential fuel, residential fuelwood and electric power generation

transportation: e.g., gasoline and diesel vehicles, propane-powered vehicles

incineration: wood waste and other types of incineration

miscellaneous sources: e.g., structural fires, pesticides and fertilizer application

Particles larger than 2.5 micrometres ($PM_{2.5-10}$) tend not to be chemically altered. Some of these particles come from natural sources such as sea salt spray, wind and wave erosion, and windblown soil and pollen. They are also produced by human activities such as construction, demolition, mining, road and tire wear, residential wood burning, and grinding processes of

soil, rock or metal (33). $PM_{2.5-10}$ consists of materials common in the earth's crust (e.g., oxides of iron, calcium, silicon, and aluminum) and sea spray (sodium and chloride) (37).

There are numerous other components of air pollution, several of which are reviewed in other chapters of this document (e.g., polycyclic aromatic hydrocarbons [PAH] [chapter 2], asbestos [chapter 4], persistent organic pollutants including some pesticides and endocrine disruptors [chapters 7 and 8, respectively]). Metals including arsenic, chromium and nickel, in addition to cadmium and lead, are also a component of air pollution (38). They are discussed in chapter 3, with airborne exposure and cancer risk being reviewed briefly here.

Environmental exposure to air pollution

Exposure to air pollution occurs primarily through inhalation of either indoor or outdoor air pollutants. Indoor air pollution is a combination of outdoor air pollution, indoor combustion sources (39), and emissions from other sources in the home (e.g., carpets, paint) (40). Involuntary smoking is also a well-known indoor air pollutant and is associated with increased lung cancer risk (41). A large amount of research and policy work has addressed involuntary smoking and will not be further elaborated here. Other than studies on involuntary smoking, most of the data relating indoor air pollution to cancer come from populations in Asia, where cooking and home heating methods lead to high levels of exposure (42). The remainder of this chapter is restricted to outdoor air pollution.

Air pollution and cancer

Most epidemiologic investigations of air pollution and cancer risk have measured one or more of $PM_{2.5}$ (or other particulates), SO_2, NO_2, or ozone. There are a number of possible mechanisms by which air pollution may influence cancer development. Fine particulate matter and ozone may increase the formation of **reactive oxygen species** that damage DNA and lead to lung cancer (43,44). Exposure to particulate matter may also affect carcinogenesis by acting as a transport mechanism for other pollutants (e.g., metals, PAH) (45,46).

No studies clearly show carcinogenic effects of SO_2 in humans or in laboratory animals (47). Neither the International Agency for Research on Cancer (IARC) nor the U.S. Environmental Protection Agency (EPA) has classified nitrogen oxides for their potential carcinogenicity (48) and there is little information regarding possible carcinogenic mechanisms.

A number of epidemiologic studies have investigated the association between air pollution and lung cancer incidence and mortality. Prior to the early 1990s, most studies used an **ecologic** approach (14), and several found an association between air pollution levels and lung cancer (49,50). Measurement of incidence and exposure data at the aggregate level and the lack of control for **confounding** factors, however, make interpretation of these results difficult. Since then a number of **case-control** and **cohort studies** have reported on the association between air pollution and lung cancer risk. Among this work, proximity to a point source of air pollution has been often used to define exposure. These include studies that examined lung cancer risk among people who live close to industrial sources that emit various metals, SO_2 and other pollutants. Exposure to point sources of airborne arsenic has been investigated most extensively, and increased lung cancer risk has been reported in some studies (42,51).

Many studies have directly measured one or more specific components of air pollution. Ten case-control studies have measured one or all of total suspended particulate matter, SO_2, or NO_2, generally combining these into a single index of air pollution (42). Four studies indicated a significant increase in lung cancer risk with greater air pollution levels in both sexes (on the order of 50% increase in risk), while two studies reported a significant increase in risk among males only. One study reported an inverse association between lung cancer risk and air pollution levels, while the last three reported associations that were not **statistically significant**.

Cohort studies have examined a variety of air pollutants for their association with lung cancer. A study in the Netherlands examined the relationship between both black smoke and NO_2, and lung cancer mortality. Small non-significant elevations in risk were observed for a 10 $\mu g/m^3$ increase in exposure to black smoke and a 30 $\mu g/m^3$ increase in exposure to NO_2 (52).

The association between particulate matter less than 10 μm in diameter (i.e., both coarse and fine particulate matter, or $PM_{<10}$), ozone, SO_2, and NO_2 and lung cancer mortality was examined among Seventh Day Adventists in California (53). Significant associations between ozone and $PM_{<10}$ levels and lung cancer death were observed in males: a four-fold increased risk associated with ozone (with an increase in exposure of 551.1 hours per year of ozone concentrations above 100 parts per billion) and nearly 2.5-fold increased risk associated with $PM_{<10}$ (with an increase of 43 days per year of $PM_{<10}$ concentrations above 100 $\mu g/m^3$). SO_2 level was positively associated with lung cancer risk with two- and three-fold increases in risk observed in males and females, respectively (with an increase of 3.72 parts per billion SO_2). Both fine ($PM_{2.5}$) and coarse ($PM_{2.5-10}$) fractions of particulate matter were estimated for a subset of the cohort data, and the association with lung cancer was stronger for $PM_{2.5}$ than for $PM_{2.5-10}$, although neither was statistically significant (54). In the Harvard Six Cities Study, $PM_{2.5}$ levels were used to assess the relationship between air pollution and lung cancer. A 37% increase in lung cancer mortality risk was observed in the city with the highest concentration of air pollution (as indicated by $PM_{2.5}$ levels) compared with the city with the lowest (29.6 $\mu g/m^3$ *vs.* 11.0 $\mu g/m^3$), although the difference was not statistically significant (26).

The American Cancer Society study is the largest cohort study to examine the association between air pollution and health outcomes (32). Measures of various air pollutants (e.g., $PM_{2.5}$, $PM_{<10}$, ozone, sulphate particles and SO_2) were obtained for 1/4 to 1/2 of the approximately 1.2 million study participants. A statistically significant, but small (8%), increase in lung cancer mortality risk was observed for each 10 $\mu g/m^3$ increase in $PM_{2.5}$ concentration among males. Risk of lung cancer mortality among females was not associated with $PM_{2.5}$ levels. Ozone and PM_{10} levels were not associated with lung cancer mortality risk. Lung cancer risk was greater in those exposed to higher SO_2 levels, but this was not statistically significant. Increased lung cancer mortality was observed with greater concentrations of sulphate particles, although the result was only significant for sulphate measurements made at one of two time periods (32).

The relationships between air pollution and cancers in sites other than the lung have not been investigated thoroughly. In general, data are inconsistent for other cancers and no conclusions can be drawn from current evidence (42).

Air pollution is a complex mixture of gases, solids, and liquids, and most studies have been limited to one or a

few of its components. These components are often correlated and few studies have separated out their distinct effects on lung cancer. For example, direct measurement of $PM_{2.5}$ has been attempted in only two studies (26,32). One of these (American Cancer Society study) compared the strength of the association between $PM_{2.5}$ and lung cancer mortality with those of other air pollution indices (32).

A general weakness in exposure measurements is the geographic scale on which they are based. Air quality is often measured at sampling stations and assigned to residences many kilometres away, likely resulting in exposure misclassification (14). In most case-control studies, the **latent period** between measurement of air quality and the cancer outcome was generally less than 10 years. Several case-control studies compensated for this through the collection of residential histories, with the assumption that past exposures could be estimated from more recent ones. Three of six studies reported significant associations.

Follow-up periods have varied from eight to 16 years in the cohort studies. In one study, risk appeared to increase with increasing follow-up (27,32), indicating that longer follow-up may be important in identifying risks.

Most of the methodologic weaknesses of these studies would likely result in underestimation of the strength of a cancer association with air pollution. This may explain some of the inconsistencies observed among studies. Overall, the evidence from these studies provides some support for an association between air pollution and lung cancer. Caution is warranted in interpreting results, as control for confounding by other factors (e.g., active smoking, involuntary smoking, and occupation) was often crude or lacking (14). The largest study conducted to date, the American Cancer Society study, did include adjustment for potential confounders, although adjustment for occupational exposure could have been improved with more detailed workplace exposure history (55).

Future research

Future studies should include $PM_{2.5}$ measurement and evaluate air pollution exposure in smaller geographic areas. Measurement of potential confounders needs to be strengthened and incorporated into future studies. Better estimates of past exposure can be addressed by either taking residential history into consideration in a case-control design or by continued follow-up in current and future cohort studies. More studies concerning the possible associations between air pollution and cancers other than lung are needed.

Current control initiatives

In the 1950s, levels of air pollution in most North American cities were 10 to 50 times higher than those found today (55), although trends vary according to type of pollutant, and the mix of pollutants has changed over time. New emission-control techniques, such as catalytic converters on automobiles, have contributed to reduced levels of particles and other pollutants (55). In Canada, more stringent emission standards for road vehicles are being phased in as of January 1, 2004. The number of vehicles, however, continues to increase.

In 2000, $PM_{<10}$, ozone, and their precursors were declared toxic substances under the Canadian Environmental Protection Act (CEPA) (35). Under the CEPA, key industries are required to set emission reduction targets. In June of 2000, the Government of Canada and the provincial and territorial governments agreed to ratify the Canada-wide Standard for $PM_{2.5}$

(30 $\mu g/m^3$ averaged over 24 hours) and committed to meeting this new standard by the year 2010 (33,56). In addition, Canada has signed an international agreement to reduce atmospheric emissions of three metals (lead, mercury, and cadmium), and requires new industrial plants to use the best available technologies to reduce emissions (57).

CHAPTER 2. POLYCYCLIC AROMATIC HYDROCARBONS

Polycyclic aromatic hydrocarbons (PAH) represent a wide class of compounds made up of two or more benzene rings (a ring of six carbon atoms attached to hydrogen atoms) (46,58). PAH are generally produced by incomplete combustion of organic materials such as coal, oil, gasoline, diesel fuel, and tobacco, resulting in their release into the environment (59,46).

Environmental exposure to PAH

Exposure in humans is generally through inhalation, ingestion, and skin contact. PAH are present in foods, drinking water, tobacco smoke, ambient air pollution, and fumes from cooking, furnaces, fireplaces, and wood stoves (19,60). The relative importance of some of these sources to overall PAH exposure has been assessed in some studies. Exposure through food, tobacco smoke, and ambient air has been studied most extensively, largely by measuring environmental exposure and relating these to PAH levels measured by **biomarkers** (e.g., PAH-related DNA or protein **adducts**, or urinary **metabolites** such as 1-hydroxypyrene).

Diet has been suggested as a major source of PAH exposure (61). PAH are produced through the charbroiling of meat and other foods (62). Atmospheric deposition on crops is another source of PAH found in foods (46). Increased 1-hydroxypyrene levels in urine were observed among forest fire fighters (63) and following feeding protocols in human subjects that involved high dietary doses of PAH through charbroiled meat consumption (64,65). A number of observational studies, however, have found no association between major dietary sources of PAH and 1-hydroxypyrene (66, 67,68) or other biomarkers (67). Possible explanations for the lack of association observed in these studies include: inadequate measurement of dietary sources of PAH (67), lack of sensitivity of biomarkers used in studying dietary exposure, and low **bioavailability** of PAH when exposure occurs through the dietary route (15).

Observational studies using PAH biomarkers have provided some evidence of increased PAH levels among children exposed to involuntary smoking at home (69,70, 71). Variation in bulky DNA adduct levels (which represent exposure to PAH and other aromatic compounds (72)) in urban and rural residents was associated with involuntary smoking in a study of Greek university students (73). Not all studies, however, have observed an association between involuntary smoking and PAH levels (67).

Several studies have examined PAH exposure through ambient air. Increased levels of PAH biomarkers have been observed in individuals who lived in highly polluted areas (74,75), but not in areas with lower levels of air pollution (76,73,67).

Failure to observe subtle effects of environmental and dietary routes of exposure on PAH biomarkers may be due to small numbers of study participants, or to **confounding** by either unmeasured or poorly measured sources of PAH. The sensitivity of laboratory measures in detecting small differences in exposure is also a concern in these studies.

PAH and cancer

Many PAH, particularly those with four to seven benzene rings, can be metabolically activated to form DNA-reactive intermediates, which are known to be **mutagenic** and **carcinogenic** in rodents (73). For example, benzo[a]pyrene, the most commonly studied PAH, has been shown to be metabolically activated to form benzo[a]pyrene-7,8-diol-9,10-epoxide (BPDE), which can bind to DNA resulting in DNA damage (77).

There are other potential mechanisms of action for reactive metabolites of PAH, including the induction of inflammatory processes resulting in the production of radical oxygen species that cause DNA damage, and the interaction of reactive metabolites with other cellular targets leading to interference with DNA transcription and replication (46).

Occupational studies have provided much of the evidence for carcinogenicity of PAH in humans. Increased lung cancer risk has been observed in workers with relatively high levels of PAH exposure. The most commonly cited high-risk group is coke oven workers. Estimates by the International Agency for Research on Cancer (IARC) in 1984 and 1987 indicated a three-fold to seven-fold increased risk for developing lung cancer in these workers (78,79). Among recent studies where PAH exposure in workers is reduced, risk estimates have ranged from 1.2 to 2.0, with three of four studies reporting significant elevations (59). Increased risk of lung cancer has also been reported in other occupational groups with high PAH exposure, including: iron and steel workers, coal gasification workers, and workers (particularly truck drivers) exposed to diesel exhaust (59).

Occupational studies also suggest an increased risk for bladder cancer resulting from PAH exposure. In the aluminum industry, PAH exposure is particularly high in the Söderberg electrolysis department (a process of electrolytic separation where PAH exposure occurs from the application of tar to carbon electrodes) and studies suggest that these workers are at increased risk. PAH exposure from coal tar is the most plausible explanation for the increased risk of bladder cancer reported in coal gasification workers (59).

Occupational studies also provide evidence of an increased risk of skin cancer resulting from PAH exposure. An increase in the risk of scrotal cancer was observed among chimney sweeps in 1775 (59); increased risk of skin and scrotal cancers also was reported among shale oil workers (59); and among textile workers (mule spinners using mineral oil where PAH is an important contaminant) (80).

Smoking is known to be a source of PAH exposure and there is evidence linking PAH in tobacco smoke to lung and bladder cancers (72). Four of five studies found that among smokers, there was a significant increase in bulky DNA adducts in lung cancer cases relative to controls. One study reported that bulky DNA adduct levels were greater in bladder cancer cases who smoked than in controls who smoked (72).

Investigations into environmental exposure to PAH and cancer risk are limited. Low levels of environmental exposure, many different sources of exposure through various routes, and exposure to mixtures of PAH make the relationship between environmental exposure to PAH and cancer risk extremely difficult to assess. Currently, no studies have attempted to relate total PAH exposure from environmental sources and cancer risk. Furthermore there is a lack of good-quality data relating specific sources of PAH exposure such as air pollution to cancer risk (46).

The IARC has evaluated the carcinogenicity of several PAH (81,79). Their assessment is shown in Table 4.

Future research

Research on PAH is complicated by the difficulties in measuring exposure. The relative contributions of different sources to total PAH exposure is uncertain. Large studies are required that include detailed assessment of various sources and routes of exposure, and sensitive instruments to detect PAH biomarkers. Also

needed is more research on the association between the bioavailability of PAH and its route of exposure. Results of these studies can guide future work relating environmental PAH exposure and cancer risk.

Table 4. Evidence for carcinogenicity of PAH in experimental animals and evaluations of carcinogenicity in humans according to the International Agency for Research on Cancer 1983 and 1987 (81,79)

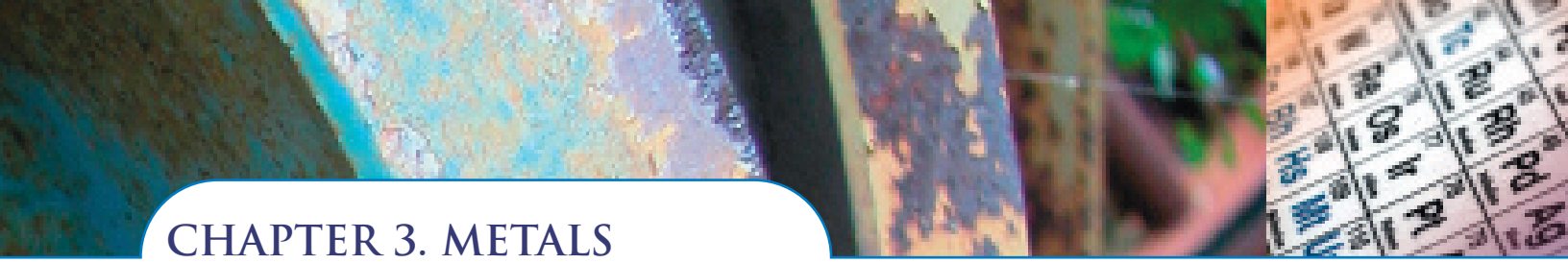
PAH compound	Animals	Humans
Benz[a]anthracene	S	2A
Benzo[a]pyrene	S	2A
Dibenz[a,h]anthracene	S	2A
Dibenzo[a,e]pyrene	S	2B
Dibenzo[a,h]pyrene	S	2B
Dibenzo[a,i]pyrene	S	2B
Dibenzo[a,l]pyrene	S	2B
Benzo[b]fluoranthene	S	2B
Benzo[j]fluoranthene	S	2B
Benzo[k]fluoranthene	S	2B
Indeno[1,2,3-cd]pyrene	S	2B

S= sufficient evidence

Current control initiatives

Five specific PAH have been designated as toxic under the Canadian Environmental Protection Act: benzo(a)pyrene, benzo(b)fluoranthene, benzo(j)fluoranthene, benzo(k)fluoranthene, and indeno(1,2,3-cd)pyrene. A number of other PAH have been designated as harmful to the environment. Specific regulations for reporting to the National Pollutant Release Inventory are in place for industries that release PAH through their manufacturing processes, and for industries in the wood preservation sector (82). Vehicular traffic is an important contributor to PAH levels in ambient air, and total PAH emissions from diesel fuel engines are much greater than those from gasoline engines (46). There are currently no Canadian standards for PAH emissions in diesel fuel. Standards in other jurisdictions include a maximum of 11% by weight for PAH emissions from diesel fuel in the European Union and 1.4% by weight set by the California Air Resources Board (83).

PAH are ubiquitous in the environment and some exposure is inevitable. Smoking is the largest single source of non-occupational exposure to PAH. The most important preventive measures for the general public are not smoking and avoidance of involuntary smoking. Owners of wood burning stoves and fireplaces should ensure that their appliances are properly vented to prevent PAH exposure from fumes leaking back into the home.



CHAPTER 3. METALS

Metals are elements that can be described by their physical and chemical properties, such as the ability to conduct heat and electricity, having a metallic lustre, being malleable and ductile, forming cations (atoms or groups of atoms with a net positive electric charge), and having basic oxides (84). Metals can exist independently but they are also often found as compounds. Many metals occur naturally in the environment; they also have been used for thousands of years, with a notable increase in production concurrent with industrialization in the middle of the 19th century (85). As a result of their wide use combined with their environmental persistence, metals are common environmental contaminants (86,87). Metals and/or their compounds classified as Group 1 or Group 2 **carcinogens** by the International Agency for Research on Cancer (IARC) have been included in this review (Table 5). Two semi-metals, arsenic and antimony, and/or their compounds similarly classified (Group 1 or 2) are also considered.

Table 5. Classification of carcinogenicity of metals

Metal	IARC (88)	EPA (89)
Arsenic and arsenic compounds	1	A
Beryllium and beryllium compounds	1	B1
Cadmium and cadmium compounds	1	B1
Chromium [VI] compounds	1	A*
Nickel compounds	1	A**
Cobalt metal with tungsten carbide	2A	
Lead compounds, inorganic	2A	B2
Antimony trioxide	2B	
Cobalt metal without tungsten carbide, cobalt sulphate & other soluble cobalt [II] salts	2B	
Lead	2B	B2
Methylmercury compounds	2B	C
Nickel, metallic and alloys	2B	

IARC= International Agency for Research on Cancer

EPA = U.S. Environmental Protection Agency

* by inhalation

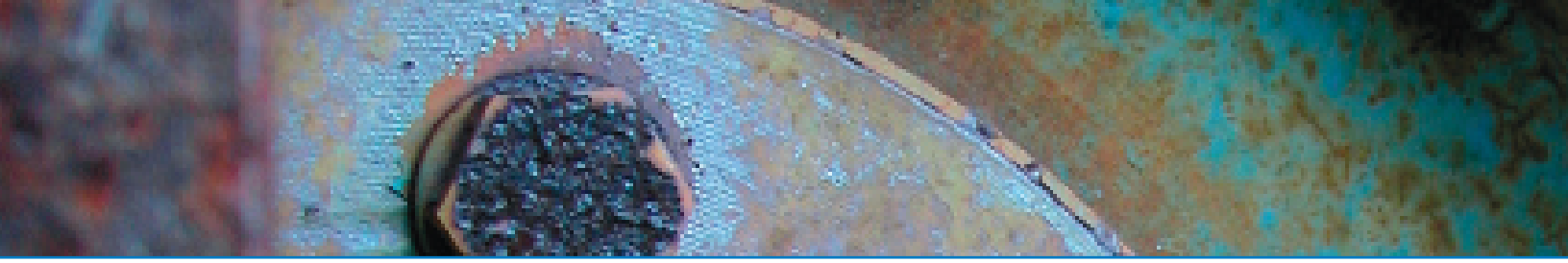
** nickel refinery dust and nickel subsulfide

Environmental exposure to metals

Metals and their compounds are released into the environment from many industrial sources including air emissions from coal-burning plants, smelters, and combustion of fossil fuels (85,87); consequently, they are a component of air pollution (see chapter 1) and contaminate the environment through atmospheric deposition (34,38). Other major sources include the manufacture and application of wood preservatives and other pesticides, fertilizers and sewage sludge, waste incineration and hazardous waste sites, and lead in household plumbing and paints (85,87,90,91,92). Surface waters, soils, and groundwaters can become contaminated, leading to uptake by food sources such as crops, vegetables, and seafood (85,93). Arsenic can also enter drinking water supplies when naturally occurring geologic deposits, or rock containing arsenic, dissolve (92,94). As a result, exposure to low levels of metals is widespread. For the general population, exposure occurs mainly through inhalation of particles from ambient air, consumption of contaminated drinking water or food, dermal contact, and ingestion or inhalation of contaminated soils and dust (especially in children) (95,87,91). Active or involuntary smoking is a major source of exposure to some metals, in particular to cadmium (85). Ingestion of food is the main route of exposure to environmental nickel, and to cadmium in non-smokers (96,85); arsenic in drinking water is the major source of human exposure worldwide (92).

Metals and cancer

Metals and their compounds are an important class of carcinogens, and in various forms arsenic, beryllium, cadmium, chromium [VI] and nickel are all recognized human carcinogens (Table 5). Several more metals and/or their compounds are suspected carcinogens in humans and have shown evidence of carcinogenicity in experimental animals. Metals and their compounds can



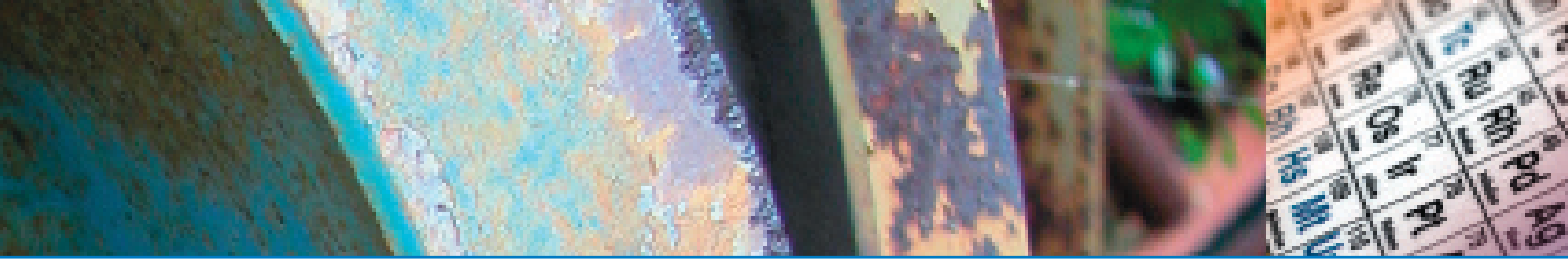
affect different mechanisms of carcinogenesis by producing **reactive oxygen species** and changes to DNA structure, as well as by inhibiting DNA repair (86,97).

Epidemiologic evidence for carcinogenicity comes mainly from studies of occupational groups where exposure to metals is highest. **Cohort studies** of workers exposed to arsenic, beryllium, cadmium, chromium [VI], or nickel compounds through inhalation have shown that each was associated with increased risk of lung cancer (51,100,98,99,96,86). Chromium [VI] and nickel were also associated with risk of nasal cancer. Although some studies of cadmium exposure have reported increased risk of prostate cancer, this has not been consistently observed (101). Evidence for a causal association between arsenic and cancer is particularly strong, as thousands of workers have been followed for several decades, and the results have consistently shown an almost ten-fold increase in the incidence of lung cancer in those with the heaviest exposure (92,95).

For cadmium the evidence is less convincing, as cohort studies were limited by **confounding** factors, in particular co-exposure to arsenic, and results of some analyses were conflicting (98). These limitations have led to differences in the evaluation of the carcinogenicity of cadmium between the IARC, which classifies cadmium as a known human carcinogen, and the U.S. Environmental Protection Agency (EPA) which classifies cadmium as a probable human carcinogen (98). Several cohort studies have recently been updated and only a small increase in risk has been reported in the groups exposed to cadmium in the absence of arsenic (101). The IARC has rejected the suggestion that cadmium be reclassified down to group 2A (85), and continues to classify it in Group 1. Evidence for beryllium's carcinogenicity is weakened by methodologic problems, particularly by inadequate adjustment for smoking, again leading to differences in assessment by the IARC and the U.S. EPA (100). The carcinogenicity of cadmium and beryllium has, however, been clearly shown in non-human experimental studies (86).

Although nickel compounds are well-recognized carcinogens, the evaluation of nickel has been hindered by the presence of several types of nickel compounds in the work environment, and the resulting inability to identify the carcinogenicity of specific compounds in humans (102,103). For metallic nickel, there is inadequate evidence that exposure produces an increased risk of cancer in humans. While chromium [VI] compounds are considered pulmonary carcinogens, epidemiologic studies of workers exposed to chromium [III] compounds (the most stable **valence** state of chromium and an essential nutrient) found no association with risk of cancer (104).

Evidence for the carcinogenicity of other metals is limited, although several have been classified as probable or possible human carcinogens. The IARC recently re-evaluated the carcinogenicity of lead compounds, and inorganic lead compounds were reclassified as probably carcinogenic to humans (105). Although the evidence for carcinogenicity in humans is still limited, the most likely cancers related to lead and lead compounds are lung, stomach, kidney, and brain (105,106). An evaluation of the recent evidence indicates that various compounds of cobalt have different carcinogenicities; specifically, cobalt metal with tungsten carbide was reclassified up by the IARC, as probably carcinogenic to humans (for the lung) (107,108). Although mercury and its compounds are widely used and present in the environment, only limited data are available on their carcinogenicity (109,110). Methylmercury chloride has been shown to



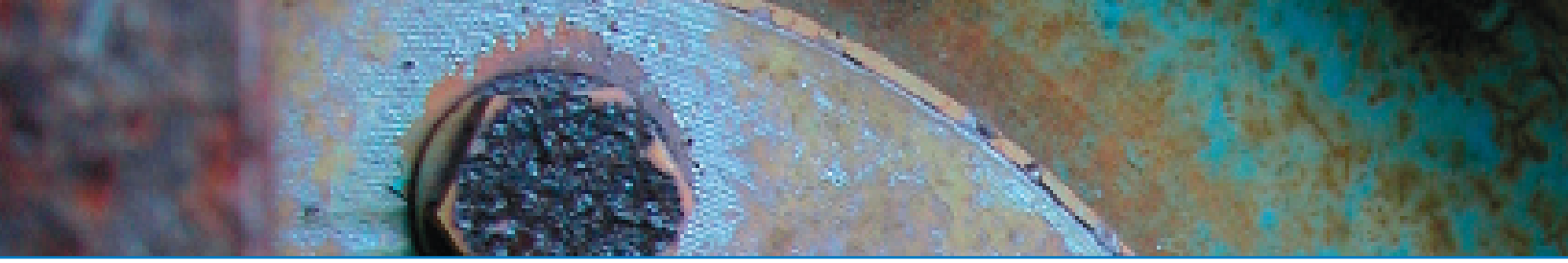
cause kidney tumours in mice, although other mercury compounds and metallic mercury have not been adequately tested in experimental animals (109). Antimony trioxide is associated with increased lung tumours in rodents, while data in humans are limited (111). Certain metals such as cobalt and antimony have been studied less extensively, likely because of their limited use in industry (111).

With the exception of arsenic, the relationship between environmental exposure to the IARC Group 1 metals and cancer risk is not well established. Few studies have examined environmental exposure to metals and cancer in the general population. For those studies conducted in the environment, the oral route of exposure (reviewed below) has been most widely investigated.

Arsenic is the most extensively studied of the metals found in drinking water (112). Numerous epidemiologic studies of human cancer have been conducted in relation to primarily inorganic and mostly naturally occurring arsenic in drinking water (22). An association between skin cancer and environmental exposure to arsenic through drinking water has been "observed and confirmed" (95). Epidemiologic studies in areas with high concentrations of arsenic in drinking water have also shown substantially elevated risks for cancers of the bladder and lung among those with high exposure levels, sometimes in a dose-dependent manner (112,22). Less consistent is the risk associated with arsenic exposure and other cancer sites, such as the kidney, liver, and colon (42). Most studies on the carcinogenicity of arsenic and drinking water have been conducted in areas with elevated arsenic content (>200 μg/L) (42,16), which is needed to find a sufficient gradient between exposure level and disease risk. Aside from a few studies of bladder cancer that have suggested a possible increased risk for low or intermediate arsenic levels, limited data are available on the risk of other cancers at lower exposure levels (42). Estimates of cancer risk at lower doses are based on extrapolation from **ecologic studies** with high exposure levels (16), but the nature of the **dose-response** relationship at lower levels is unclear.

A few studies have been conducted in residential populations with environmental exposure to chromium [VI] compounds through drinking water, soil, or **slag** around heavily contaminated sites, or in close proximity to industrial areas (113). None of these studies found an association with any cancer, although they each suffered from methodologic weaknesses such as relatively short follow-up periods or lack of quantitative measures of exposure; thus, a definitive assessment of risk based on these studies alone is precluded (113). In contrast with inhaled chromium [VI] in occupational settings, a weight-of-evidence review concluded that chromium [VI] is not carcinogenic in humans via the oral route of exposure at levels permissible in drinking water concentrations in the United States (i.e., 100 parts per billion) (113). There is evidence of a threshold for chromium [VI] carcinogenesis (17). At low levels of exposure, chromium [VI] compounds can be reduced to chromium [III] compounds (not known to be carcinogenic) before the former can interact with DNA (104,17). A recent study measuring the absorbed dose of chromium [VI] following ingestion of tap water further confirmed this finding (18).

Some studies examined environmental exposure to cadmium through the diet, or in populations with high concentrations of cadmium in the surrounding soil, generally not finding an increased cancer risk (101,98). As with chromium, however, all of these studies have limitations such as small study size (98). One ecologic study that examined nickel concentrations in drinking water found significantly greater rates of bladder and lung cancers in males, but not in females, in towns with



elevated levels of nickel (114). Several studies in mice and rats have investigated the carcinogenic potential of nickel-soluble salts after ingestion and found no effect (115). The carcinogenicity of soluble nickel after oral exposure in both experimental animals and humans, however, cannot be determined based on the available data. No studies examining beryllium carcinogenicity from the oral route of exposure have been identified (100), although this is not considered an important mode of exposure for this particular Group 1 metal (95).

Studies of metal exposure in occupational settings have demonstrated difficulties in exposure measurement of specific metals and their compounds. Limited evaluations have been made on co-exposure to other metals, including arsenic, and confounding by tobacco smoke. Because exposure levels in the environment are generally of lower concentrations than occupational exposure, and occur in mixtures of metals and their compounds, the difficulty in measurement increases.

Several studies of environmentally exposed populations and cancer measured concentrations of metals in the surrounding air, water, soil, or slag. In general, these are not considered reliable exposure indicators. For example, in assessing the risk from exposure, the dose an individual may receive from these sources may not be equivalent to the amount absorbed, ingested or inhaled, and **bioavailability** must be considered (116). Work by Elliott et al. (117) assessed cadmium exposure based on geographic distribution of cadmium in the soil. Although the soil concentration of cadmium was high, the mean intake through diet may still have been low; thus, soil content cannot readily be translated into human health risks.

The use of **biomarkers** is preferable in the measurement of exposure to metals and subsequent assessments of risk (116,117). A few studies have assessed environmental cadmium exposure through the use of urinary biomarkers (118,119,120). In general, there have been too few studies to adequately evaluate cancer risk following environmental exposure to metals other than arsenic.

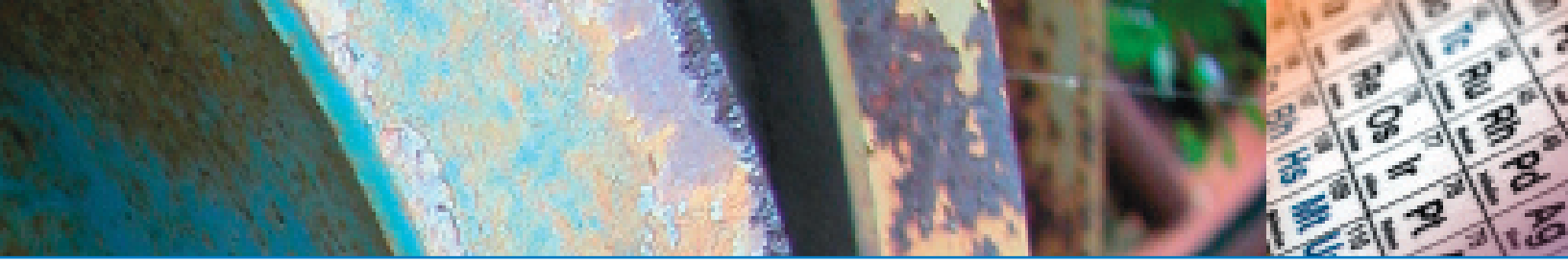
Future research

The U.S. EPA has calculated risk estimates for ingestion of low-levels of inorganic arsenic, as well as for exposure to air containing low-levels of each of the Group 1 metals, using mathematical models (89). Nonetheless, the long-term effects of continuous low-level environmental exposure of recognized carcinogenic metals have yet to be determined. For example, the carcinogenicity of high levels of inorganic arsenic in drinking water has been clearly established; however, studies at lower exposure levels are required to validate risk estimates based on extrapolation.

In general, studies with improved exposure measurement, larger samples, and longer follow-up are needed on environmentally exposed populations (117). To adequately assess metal exposure, further development and increased implementation of biomarkers in studies are needed. In addition, increased research on the carcinogenic potential of environmental exposure to metal mixtures, and further experimental studies to examine the role of metal–metal interactions in human carcinogenesis, are required (121).

Current control initiatives

Health Canada has set guidelines for the levels of both arsenic and lead in drinking water (0.025 mg/L and 0.010 μg/L of water, respectively) (94,91). The guideline for arsenic is considered an interim measure until arsenic levels can be further reduced in drinking water.



For regions known to have high levels of arsenic from natural sources, regular testing of well water is recommended. In addition, Health Canada offers other recommendations to reduce arsenic levels for those using well water, such as extending the well casing into deeper groundwater or investing in in-home water treatment devices. Health Canada also recommends that individuals run their cold water before drinking, to remove lead that may have leached out of pipes. Children should be prevented from playing in soil near uncontrolled hazardous waste sites where metals may have been discarded (51,96,98,99,122). Individuals can also reduce exposure to some metals, particularly cadmium, by not smoking.

CHAPTER 4. ASBESTOS

Asbestos is a generic name referring to a group of six fibrous minerals, made of magnesium, silicon, and other elements, found naturally in soil and rocks around the world (123,124). The fibres have valuable properties including strength, durability, and resistance to heat, and as a result, have been used extensively by industry in insulating and friction materials (123,124). Asbestos fibres are derived from two broad mineralogical categories: serpentine (chrysotile); and amphibole, consisting of actinolite, amosite, anthophyllite, crocidolite, and tremolite (125). Chrysotile is the main form of commercially used asbestos.

Environmental exposure to asbestos

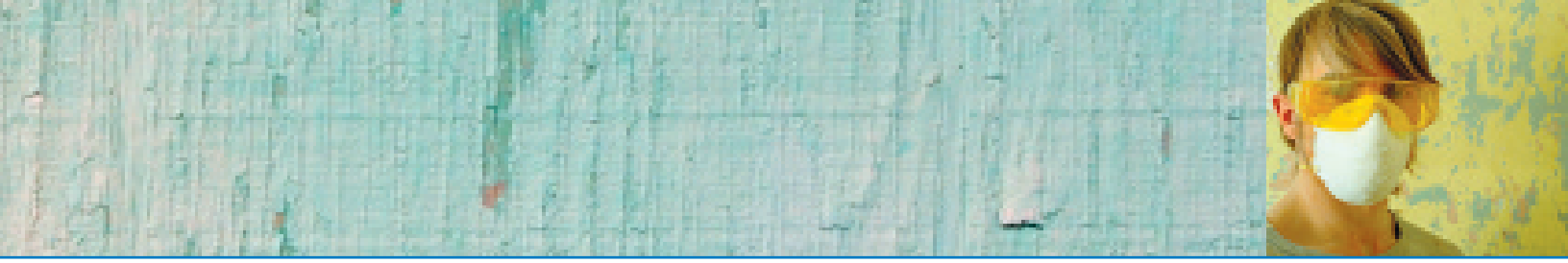
Asbestos is common in the environment: small concentrations of its fibres occur in the air, water, and soil, from both natural and human-made sources (124). Fibres are released into the environment when asbestos-containing products are damaged or worn down, or from the weathering of naturally occurring deposits (125). The main route of exposure is inhalation of fibres, which form a dust that floats in the air (123). Asbestos can also be ingested through water contaminated from natural or industrial sources, or flowing through asbestos-containing pipes (125).

Aside from low levels in the ambient air (typically 0.00001 fibres/mL in rural areas and 0.0001 fibres/mL in urban areas) (125), environmental exposures to asbestos can be grouped into household and neighbourhood exposures (23). Household exposure can occur during removal or repair of asbestos-containing products, or from release of fibres from damaged encasements; exposure has also occurred in the past when family members of asbestos workers inhaled dust brought home on workers' clothing (23,125). Examples of neighbourhood exposure include outdoor air pollution due to asbestos mining or manufacturing close to places of residence (23), where concentrations can be 0.01 fibres/mL or higher (125). Levels can also be increased from release of asbestos fibres from sources such as asbestos-containing brake materials, buildings being torn down, waste sites where asbestos is not properly stored, or from erosion or disturbance of asbestos-bearing rocks (23,125).

Asbestos and cancer

A large body of evidence, primarily from occupational studies, has established that inhalation of asbestos increases the risk of pleural mesothelioma, peritoneal mesothelioma, and (particularly among smokers) lung cancer (125). This has been confirmed in numerous experimental studies in mice, rats, and hamsters (126). As a result, asbestos is classified as a human **carcinogen** by several agencies, including the International Agency for Research on Cancer (IARC), the U.S. Environmental Protection Agency (EPA) and the U.S. National Toxicology Program (126,127,95). There is some evidence that asbestos can increase the risk of other cancers, including those of the gastrointestinal system and larynx, although the evidence is not as strong as for mesothelioma and lung cancer (125,128,129,130). While the mechanisms by which asbestos induces malignancy are not entirely clear, it is hypothesized that chronic inflammation leads to the release of **reactive oxygen species** that damage DNA (131,132).

A **meta-analysis** of 37 asbestos-exposed occupational cohorts reported a **statistically significant standardized mortality ratio** of 1.6 for lung cancer, and strong evidence of a **dose-response** relationship (130). People at highest risk were those with the heaviest exposure, usually after many years of working in an asbestos industry. Smoking and occupational



exposure to asbestos have been shown to interact synergistically to increase the risk of lung cancer (95). Strong associations between development of mesothelioma and occupational exposure to asbestos have been observed in many **case-control studies** (increased risks generally range from 2–10) (125). The estimates of mesothelioma attributable to asbestos exposure range from 60% to 88% and there is general agreement that occupational exposure to asbestos accounts for the majority of mesothelioma cases (133). Nearly all mesotheliomas associated with occupational exposure to asbestos have a **latent period** of more than 15 years, and a median latency of about 30 years (134).

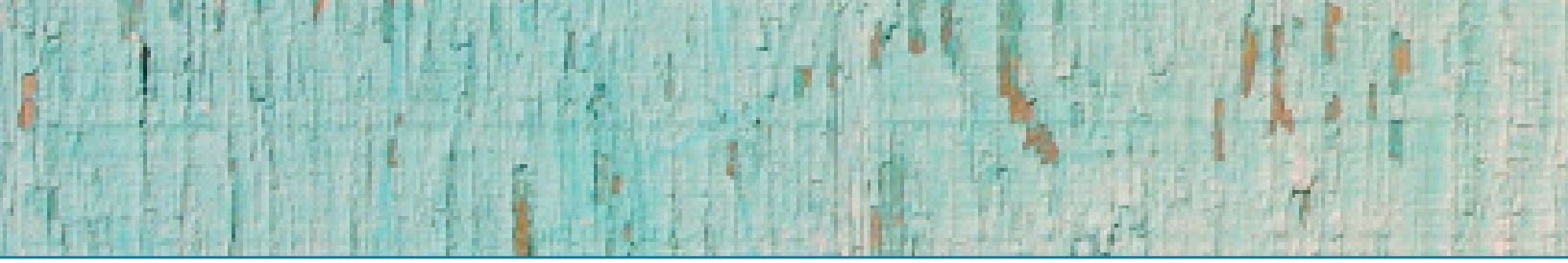
Fibre type and size (length and thickness) may also be important in cancer risk (125). It is generally accepted that all forms of asbestos are carcinogenic (126,23). There continues to be debate as to whether some forms of asbestos pose a greater **relative risk** than others (e.g., amphiboles *vs.* chrysotile) (135,136). Amphiboles and chrysotile are different in both structure (straight *vs.* curly fibres) and chemical properties (125). When inhaled, amphibole fibres stay in the lungs longer than chrysotile fibres and thus may be more likely to cause damage leading to disease (124). Fibre size has also been shown to be important: studies have indicated that longer fibres (> 5 micrometres) may be more carcinogenic than shorter fibres because they are less easily exhaled from the lung (125). Also, thicker fibres may not be able to penetrate into the lower regions of the lung.

Evidence of health effects of asbestos from environmental exposure is limited, compared with evidence from occupational settings (23). Exposure via inhalation has been studied most extensively. A meta-analysis of environmental exposure (household and neighbourhood) to asbestos and pleural mesothelioma yielded a significant summary relative risk of 8.1 for household exposure, and of 7.0 for neighbourhood exposure (23). The summary estimates indicate a substantial risk for both sources of environmental exposure. These studies, however, were conducted in populations with high environmental exposure levels due, for example, to proximity to an asbestos mine. The magnitude of risk at the low levels of environmental exposure commonly encountered by the general population cannot be estimated from these studies. In general, the measurement of environmental asbestos exposure is difficult: exposure levels are usually low, they will have occurred many years before disease onset, and factors such as duration and frequency of exposure, and type of fibre, are not known accurately (23,133). Neighbourhood exposure to asbestos and risk of lung cancer has been examined, with some studies finding an increased risk, and others not (42). These inconsistent findings may be due to inadequate control for **confounding** variables such as tobacco smoke and exposure to other lung carcinogens.

The evidence regarding the carcinogenicity of asbestos exposure through ingestion is equivocal (137). The majority of epidemiologic studies of populations with high concentrations of asbestos in drinking water have been **ecologic** (112). They have been limited by lack of control for confounding factors and short follow-up times. Some studies have suggested increased risks for cancers of the stomach, kidney, pancreas (112), esophagus, and intestines (127). In general, the results are inconsistent, both within and across studies (125), and the available data are insufficient to evaluate the cancer risk via this mode of exposure (112).

Future research

Although asbestos is a well-established carcinogen, uncertainty remains as to the risk from low levels of



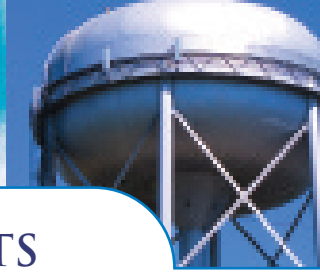
environmental exposure. The U.S. EPA uses predictive models to estimate the cancer risk from exposure to air containing low levels of asbestos (127), but there are few epidemiologic data examining cancer risk from common environmental sources such as buildings or the general urban environment. Further research is needed to better understand risk and carcinogenic thresholds (133,138), particularly for chrysotile, given its commercial use; to determine the influence of fibre length and thickness on carcinogenicity (125); and to more clearly define the proportion of mesothelioma cases related to purely environmental exposure (133). Measurement of asbestos levels in drinking water may also be useful.

Current control initiatives

Many countries have restricted or banned the use of asbestos (23). The use of amphibole asbestos has been drastically controlled; chrysotile asbestos is found in most asbestos products available today (124). Canada continues to be one of the world's largest producers of chrysotile asbestos (139). Some have called for an international ban on the mining and use of asbestos, while others claim that a ban should be based on a comparative risk assessment between chrysotile asbestos and its substitutes (135,140,141).

In Canada, several measures are in place to protect the public against exposure to asbestos (124). The sale of pure asbestos and some consumer products composed of or containing asbestos fibres has been banned under the Hazardous Products Act. Asbestos is still used in the manufacture of a number of products including asbestos cement, industrial insulating material, and friction products such as brake linings (139). Asbestos emissions from mining and milling operations are subject to the Canadian Environmental Protection Act (124). The adoption of strict workplace exposure limits for asbestos by provincial occupational health authorities is encouraged (124), although provincial regulations vary. In Ontario, workplace exposures are regulated under the Occupational Health and Safety Act (142).

Individuals who suspect asbestos in their homes are advised to have it inspected and removed by a qualified professional (123,143). If individuals must remove a small amount of damaged asbestos-containing material themselves, the Canadian Cancer Society and Health Canada offer several guidelines to follow, such as sealing off the work area, wetting the material to repel dust (providing it is not in contact with electricity), wearing appropriate protective clothing including a respirator, and washing or disposing of clothing after completing the job (143,124).



CHAPTER 5. WATER DISINFECTION BY-PRODUCTS

Viral, bacterial, and parasitic diseases can all be transmitted through unclean water supplies. Prior to the introduction of water disinfection, major outbreaks of waterborne disease, such as cholera, were common in Canada. One of the greatest achievements in public health has been the provision of disinfected public drinking water. In the early 1970s, however, evidence suggested that the process of disinfecting drinking water could pose a risk to humans (144).

Chlorine is currently the most widely used disinfectant in Canada because of its effectiveness and low cost (145). Chlorine reacts with the naturally occurring organic compounds in raw water to produce chlorinated organic compounds, otherwise known as chlorination disinfection by-products. Brominated by-products are produced from the reaction of chlorinated by-products and bromide, which are present at low levels in drinking water (42).

The commonly found disinfection by-products can be organized into two groups (Table 6). The more common disinfection by-products are trihalomethanes (THMs), among which chloroform is the most prevalent (146). The other main group of by-products is the haloacetic acids (HAAs) that include the mono-, di- and trichloroacetic acids; the latter two are the most common (144). Other, less prevalent, THMs include bromodichloromethane, chlorodibromomethane, and bromoform (144). The concentration of THM is strongly related to the amount of organic precursors in the raw water (145).

Table 6. Common disinfection by-products and their classifications according to the International Agency for Research on Cancer (IARC)

Disinfection by-product	IARC classification (88)
Trihalomethane	
Chloroform	2B
Bromodichloromethane	2B
Chlorodibromomethane	3
Bromoform	3
Haloacetic acid	
Monochloroacetic acid	NC
Dichloroacetic acid	2B
Trichloroacetic acid	3
Monobromoacetic acid	NC
Dibromoacetic acid	NC

NC = not classified

Environmental exposure to water disinfection by-products

The amount of organic material in source water determines the concentration of disinfection by-products (112). Organic materials have two possible sources of origin: point sources and non-point sources (144). Point sources contaminate by discharging directly into the water system, e.g., industry, sewage treatment plants, mining, landfills, storm overflows (144). Non-point sources contaminate in a more diffuse nature over a broader geographic area, e.g., agricultural run-off (pesticides, fertilizers, fecal matter) and urban run-off from roads and roofs (144). Surface waters (lakes, rivers, and reservoirs) have greater amounts of organic material and thus yield higher levels of disinfection by-products than ground waters (wells, springs) (112,146). Most water in Canada comes from surface waters (112).

Ingestion is one route of exposure to disinfection by-products. Exposure also occurs through dermal absorption and inhalation while bathing. There is some evidence to suggest that THMs are associated with a greater increase in risk when inhaled (i.e., as vapours) than when ingested (147). However, epidemiologic studies have only examined exposure through ingestion (148).

Water disinfection by-products and cancer

The specific disinfection by-products or disinfection by-product combinations that are **carcinogenic** to humans are unknown (112). Chloroform has been shown to stimulate growth of tumours in laboratory animals but there is little evidence to indicate that chloroform or its **metabolites** react directly with DNA (145). In contrast, both brominated THMs and HAAs are **mutagenic** compounds (145).

Research into the risks associated with disinfection by-products began in the 1970s. The early studies showed a positive association between disinfection by-products and cancer risk, most frequently for cancers of the bladder, colon, and rectum (112). The quality of studies has improved greatly over time; recent studies have improved study design (based on incident cases rather than mortality) and have collected more accurate exposure data. These studies have examined chlorinated drinking water or levels of THMs as representive of the mixture of chlorination by-products.

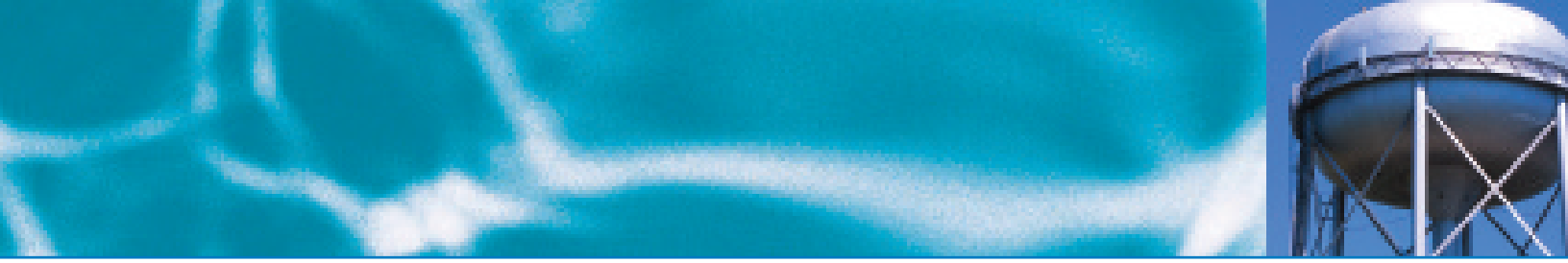
The association between bladder cancer and exposure to water disinfection by-products has been consistent in most studies. Of six studies with improved quality (as identified by Cantor (112)), three found a **statistically significant** relationship between disinfection by-products and risk of bladder cancer with **relative risks** ranging from 1.6–1.8, whereas the other three studies reported positive associations that were not statistically significant (146).

Most of the above studies were considered, along with others, in a **meta-analysis** of bladder cancer risk and individual consumption of chlorinated drinking water (148). Statistically significant summary relative risks for bladder cancer of 1.2 and 1.4 were reported for study participants who were ever exposed to chlorinated drinking water, and those participants with long-term exposure (> 40 years of chlorinated water consumption), respectively.

Findings for colon and rectal cancers are less consistent than results for bladder cancer. Of the four studies with improved quality (112), one found a statistically significant relationship between colon cancer and disinfection by-products, with a relative risk of 3.4 (146). There was no clear trend in the statistically non-significant findings. Of the two studies that assessed rectal cancer risk, one found a statistically significant relationship with disinfection by-products, with a relative risk of 1.7 (112,146).

A lack of historic surveillance of water disinfection by-product levels in many areas hinders measurement of long-term exposure and identification of appropriate control groups. Due to the multitude of mixtures possible in disinfection by-products, exposures to individual compounds are difficult to quantify. The observed risks may be due to other disinfection by-products or mixtures of these, or due to other associated factors (149).

In 1991, the International Agency for Research on Cancer (IARC) evaluated the carcinogenicity for chlorinated drinking water and found inadequate evidence to classify chlorinated drinking water as carcinogenic to humans or laboratory animals (IARC Group 3) (150). This evaluation was based on earlier studies. In 1999, the IARC re-evaluated the carcinogenicity of specific THMs (Table 6); chloroform and bromodichloromethane were classified as possibly carcinogenic to humans, given inadequate evidence in humans for carcinogenicity, but sufficient evidence in experimental animals (151,152). Chlorodibromomethane and bromoform were not classifiable for carcinogenicity to humans (152). The more common HAAs— dichloroacetic acid and



trichloroacetic acid— were recently classified as Group 2B and Group 3 carcinogens, respectively (153,154).

Other research suggests that while there is no conclusive research to establish a causal relationship, the weight of epidemiologic and toxicologic evidence favours an association between water disinfection by-products and cancer risk (145). An expert Canadian panel concluded that "it was possible … to probable … that chlorination by-products pose a significant risk to the development of cancer" (146).

Future research

An expert panel sponsored by Health Canada reviewed health risks related to disinfection by-products and cancer risk, and addressed future research needs (146). Although no consensual statement was issued, panel members provided suggestions for future research initiatives. These included improved exposure assessment by estimating specific THM concentrations, as well as concentrations of other major types of chlorination by-products such as the HAAs. Also among the suggestions was to conduct studies concerning the risk of cancer of the colon or rectum from these exposures (146). Recommendations from another comprehensive review suggested that future efforts should focus on assessing and monitoring contaminants for which there is little information (144).

Current control initiatives

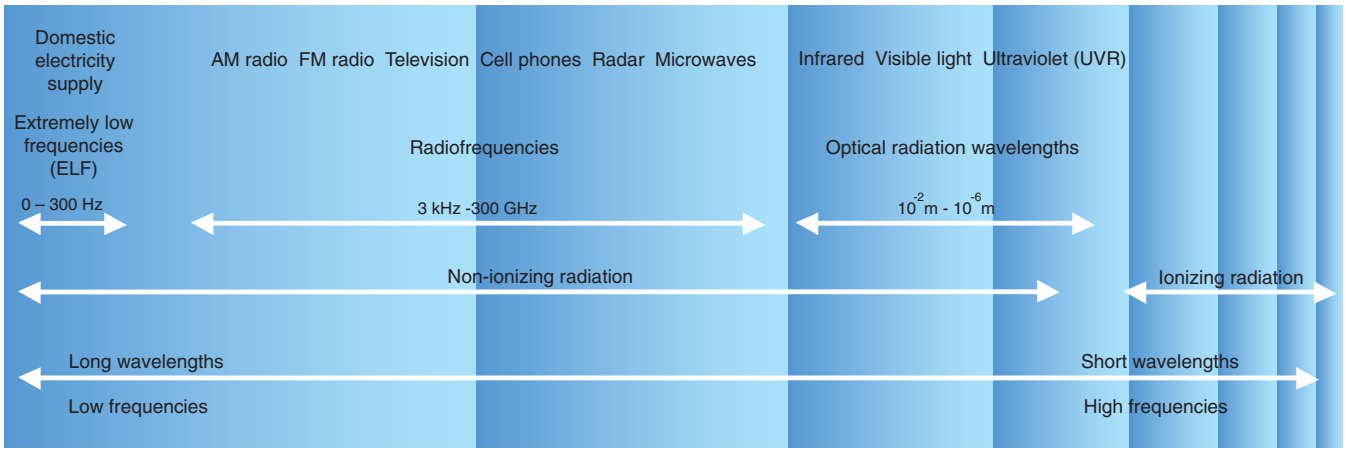
Water disinfection is a necessary public health measure. The World Health Organization (WHO) recommends that when a choice needs to be made between meeting microbiologic quality and meeting guidelines for disinfectants, microbiologic quality should take precedence (144). To rephrase, the hazards of consuming chlorinated water are outweighed by the hazards of consuming untreated water (155,156).

The possible link between chlorination and cancer has encouraged the development of other water disinfection methods. In Europe, ozone is used as an alternative method for disinfecting drinking water. While ozone produces the lowest levels of mutagens, bromate is a carcinogenic by-product (145). A major barrier to implementing alternative water treatments, such as ozone or ultraviolet radiation, is the expense of operating large systems to serve entire communities (144).

Other methods of reducing exposure to water disinfection by-products include decreasing the amount of organic compounds in water that result in higher levels of disinfection by-products. Research into the development of such systems is currently underway. At an individual level, Health Canada states, "activated carbon filters can be used to remove chlorine and its by-products" (157).

CHAPTER 6. RADIATION

Figure 2. The electromagnetic spectrum*



* Not to scale; spectrum segments shown are ill-defined and overlapping

Energy radiating in the form of electromagnetic waves is ubiquitous, from both natural and artificial sources. The electromagnetic spectrum extends from radiation at extremely low frequencies with long wavelengths, through high frequencies with short wavelengths (see Figure 2).

Electromagnetic fields (EMFs), infrared, visible, and long wavelength ultraviolet radiation (UVR) are often referred to as **non-ionizing radiation**. Compared with **ionizing radiation**, this lower-energy radiation is more widespread and less controlled, and its potential for causing cancer is less well understood, than that of ionizing radiation.

EMFs include the earth's naturally occurring static magnetic field and fields from electrostatic charges. The latter are usually described in terms of frequency and measured in **Hertz (Hz)**. "Extremely low frequency" (ELF) fields are those below 300 Hz. Radiofrequency waves occur at higher frequencies; although terminology varies, a broad definition spans the range 3 kHz-300 GHz.

UVR, like infrared radiation and visible light, is within the "optical radiation" section of the electromagnetic spectrum, where energy is described in terms of wavelengths. UVR covers the wavelength range 100 - 400 nm. UVR is divided into three bands: UVA, UVB and UVC.

Energy at the upper end of the electromagnetic spectrum is ionizing radiation, with enough energy to cause cancer by breaking atomic bonds and causing chromosomal aberrations. As the cancer-causing nature of ionizing radiation is well established (158), radon was the only form of ionizing radiation stipulated for further consideration by the expert panel advising Cancer Care Ontario (8). Radon-222, a colourless, odourless radioactive gas released from the normal decay of uranium in rocks and soil, is the principal exposure source of ionizing radiation for the general population. Radon decays into a series of solid elements called radon progeny, or daughters.

Environmental exposure to electromagnetic fields, ultraviolet radiation, and radon

The major sources of electric and magnetic fields in the ELF range are the fields generated in electric power systems (60 Hz in Canada). Residential exposure is mostly from power lines, household wiring, and electrical appliances. Any system of electric charges (as in a power cord for a lamp, or an electric motor) produces an electric field. When the charge flows as a current (when the lamp is switched on), it produces a magnetic field. The greater the current, the stronger the magnetic field. Field strength decreases with distance from the source. Homes beneath power lines have high magnetic field strengths indoors, and high electric fields outdoors, as building materials shield electric but not magnetic fields. Both high magnetic fields and high electric fields have been associated with cancer in epidemiologic studies (159,160,161). For magnetic field, investigators commonly use a related measure, magnetic flux density, usually expressed in microtesla or milligauss. Occupational exposures include electric and telephone utilities, electronics industries, welding, and electric motors (162).

Sources of radiofrequency fields include some industrial and medical equipment, anti-theft devices, computer monitors and television sets, radio and television broadcast, and radar. Cellular (or mobile) telephones are now the greatest source of exposure for the general public; because of their widespread use, any small increase in risk of tumours in the most exposed areas (brain, and other head and neck tissues) could have large public health implications.

Sunlight is the main source of UVR. The UVR reaching the earth's surface is largely UVA, with a small UVB component. The proportion of the sun's UVB wavelength radiation reaching the earth's surface (currently about 10%) may be increasing slightly with the thinning of the earth's ozone layer. No UVC penetrates the earth's atmosphere. UVR levels increase closer to the equator, and at higher altitudes. Ontario UVR levels are highest from May through September, and between 10 A.M. and 4 P.M. Snow and water reflect UVR and so increase human exposure. Artificial sources include sunbeds for tanning, industrial lamps, arc welding, and medical UVR therapies for skin conditions (163).

Radon-222 comes from the natural breakdown of uranium, and can be found in high concentrations where soils and rocks contain uranium, granite, shale, or phosphate. Radon can also be found in soils contaminated with certain types of industrial wastes, such as the by-products of uranium or phosphate mining. Radon trapped in water from deep wells can be released into the air when the water is used (164). It disperses to minimal levels outdoors, but seeps into buildings, where it can accumulate to high levels. Levels vary considerably with local geology, atmospheric conditions, and ventilation.

Extremely low frequency electromagnetic fields

EMFs of different frequencies interact with the body in different ways. Extremely low frequency EMFs affect various physiologic processes including heart rate, sleep patterns, and brain activity. EMF fields in the normal environment are often orders of magnitude below those showing biological effects in the laboratory. Expert panels reviewing the research on ELF EMF in 1998 and 2001, found no clear evidence that weak ELF EMF (<0.1 millitesla) can affect biological processes (165,166). They reviewed laboratory and human volunteer studies of tumour induction, serum melatonin, and immune response, and found no

convincing evidence that ELF EMF increase the risk of cancer in humans (165).

Occupational studies during the 1980s and early 1990s suggested a possible increased risk of leukemia, brain tumours, and male breast cancer in jobs with presumed above-average exposure to ELF EMF. A few among many studies conducted in the 1990s with improved methods reported a two-fold increased risk of brain cancer in utility workers or leukemia in railway employees, although most studies reported non-significant increased risks lower than two, and no consistency as to **dose-response** or specific subtypes of leukemia or brain cancer (167). Exposure assessment was usually by job title; in studies that used individual exposure meters, no consistent association was found with any particular malignancy (167). In addition, most studies measured magnetic fields rather than electrical fields, because the latter are more difficult to measure; however, both may be important when trying to determine a causal association (161). More recent studies remain mixed. Increased risk of several cancers has been reported for work in high-exposure jobs compared with low exposure ones: leukemia (168), particular types of brain cancer (glioblastoma multiforme in men (169)), prostate cancer (170), and non-Hodgkin lymphoma (NHL) (160). A Swedish **cohort study** of engineering workers assumed to have used resistance welding found a three-fold increased risk in women for **astrocytoma**; suggestive but not significant findings for several other cancers were based on few cases (171).

Several international and national organizations, shown in Table 7, have reviewed the literature on ELF and cancer (167,159,165,166). Conclusions were similar: limited evidence of a link between childhood leukemia and high-intensity ELF magnetic fields; ELF EMF fields (or ELF magnetic fields only) are a possible human **carcinogen**. A pooled analysis of several studies published in the 1990s yielded a two-fold increased risk for childhood leukemia with bedroom exposures to ELF EMF of > 0.4 microtesla (167). Studies on childhood cancer and electrical appliance use have been inconsistent. **Odds ratios** for electric blanket use and leukemia, for instance, range from 2.2 to 7.0 but generally are not **statistically significant** (167). Residential ELF EMF studies of leukemia or brain cancer in adults, published during the late 1980s and the 1990s, did not report increased risks (167). Links with other cancers are not well established, although one agency listed weak evidence for chronic lymphocytic leukemia from occupational exposure, consistent with the studies from the 1980s and 1990s noted above (166). Three large recent studies from the U.S. found no association between breast cancer and residential EMF (172,173,174).

Exposure assessment difficulties include: the wide variety of exposure sources and the variation in their electromagnetic fields (occupational or school as well as residential); uncertainty about the relevant time period and type of measurement (any or all of time-weighted average exposure, rapid changes, short periods of high exposure); and the difficulties of measuring past exposures and electrical field strength (159).

Radiofrequencies

A recent expert panel review of the research on radiofrequency fields found little evidence and no known mechanism to support an effect of radiofrequency on carcinogenesis from ***in vitro*** models, and no evidence from studies on laboratory animals that they increase the risk of cancer (175).

Risk of brain cancer, leukemia, and lymphoma has been studied in a variety of occupational groups with

Table 7. EMF and cancer: expert panel reviews

Agency	Conclusions
World Health Organization (WHO)	
International Agency for Research on Cancer (IARC), 2002[167]	Childhood leukemia: limited evidence Other childhood / adult cancers: inadequate evidence ELF magnetic fields: possibly carcinogenic to humans (2B) ELF electric fields: carcinogenicity to humans unclassifiable (3)
International Commission on Non-Ionizing Radiation Protection Standing Committee on Epidemiology, 2001[159]	EMF–cancer causal relationship: none established; strongest evidence for childhood leukemia at high exposures
National Radiological Protection Board (NRPB) (UK)	
Advisory Group on Non-ionising Radiation (AGNIR), 2001[165]	Childhood leukemia at high exposures: some evidence Adults: nil established
National Institute of Environmental Health Sciences (NIEHS) (U.S.)	
EMF-RAPID Program, 1999[166]	ELF electric & magnetic fields: possible human carcinogen Childhood leukemia: weak evidence Chronic lymphocytic leukemia: weak evidence (occupational exposures)

potential for high radiofrequency exposure. Risk estimates for leukemia as high as 8.0 have been reported (among radio and television repairmen), and for brain tumours as high as 3.0 in military personnel (175). Elevated risks were reported in the early to mid 1990s for some other cancers as well: ocular **melanoma** (176) and testicular cancer (177) for self-reported microwave/radar exposure; male breast cancer for radio and communications workers (178). Many studies have, however, failed to show any increase in risk of these and other cancers associated with high radiofrequency exposure from work or hobbies. A recent review concluded that the literature overall neither indicates increased risk from occupational exposure nor gives strong evidence that no risk exists (175). This group called for improved studies (175). Although several studies of mobile phone use and brain or other cancers yielded odds ratios close to 1.0, occasional findings of higher risk of **gliomas** associated with first-generation (analogue, as opposed to digital or cordless) cell phones (odds ratio 2.1) and for ocular melanoma point to the need for studies with better methods, longer exposure periods, and sufficient numbers to allow for subgroup analysis (175). The review panel noted that little has been published on childhood exposure, and most cell phone studies have been unable to look at long-term use (175).

Exposure measurements in cell phone research must address the complexity of use patterns, recall bias, exposure variation with distance from cellular base station, interference from buildings, type of phone, antenna position, and side of head (175).

Ultraviolet radiation

Both UVB and UVA radiation damage DNA, UVB by direct absorption and UVA through the generation of **reactive oxygen species**. They may also activate **oncogenes** and enzymes implicated in carcinogenesis. UVA, UVB, and UVC are all carcinogenic to experimental animals (163,179).

UVR causes more human cancers than any other form of radiation. The International Agency for Research on Cancer (IARC) evaluated solar radiation as carcinogenic to humans (Group 1) and the U.S. National Toxicology Program (NTP) considered it a known human carcinogen. The IARC has judged UVA, UVB, UVC, and the use of sunlamps and sunbeds as probably carcinogenic (Group 2A); the U.S. NTP similarly classifies UVA, UVB, and UVC as probable human carcinogens, but has assessed exposure to sunbeds and sunlamps as a known carcinogen (180,95). Referencing the same papers as the U.S. NTP, the Advisory Group to the U.K.'s National Radiological Protection Board assessed the relationship between sunlamps or sunbeds and cancer as uncertain because of inconsistent findings and methodologic problems (163). UVR from exposure to fluorescent lighting was evaluated by the IARC as not classifiable as to its carcinogenicity to humans (Group 3) (180).

Most UVR-related malignancies are **squamous cell cancers** and **basal cell cancers** of the skin, together sometimes termed "nonmelanoma skin cancer." Although rarely fatal, these represent a substantial cost to the health-care system. Squamous cell cancer risk appears to increase with increasing cumulative lifetime dose of UVR; for basal cell cancer, there is evidence that risk plateaus at a certain dose and that intermittent exposure may be more important. Although risk of melanoma, a more serious but less common form of skin cancer, is associated with excessive UVR exposure, the relationship appears to be complex, and the relative importance of exposure during childhood and/or in brief, intense episodes is not well understood (163). Table 8 summarizes the evidence on sunburns and types of sun exposure for these three skin cancers.

Occupational sun exposure has been associated, in overviews of published studies, with statistically significant increased risks of 1.2 and 1.6 for basal and squamous cell cancers respectively, but reduced risk for melanoma. The lower risk for melanoma may mean that chronic exposure associated with outdoor work confers protection compared with the intermittent exposure of indoor workers (179).

Table 8. Personal sun exposure associated with skin cancer

Type of sun exposure	Basal cell cancer	Squamous cell cancer	Melanoma
Total		✔	✔
Occupational	✔	✔	
Intermittent	✔		✔
Sunburn at any age	✔		✔

Adapted from Armstrong 2004 (25)

There is some evidence that high occupational UVR exposure causes some lip and eye cancers. While far more rare than in the skin, melanoma in or near the iris of the eye (ocular melanoma) can occur. Studies have been inconsistent (between no and 11-fold increased risk) as to a relationship between ocular melanoma and exposure to arc welding sources (163). An Australian study found approximately doubled risks, statistically significant, in people with the most occupational sun exposure compared with the group who had none (181). Lip cancer is more common in outdoor than in indoor workers; a **meta-analysis** of studies on lip cancer in male farmers yielded statistically significant **relative risks** of 2.0 (163).

Susceptibility to UVR damage is high in individuals with the least melanin protection from UVR— people with pale skin, eyes, and hair, and a tendency to burn rather than to tan— especially if they live where UVR is high (163). Reported relative risks of melanoma for those with red or blond hair, and for blue versus brown eyes, have been 2.0 to 3.0, with typical risks ranging from 0.9 to 4.0 for lighter hair, and 1.0 to 2.4 for lighter eyes

(163). Australians of European origin whose skin never tans have shown increased melanoma risk over 3.0 compared with those who tan deeply (179). Treatment with UVA plus oral **psoralen** for skin conditions appeared to substantially increase the risk of squamous cell cancer in a meta-analysis of eight studies (163).

Susceptibility to UVR skin damage is high in people with some rare genetic conditions and in those especially sensitive to small amounts of UVR because of immune reactions to UVR, or increased sensitivity caused by some drugs, dietary agents, herbal remedies, and sunscreens (163). UVR's depression of the immune system may play a role in cancer susceptibility (163).

Data on risk from sunlamp or sunbed use have been inconsistent, possibly because of errors in exposure measurement. Typical risks for melanoma range from 0.9 to 8.1, depending on the age group and exposure frequency (163,182).

Until recently general population studies have suggested no relationship, or at most a weak relationship, between ocular melanoma and solar UVR (163); an Australian study has shown increased risks of between 2 and 3 for some types of ocular melanoma and total sun exposure in men (181).

In addition to the lip cancer studies of outdoor workers, a study of females found a statistically significant risk for lip cancer of 4.7 for the highest level of time spent in outdoor activity (183).

Evidence for an increased risk of NHL and UVR is indirect, based on the rising incidence in both NHL and skin cancers, and increased occurrence of melanoma and NHL in the same individuals (163). Geographic data are inconsistent, with reports of both increased and decreased NHL incidence with increasing ambient UVR (163).

Problems plaguing exposure assessment include recalling past exposure, especially recall bias, as the association with UVR exposure has become more widely known.

Radon

Radon is inhaled and absorbed through the lungs; damage results from the products of its decay (radon progeny), which are solid particles and may be deposited in lung tissue. Radon progeny include several that emit alpha particles (two protons and two neutrons). Although these do not penetrate deeply into tissue, they carry enough energy to cause changes to DNA structure, gene mutations, and transformation in the cells they reach (158).

Radon is recognized as a human carcinogen (Group 1) (184). Radon is associated with lung cancer in underground workers in uranium and other mines with high levels of radon decay products. Relative risk rose linearly with increasing cumulative exposure (24).

Most residential studies of radon have had inadequate power to detect a risk on their own, although a weighted average of published studies of lung cancer gave an estimated non-significant relative risk of 1.06 at 100 **becquerel** (**bq**)/m^3 *vs.* 0 bq/m^3. Some risk of lung cancer appears to exist even at low levels (24). The risk to non-smokers is uncertain because of methodologic limitations and the relatively limited numbers of non-smokers included in published studies (185). Research has failed to establish any clear link with leukemia. Although a recent review found correlations as high as 0.86 ($p<0.01$) for leukemia and estimated radon exposure in **ecologic studies**, **case-control studies** have not supported the association (186). The large UK study of childhood cancers found no evidence of increased risk with increasing radon concentration (187).

Exposure assessment can be inaccurate because current dose varies according to several factors, including local geology, atmospheric pressure, season, prevailing winds, and construction methods, all of which may have been different for any person's past times and locations (24,184).

Future research

The World Health Organization, the UK National Radiological Protection Board, and the U.S. National Institute of Environmental Health Sciences all agree on priorities for research into ELF EMFs and cancer for epidemiology; they call for researchers to improve exposure measures (including occupational measures), to learn more about different exposure patterns and sources, and to study childhood leukemia only where exposures are high and where selection bias can be minimized with population registries. Research is also needed on potential mechanisms of carcinogenic action.

Several epidemiologic studies related to cell phones are now in progress, including a large IARC multinational mobile telephone study looking at brain, head, and neck tumours (188) and one on early childhood cancers associated with residence near mobile phone base stations (175). The IARC hopes for sufficient data to assess the carcinogenicity of radiofrequency fields by 2004–2005 (189).

Understanding risk in genetically susceptible individuals is an important avenue of investigation into UVR exposure and cancer. Investigations continue into genetic susceptibility to melanoma and its interaction with UVR exposure. The relative importance of cumulative, intermittent, and childhood UVR exposure needs to be more thoroughly investigated. Better exposure measurement in sunlamp and sunbed studies is also needed.

Large international collaborations are underway to better assess lung cancer risk from residential radon exposure by pooling study results (24).

Current control initiatives

Where cancer risks have not been established, the provision of credible and timely information to the public on the current state of knowledge is important. The U.S. EMF-Rapid Program and the UK National Radiological Protection Board web sites both link to lay-language explanations of EMF (165,190). The International EMF Project is scheduled to complete its health risk assessments of EMF in 2007 (191). In the meantime, Switzerland is one jurisdiction that has adopted precautionary measures to limit exposure levels (192).

Recommendations for UVR protection include personal measures such as sun avoidance between 11 A.M. and 4 P.M., tanning parlour and sunlamp avoidance, and the use of protective headware, clothing, eyewear, and sunscreen; and policy measures such as employer provision of protective attire and supplies, and the provision of shade in playgrounds, outdoor recreational areas, and other public places (193,194).

Health Canada recommends action to reduce residential radon exposure above 800 bq/m^3 but notes that homeowners may want to reduce exposure regardless of level (164). Recommended action levels are lower in several other countries (195). Steps to reduce radon exposure include renovating basement floors, particularly earth floors; ventilating any sub-floors of basement floors; and sealing cracks in walls, floors, and around pipes and drains (164).

CHAPTER 7. PESTICIDES

Pesticides are substances intended to kill or otherwise control insects, weeds, fungi, or any other organisms declared to be pests. Their most common uses are in agriculture, horticulture, and the control of disease-causing insects in public health programs (196).

The use of chemical insecticides, such as the chlorinated hydrocarbons that include dichlorodiphenyltrichloroethane (DDT), chlordane, and others, became widespread in the 1940s against malaria and other insectborne diseases (197). From the early 1940s until the 1960s, DDT was used widely in North America for insect control in forestry, agriculture, and building protection (31). At the same time, chlorophenoxy herbicides such as 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) were developed for controlling broadleaf weeds in agricultural crops and grasslands. Organophosphate insecticides, such as malathion, were introduced in the 1950s. By the 1990s, more than 34,000 pesticides, derived from about 600 active ingredients, were registered for use in the U.S. (198) and Canada. At present, 405 pesticide active ingredients are being re-evaluated in Canada (199).

By the 1970s, most developed countries had banned the use of DDT and other chlorinated compounds because of their potential for **bioaccumulation** and long-term toxicity. The new generation of pesticides tends to be more effective at lower doses, does not persist in the environment, and is less toxic to humans. Examples of the newer pesticides include organophosphates, carbamates, pyrethroids, and sulfonylureas.

Natural substances such as pyrethrum (found in chrysanthemums) and beneficial insects are also used as pesticides, but will not be considered here. This discussion also will not include classes of pesticides, such as the organochlorides, that have been banned in Canada or that are known to be **endocrine** disruptors (see chapter 8).

Environmental exposure to pesticides

Human exposure to pesticides can be through inhalation, ingestion, or absorption. Pesticide residues can be found in or on air, soil, water, fresh food, and household surfaces. Outdoor exposure is primarily from agricultural, lawn, or pest control spraying. Pesticides enter the home from indoor use, or are tracked in or drift in from outdoors or on the clothing of occupational users (200). Household dust has been found to contain up to 17 parts per million of organophosphorous insecticides in the residences of farm families (201). One of the difficulties in studying pesticides in human populations is measuring actual exposure. The Minnesota Children's Pesticide Exposure Study, designed to assess multi-pathway exposures in children, including personal measurements (air, hand rinse, food residues) and environmental measurements (residential indoor/outdoor air, drinking water, residential surfaces, soil), demonstrates that detailed exposure assessment is difficult but possible (200).

Pesticides and cancer

The U.S. National Cancer Institute's Bioassay Program, and its successor, the U.S. National Toxicology Program (NTP), have assayed many of the registered pesticides for **carcinogenicity**. Of the 47 pesticides tested on rats and/or mice between 1977 and 1992, evidence of carcinogenicity was found for 23 (196). Among the most common tumours associated with pesticide exposure in these bioassays were tumours of the liver, gastrointestinal system, and thyroid. Some, but not all, of the pesticides tested were found to have **mutagenic**

effects in mice and rats. In general, pesticides that exhibit carcinogenic effects in toxicological studies are not approved for general use.

Early studies that found associations between pesticides and cancer often focused on compounds no longer approved for use (such as DDT and 2,4,5-T). Two of the most common pesticides presently in use are considered here as examples of the current literature.

2,4-dichlorophenoxyacetic acid

2,4-D is one of the most widely used broadleaf herbicides. It is one of the components of Agent Orange, which was used during the Vietnam War, and it has been studied extensively for chronic health effects. The chlorophenoxy herbicides as a group have been classified by the International Agency for Research on Cancer (IARC) as having limited evidence as human carcinogens (2B) (79). This group of herbicides includes 2,4,5-T, which has been banned, in part, because of the likelihood of contamination with dioxins (specifically 2,3,7,8-tetrachorodibenzo-p-dioxin, TCDD) during the manufacturing process. The U.S. Environmental Protection Agency (U.S. EPA) lists 2,4-D as not classifiable for human carcinogenicity (Group D) (202), although both the U.S. EPA and Health Canada are presently reviewing the status of this chemical.

Studies with rodents have not demonstrated **oncogenic** or carcinogenic effects of 2,4-D (203). The epidemiologic link between 2,4-D and cancer comes primarily from occupational studies of forestry workers, farmers, and pesticide applicators and producers (196). Both forestry workers and farmers are exposed to a wide variety of chemical and biological agents, which makes interpretation of the results of studies that focus on these occupations problematic. In 11 **cohort studies** of chlorophenoxy herbicide manufacturers and/or applicators, **relative risks** of soft tissue sarcomas ranged from 0.9 to 2.5; non-Hodgkin lymphoma (NHL) from 0.9 to 1.6; and Hodgkin lymphoma from 0.3 to 1.7 (203). No risk estimate was **statistically significant**. Results from **case-control studies** are also inconsistent, perhaps partially due to difficulties in exposure measurement and control for the presence of TCDD. Risk estimates for soft tissue sarcomas included two significant results (**odds ratio** 5.3 and 6.8), but both included subjects with known exposure to TCDD. Six other studies showed no significant increase in the risk of soft tissue sarcomas. Similar results were reported for NHL and Hodgkin lymphoma (203).

Malathion

Malathion is an organophosphorous pesticide used for the control of adult mosquitoes and a variety of agricultural crop pests. In the U.S., it is the most commonly used of the organophosphates (204). A recent re-evaluation by the Canadian Pest Management Regulatory Agency concluded that it is "unlikely to possess carcinogenic potential for humans" (205). The U.S. NTP bioassay showed no clear evidence of carcinogenicity.

It has been shown, however, that organophosphorous pesticides can induce changes in the epithelium of the mammary gland of rats, influencing the process of carcinogenesis (206). There are few epidemiologic studies focused on this insecticide.

A recent review of the pesticides literature initiated by the Environmental Health Committee of the Ontario College of Family Physicians concluded that there was sufficient evidence to suggest a positive association between exposure to pesticides and the risk of developing cancer (207). The Advisory Committee on Pesticides (ACP) from the United Kingdom recently evaluated the Ontario review, however, and disagreed

with its conclusions (208). The ACP cited flaws in the methods employed in the review, most notably a failure to include relevant epidemiologic literature and a biased selection of literature, as well as a lack of consideration of the strengths and weaknesses of individual studies and their impact.

Future research

Researchers interested in studying the chronic effects of pesticides in human populations are faced with a dilemma. On the one hand, individuals are rarely exposed to only one chemical; from public health efforts to eradicate mosquitoes, spraying of lawns and other public areas to control weeds, residues on fresh fruits and vegetables, and pest control within the home, exposure to an array of chemicals is the norm. On the other hand, regulatory agencies often require results that can be attributed to a specific chemical in order to make a case to restrict or ban its use.

Much of the research on the association between pesticides and cancer has focused on occupational exposures. It is possible that vulnerable populations, such as children and those whose immune systems are compromised, may be at higher risk; further research is required among these populations. Future studies should include complete exposure assessment from multiple sources, such as personal measurements of exposure from air and food as well as environmental measurements of pesticides in drinking water, indoor and outdoor air, and soil.

Current control initiatives

Before use in Canada is allowed, pesticides undergo review by the Pest Management Regulatory Agency of Health Canada (PMRA). Once the use of a product is evaluated, it is registered for a specific set of applications. PMRA is also undertaking a re-evaluation of older pesticides. Of the 405 active ingredients under review, 61 had been re-evaluated by March 2003, of which seven were fully evaluated and found to meet modern standards. Standards are set for dose, mode of application, protective measures, and maximum residue limits. These are based on scientific reviews that rely heavily on data obtained from the U.S. EPA. In addition, both provincial and municipal levels of government share the regulation of these substances through various acts, regulations, guidelines, directives, and bylaws (209). In the U.S., occupational exposure limits for 2,4-D have been set at 10mg/m^3 (the concentration to which most workers can be exposed without adverse effects) (205).

To reduce the use of herbicides and insecticides on domestic lawns, Health Canada promotes good maintenance practices, including mowing "high" (210), using beneficial insects, and physical control (211). Several municipalities in Ontario have instituted, or are considering, a ban on all non-commercial use of herbicides for lawn care.

All pesticides should be treated as toxic substances, and used and stored accordingly. Pesticide applicators are required to post notices, and these warnings should be heeded. Children and pets particularly should be kept away from newly sprayed areas at least until the pesticide is completely dry. Fresh fruits and vegetables should be washed thoroughly before consumption.

Health Canada publishes general safety precautions for the use of pesticides in and around the home (212). These include following all label directions, using only for the designated purpose and in the designated manner, keeping children and pets away from areas of use, covering all food and utensils, and washing hands and other exposed skin immediately after use.

The health risks associated with pesticide exposure are more likely to be associated with their toxicity than with their carcinogenicity, and these risks must be taken into account when weighing the possible benefits of pesticides against the potential costs of their continued general use.

CHAPTER 8. ENDOCRINE DISRUPTORS

Known by a variety of pseudonyms, including: environmental estrogens, pseudo hormones, environmental hormones, xenoestrogens, endocrine modulators, hormonally active agents and phytoestrogens, endocrine disruptors are an extensive array of synthetic chemicals and natural plant-derived compounds. An endocrine disruptor is defined as "an **exogenous** substance or a mixture that alters function(s) of the **endocrine system** and consequently causes adverse health effects in an intact organism, or its progeny, or (sub) populations" (213).

Due to their chemical similarity to natural hormones, endocrine disruptors are suspected to alter normal endocrine functioning by: 1) binding to hormone receptors to mimic the effects of natural hormones; 2) blocking the natural binding of hormones and receptors, thereby negating the normal cellular signals of the **endogenous** compounds; 3) altering the production and breakdown of natural hormones; or 4) modifying the production and function of hormonal receptors. Endocrine interference is not a toxicologic end point on its own, but rather a physiological change that may lead to adverse health events. The health effects of endocrine disruptor exposure are dependent on timing in the life cycle or developmental stage, duration and dose of the exposure, chemical characteristics (e.g. toxicity) of the compound, and numerous interactions between endogenous and exogenous factors (214). The adverse health effects of endocrine disruptors in the environment is a topic of intense scientific and political debate (215,216,217,218).

A plethora of chemicals and natural compounds with known or suspected endocrine disruptor properties have been cited in the scientific and policy literature. The U.S. Environmental Protection Agency (EPA), for example, is testing some 70,000 to 87,000 chemicals for endocrine disruptor effects (219). The most commonly cited endocrine disrupting substances include pesticides such as atrazine, now banned substances such as dichlorodiphenyltrichloroethane (DDT), and dieldrin; industrial chemicals such as polychlorinated biphenyls (PCB); alkylphenyls (e.g., bisphenyl A; penta- to nonyl- phenols); some metals; a formerly prescribed pregnancy and contraception drug diethylstilbestrol (DES); and polycyclic aromatic hydrocarbons (PAH) (e.g., benzo[a]pyrene). (220,221). Some of these chemicals have been banned by regulatory agencies due to their high toxicity and persistence in the environment (222).

Phytoestrogens are naturally-occurring estrogen-like compounds found in a variety of plants. Unlike the more toxic synthetic endocrine disruptors, phytoestrogens are generally thought to exhibit mild chemopreventive effects, perhaps because of the longer period of co-evolution between animals and plants with such natural estrogens, and are reviewed extensively elsewhere (223,224).

Environmental exposure to endocrine disruptors

Humans and wildlife are potentially exposed to chemical endocrine disruptors through food (perhaps the most important route of exposure in humans), water, soil, sediment, industrial combustion by-products, and contaminants in consumer products such as some plastics and fire retardant materials. While some endocrine disruptor chemicals are released intentionally into the environment (e.g., pesticides), most are released unintentionally, for example, as combustion by-products (e.g., polychlorinated dibenzodioxins or PCDD) (214).

An international expert panel commissioned by the World Health Organization has argued that the

availability of accurate endocrine disruptor exposure data is the weakest link in identifying causal associations between endocrine disruptors and adverse health effects (214). Most of the current endocrine disruptor exposure information relates to environmental chemical levels (air, water, food) and not to endocrine disruptor chemicals in tissues and blood, where they would be biologically relevant; however, there are some limited tissue data from studies such as the U.S. Centers for Disease Control and Prevention (CDC) annual biomonitoring program. Additionally, much of the current evidence for endocrine disruptors and adverse health effects comes from wildlife populations exposed to extremely high levels of pollutants, or from laboratory animals exposed to high doses of endocrine disruptor chemicals. The health effects of endocrine disruptors at low, or typically ambient, levels are less well understood. An expert panel convened by the National Toxicology Program (NTP) (225) concluded that there was sufficient evidence of low dose effects in laboratory animals from exposure to low levels of endocrine disrupting chemicals; however, the review focused on biological changes rather than adverse biological outcomes (such as cancer), since the long term effects of altered endocrine function are largely unknown.

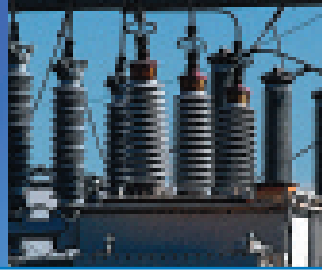
Endocrine disruptors and cancer

In some parts of North America and Europe, rates of endocrine-related cancers (e.g., those of the breast, uterus, prostate, and testis) have increased, leading some to speculate that increased exposure to endocrine disruptors in the environment has been the cause (226,227). Improved diagnostic and screening technologies are other possible explanations for some, but not all, of these increasing trends.

More than 30 **case-control studies** conducted since the mid-1980s have investigated the relationship between DDT and PCB (and their associated **metabolites**) and breast cancer risk (214,30,228). In 1993, Wolff et al (229) reported three-fold increased risks of breast cancer in women with high dichlorodiphenylethylene (DDE) and PCB levels in their blood; more recent work from the same group failed to confirm these results (230). Positive studies have been reported from Mexico (231), Colombia (232) and Canada (233), with significant increases in cancer risk on the order of 2.0 and greater. Recent combined analyses (29) and reviews (30,31), however, suggest no association between DDT and PCB exposures (and their associated metabolites) and breast cancer risk. Laden et al. (29) used a combined analysis of five U.S. studies and reported no increased risk in the highest versus the lowest exposure groups for DDE.

Hoyer et al. (234) reported a two-fold increase in the risk of breast cancer among women with the highest dieldrin levels in their blood, but found none of the other 45 compounds in their study to be associated with disease risk. Dorgan et al. (235) also found no significant association for dieldrin or for the majority of other organochlorine pesticides and PCB in their study. There is a paucity of data for other organochlorines and breast cancer risk, although TDCC and polybrominated biphenyls (PBB) have been addressed, with equivocal results (236,237).

The uterus is highly estrogen sensitive. One of the strongest risk factors for endometrial cancer is hormone replacement therapy with estrogen alone, rather than in combination with progesterone, suggesting that endocrine disruptor chemicals might influence cancer risk in this tissue. There is, however, a lack of data supporting this hypothesis. One case-control study in the U.S. reported no association between endometrial cancer and serum concentrations



of organochlorines, although the sample was small (90 cases, 90 controls) (238). Likewise, a population-based case-control study from Sweden reported no association between endometrial cancer and 10 chlorinated pesticides and 10 PCBs (239).

An **ecologic study** in the U.S. found no association between DDT and DDE levels and testicular cancer mortality rates (240). Hardell et al. (241) reported a six-fold increased risk of seminoma testicular cancer among polyvinyl chloride (PVC) workers. PVC contains a plasticizer called phthalate, a known endocrine disruptor. Others have failed to replicate these findings (242). Data on the risk of testicular cancer among men exposed to DES, a potent synthetic estrogen ***in utero***, are controversial, with no clear consensus at present (243,244). The increased risk of vaginal cancer among women exposed to DES *in utero* is, however, well established (245).

While prostate cancer is hormone sensitive (246), little is known of the relationship between endocrine disruptors and prostate cancer risk. Most research comes from occupational studies that relied on personal recall or job exposure history for exposure measurements. Recent work from the U.S. National Health Interview Study reported no increased risk of prostate cancer among workers exposed to pesticides (247), nor was PCB exposure among U.S. electric workers associated with any cancer site, with the exception of a small increased risk of prostate cancer (170).

A pilot study examining 30 PCB compounds and 18 organochlorine pesticide compounds from serum found that oxychlordane and PCB180 were associated with increased risk of prostate cancer (248), although the many compounds examined would lead to a few significant effects by chance alone.

Future research

The International Programme on Chemical Safety (214) report on endocrine disruptors identified several broad research categories as a priority. These included efforts to increase understanding of how endocrine disruptors disturb normal physiologic processes and influence cancer, improve technical ability to measure endocrine disruptors at lower level exposures with more sensitive and specific **biomarkers**, identify endocrine disruptor chemicals likely to be relevant to disease risk at ambient levels, and collaborate internationally to amass endocrine disruptor relevant information in shared and open forums (214).

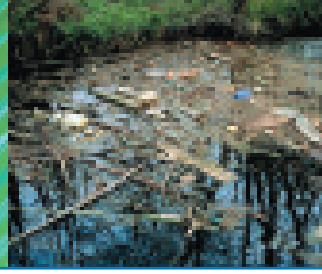
In general, endocrine disruptor exposure and cancer risk has not been studied extensively. The relationship between breast cancer and exposure to DDT and PCB is an exception, but even here, more research is required. Further work on endocrine disrupting exposures during susceptible developmental periods, such as prenatal or early life, is especially needed as adulthood may not be the relevant exposure period. Future studies on endocrine disruptors and cancer should use prospective cohorts with direct measures of endocrine disruptor chemicals from serum or tissue.

Current control initiatives

The risks, particularly for non-cancer endpoints, to wildlife exposed to high levels of endocrine disrupting chemicals clarify the need for limiting environmental exposures to these agents. Improved environmental monitoring and testing of these exposures will help further discern their potential adverse health effects among humans. As this knowledge advances, regulations or safeguards to limit exposure can be refined and improved. Two major international efforts are currently under way to develop new or revised test methods. One is led by the Organization for Economic

Cooperation and Development, the other by the U.S. EPA. Canada is represented by the Pest Management Regulatory Agency (PMRA) of Health Canada in various aspects of these programs (personal communication, PMRA Information Service, 11 March 2004).

The World Wildlife Fund of Canada (WWF) suggests several personal measures that can be taken to avoid exposure to endocrine disruptors including: reducing the consumption of animals high in the food chain in which chemicals with endocrine disruptor properties may **bioaccumulate**; not microwaving in plastic; reducing or avoiding the use of pesticides around the home; washing hands, floors, and windowsills frequently; avoiding super strength specialty cleaners; and avoiding mercury fillings. Further preventive measures suggested by the WWF include ensuring that batteries are treated as hazardous waste, reading labels of products purchased, calling the provided 1-800 numbers if there are questions regarding product formulations, and adhering to fish consumption advisories.



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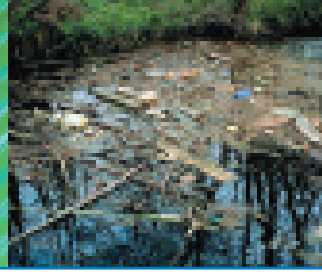

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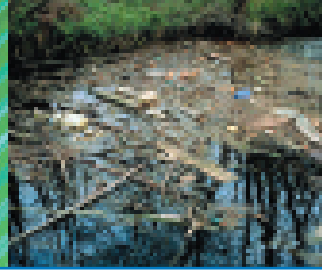

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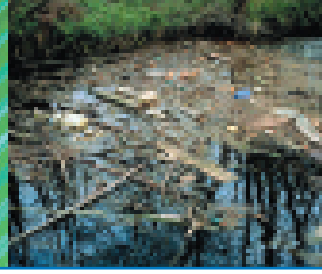

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GLOSSARY

Adducts
Stable complexes of reactive chemicals and macromolecules (very large molecules, or units of chemical substances formed by atoms) made in an organism's cells. Examples of macromolecules in the body are DNA or protein. DNA adducts are complexes of a chemical with DNA, the genetic material, and are thought to play a role in causing cancer by inducing changes in DNA sequences.

Astrocytoma
A tumour that begins in the brain or spinal cord in small, star-shaped cells called astrocytes.

Basal cell cancer
A type of skin cancer that arises from the basal cells, small round cells found in the lower part (or base) of the epidermis, the outer layer of the skin.

Becquerel (bq)
The standard international unit of radioactivity, defined as the activity of a quantity of radioactive material in which one atom decays per second.

Bioaccumulation, bioaccumulate
An increase in the concentration of chemicals, such as pesticides, in living organisms. These compounds are not usually decomposed in the environment or metabolized by the organisms, so that their rate of absorption and storage is greater than their rate of excretion. The chemicals are normally stored in fatty tissues.

Bioavailability
The ability of a substance to be absorbed and used by the body.

Biomarker
A normal metabolite that, when present in abnormal concentrations in certain body fluids, can indicate the presence of a particular disease or toxicological condition.

Carcinogen, carcinogenic, carcinogenicity, carcinogenesis
Any substance that can cause cancer. Such substances are termed carcinogenic, or able to cause cancer; this is the property of carcinogenicity. Carcinogenesis is the process of beginning or promoting the changes that result in cancer.

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

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

Confounders, confounding
Variables that can cause or prevent the outcome of interest, are not intermediate variables, and are associated with the factor under investigation. Unless it is possible to adjust for confounding variables, their effects cannot be distinguished from those of factor(s) being studied.

Dose-response
Dose-response is the change in effect on an organism caused by differing levels of exposure to a substance. A dose-response relationship is the relationship of observed outcomes in a population to varying levels of an agent.

Ecologic study
A study in which the units of analysis are populations or groups of people, rather than individuals.

Endocrine system
A control system of ductless glands secreting hormones that circulate within the body via the bloodstream to affect distant organs.

Endogenous
Originating inside an organism. Compare **exogenous**.

Exogenous
Originating outside an organism. Compare **endogenous**.

Glioma
A cancer of the brain that begins in glial cells (cells that surround and support nerve cells).

Hertz (Hz)
The standard international unit of frequency, equal to one cycle per second.

in utero
Before birth. Latin for *in the uterus.*

in vitro
In the laboratory (outside the body). The opposite of *in vivo* (in the body). Latin for *(with)in glass.*

Ionizing radiation
Radiation of sufficiently high energy to cause ionization (change the electrical charge of atoms) in the medium through which it passes. It may consist of a stream of high-energy particles (e.g. electrons, protons, alpha-particles) or short-wavelength electromagnetic radiation (ultraviolet, X-rays, gamma-rays). This type of radiation can cause extensive damage to the molecular structure of a substance either as a result of the direct transfer of energy to its atoms or molecules, or as a result of the secondary electrons released by ionization.

Latent period
Time between exposure to a disease-causing agent and the appearance of manifestations of the disease.

Melanoma
A form of cancer that arises in melanocytes, the cells that produce pigment. Melanocytes predominantly occur in the skin but can be found elsewhere, especially the eye. The vast majority of melanomas originate in the skin.

Meta-analysis
Meta-analysis is a collection of systematic techniques for resolving apparent contradictions in research findings. Meta-analysts translate results from different studies to a common metric and statistically explore relations between study characteristics and findings.

Metabolite
A product of metabolism, the total of all chemical changes that take place in a cell or an organism. These changes produce energy and basic materials needed for important life processes.

Mutagenic
A chemical or physical agent that causes an increase in the number of mutations (changes in DNA) either by changes to the genes themselves, or by causing chromosome damage.

Non-ferrous
Not composed of or containing iron.

Non-ionizing radiation
The part of the electromagnetic spectrum covering two main regions: electromagnetic fields (EMFs) and most optical radiation. Fields in this part of the spectrum have insufficient energy to remove electrons from atoms and are thus less damaging to human tissue.

Odds ratio
The ratio of the odds (probability of the occurrence of an event to that of non-occurrence) of an event occurring in one group to the odds of it occurring in another group. It is often used as an estimate of risk of disease. See also **relative risk**.

Oncogene, oncogenic
A gene that normally directs cell growth. If altered, an oncogene can promote or allow the uncontrolled growth of cancer. Alterations can be inherited or caused by an environmental exposure. An oncogenic exposure is one that can activate oncogenes.

Particulate matter
Tiny particles of solid or liquid suspended in the air, from both natural and human sources. The composition of fine particles depends on the source. In general, the smaller and lighter a particulate is, the longer it will stay in the air. Larger particles tend to settle to the ground by gravity in a matter of hours whereas the smallest particles can stay in the atmosphere for weeks and are mostly removed by precipitation. The size of the particle also determines where in the body the particle may come to rest if inhaled.

Psoralen
A substance that binds to the DNA in cells and stops them from multiplying. It is used in the treatment of some skin conditions.

Reactive oxygen species
A type of free radical, a highly reactive chemical that often contains oxygen. They play an important role in a number of biological processes but, because of their reactivity, can participate in unwanted side reactions resulting in damaged DNA or other parts of the cell.

Relative risk
The ratio of the risk or rate of disease or death among the exposed, to the risk or rate among the unexposed, or the ratio of the cumulative incidence rate in the exposed, to the cumulative incidence rate in the unexposed. See also **odds ratio**.

Slag
The left-overs from the removal of non-metallic impurities during the smelting of metals.

Squamous cell cancer
Cancer that begins in squamous cells, which are thin, flat cells that look like fish scales. Squamous cells are found in the tissue that forms the surface of the skin, the lining of the hollow organs of the body, and the passages of the respiratory and digestive tracts.

Standardized Mortality Ratio
The ratio of the number of deaths observed in the study group or population to the number that would be expected if the study population had the same age specific mortality rates as a defined standard population.

Statistically significant
A finding is said to be statistically significant if it is different from what would be expected to happen by chance alone.

Valence
A number used to predict with how many neighbouring atoms a certain atom can form a chemical bond.

Glossary definitions were taken or adapted from:

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INSIGHT ON CANCER

environmental exposures and cancer

cancer care ontario | action cancer ontario

Cancer Care Ontario is dedicated to improving the quality of care for cancer patients by creating a seamless journey for them as they access the highest quality programs in cancer prevention, early detection, treatment, supportive care, palliative care and research. Working with partners, including the Cancer Quality Council of Ontario, CCO will measure, evaluate and report on quality improvement in the cancer system. Cancer Care Ontario is a policy, planning and research organization that advises government on all aspects of provincial cancer care.

Insight on Cancer can be found on both the Canadian Cancer Society's and Cancer Care Ontario's websites. Please visit the "library section" of the Ontario pages of the Canadian Cancer Society's website located at www.cancer.ca, or visit www.cancercare.on.ca.

Canadian Cancer Society | Société canadienne du cancer

The Canadian Cancer Society is a national, community-based organization of volunteers whose mission is the eradication of cancer and the enhancement of the quality of life of people living with cancer.

The Canadian Cancer Society, in partnership with the National Cancer Institute of Canada, achieves its mission through research, education, patient services and advocacy for healthy public policy. These efforts are supported by volunteers and staff and funds raised in communities across Canada.

271455.06/05