COMMUNICATION

*National Cancer Institute of Canada*

# Report of a Panel on the Relationship between Public Exposure to Pesticides and Cancer

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**BACKGROUND.** Pesticides, which by their nature are biologically active compounds, continue to raise public concern regarding their possible role as important etiologic agents in the development of human cancer.

**METHODS.** To examine this potential role, the National Cancer Institute of Canada convened an Ad Hoc Panel on Pesticides and Cancer to examine the possible contribution of pesticide exposure, particularly in the general population, to the development of human cancer.

**RESULTS.** The Panel focused primarily on exposure in the general population and reviewed a range of studies that addressed issues related to dietary exposure as well as incidental home and garden uses. In addition, the Panel examined the regulatory framework that exists to safeguard the public from potentially carcinogenic pesticides and also reviewed some potential benefits of pesticide use, including the availability of an abundant and low cost supply of fresh fruits and vegetables as an important strategy in the overall mitigation of cancer risk.

**CONCLUSIONS.** The Panel concluded that it was not aware of any definitive evidence to suggest that synthetic pesticides contribute significantly to overall cancer mortality. The Panel also concluded that it did not believe that any increased intake of pesticide residues associated with increased intake of fruits and vegetables poses any increased risk of cancer. The Panel further concluded, among other things, that tobacco use continues to be the most important preventable cause of cancer and premature mortality and thus is an appropriate focus for cancer control strategy. [See editorial on pages 1887–8, this issue.]
***Cancer* 1997;80:2019–33.** © *1997 American Cancer Society.*

**KEYWORDS: cancer, pesticides, exposure, risk, dietary, residue.**

The National Cancer Institute of Canada's Advisory Committee on Cancer Control (ACOCC) wishes to thank the Panel for their careful consideration of the issues, Peter Nicoll who assisted in compiling the material, and Janet McCann who assisted in the preparation of the final article.

The members of Advisory Committee on Cancer Control are: Dr. Heather Bryant, Dr. Paul Engstrom, Dr. Anthony Fields, Dr. Eric Holowaty, Dr. Neill Iscoe, Dr. Elizabeth Maunsell, Dr. John Morris, Dr. Don Wigle, and Dr. Barbara Whylie.

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Received January 16, 1997; revision received May 9, 1997; accepted May 22, 1997.



There has been a growing concern on the part of many Canadians that exposure to pesticides, either as food residues or when applied to lawns and gardens, may be a major cause of cancers. This concern has been fueled further by some studies that are suggestive of a link between certain agricultural chemicals and cancer in pesticide applicators and farmers.[1–3] Some authors have reported that farmers exposed to phenoxy herbicides may be at an increased risk of developing non-Hodgkin's lymphoma (NHL).[4,5]

In view of this concern, the Canadian Cancer Society (CCS) requested the National Cancer Institute of Canada's Advisory Commit-

tee on Cancer Control (ACOCC) to address the issue of public exposure to pest control products and to assess whether there was a sufficient level of risk to necessitate the CCS changing its priorities. Currently, the CCS places the highest priority on tobacco control strategies. ACOCC established an Ad Hoc Panel on Pesticides and Cancer. In developing the framework for its deliberations, the Ad Hoc Panel decided to examine the following issues:

- Epidemiologic analysis has suggested that not more than 2% of all cancers are attributable to the use of man-made pesticides.[6] Does this estimate reflect recent evidence and current thinking?
- What types of pesticides and pesticide exposures are most likely to be involved in carcinogenesis? Is exposure to these agents current or historic?
- To what extent might the relationship between dietary fat and cancer reflect pesticide contamination of animal fat tissue?
- What new research or public education initiatives should be considered?

The primary purpose of the Panel was to assess cancer risk due to pesticide exposure in the general population. The Panel was aware of reports on cancer risk to individuals occupationally exposed to high levels of pesticides (farmers, manufacturers, applicators); however, the Panel did not consider these studies to have direct relevance in the assessment of risks to the general population other than identifying potential endpoints of interest. Unlike the general population, occupationally exposed individuals experience high pesticide exposure for extended periods of time and at a greater frequency. It was believed these differences were such that any conclusions derived from occupational exposure studies could not be extrapolated to the general public.

All human activity entails risk. As individuals and as a society, we make daily conscious and unconscious risk/benefit evaluations. However, these decisions are more complicated when chronic diseases such as cancer result from inappropriate or incorrect decisions made many years earlier and particularly when we perceive that these decisions are imposed on us or represent values over which we can exercise only little, if any, influence. Involuntary risks of these types usually are perceived to be greater in both severity and magnitude than voluntarily assumed risks.[7]

Unfortunately, decisions to reduce risk or increase benefit to one sector of society often result, or are perceived to result, in an increased risk or decreased benefit to another sector. Therefore risk/benefit decisions should be informed, reflect the overall values of those for whom the decision is being made, and, ideally, involve those directly affected in the decision making process.

The subject of human health risks associated with pesticide use and exposure and specifically the risk of cancer has been the subject of intense scientific interest for many years. In this article, some of the evidence specific to cancer risk and pesticide exposure will be reviewed and evaluated, with reference to the benefits derived from pesticide use, particularly with regard to cancer prevention. The Panel did not attempt to evaluate any other potential risks associated with pesticide use.

## Pesticides: An Overview

The term ''pesticide'' is used to describe a very broad range of chemicals and biologic agents with diverse activity that are designed to control or eliminate unwanted plants or animals, including insects.

Insecticides represent one group of pesticides that traditionally have been utilized in large quantities against a broad range of insect pests. Insecticides commercially in use in Canada include organophosphorus, carbamate, the synthetic pyrethroids, insect growth regulators, and the organochlorine class of compounds. Also included in this class of insecticides are the so-called botanical insecticides, nicotine, and the rotenoid compounds. Arachnicides are similar compounds used to control spiders and mites.

Herbicides, the class of pesticide utilized to control unwanted plants and weeds, are a heterogeneous group of compounds including the chlorophenoxy, bipyridals, substituted ureas, triazene, dinitroaniline, arylaliphatic acids, sulfonyl ureas, and organic arsenicals. Approximately 75% of all man-made pesticides used in Canada are herbicides and $>$ 90% of herbicide use occurs within the agricultural sector.[8] This large scale use of herbicides in Canada has resulted in many of the long term health effects studies in humans being directed at this class of pesticides.

Fungicides, utilized to control diseases caused by fungi, also are a heterogeneous group of compounds that may include the dicarboximides, the substituted aromatics, the dithiocarbamates, and the nitrogen heterocyclics. Rodenticides, utilized primarily in the control of rodents, include anticoagulants such as warfarin.

Fumigants are used in the control of insects, rodents, and soil nematodes (worms and worm-like organisms). They share the common property of being in gaseous form at the site of action, thereby facilitating their penetration into otherwise inaccessible areas. Typical fumigants include chloropicrin and ethylene dibromide.

### *Man-made versus natural pesticides*

Although pesticides often are linked in peoples' minds with man-made chemicals, this is not necessarily the case. Some pesticides, such as arsenic (used as a weed killer or insecticide), occur naturally as a mineral, whereas many plants produce complex organic molecules that are essential to their survival as defense against insects and parasites. For example, the well known insecticide pyrethrum is produced naturally in plants of the chrysanthemum family. Nicotine, well known as the addictive substance in tobacco, also is a naturally occurring pesticide developed by the tobacco plant as a defense against insects and parasites. Naturally occurring compounds often are assumed to be safe although many are in fact among some of the most toxic substances known. Some of these extremely toxic natural substances include many snake venoms, tetrodotoxin from the puffer fish, and several microbial toxins such as tetanus toxin, diphtheria toxin, and botulinus toxin.[9–11] Aflatoxin, produced by the *Aspergillus* fungus found on ground nuts, not only is a powerful liver toxin but is one of the most potent human carcinogens known to science.[12]

One common feature of all pesticides is that they are biologically active and are designed to interfere with the natural biologic processes of the animal or plant being controlled. A pesticide may target a limited number of species, or it may attack a very broad spectrum of pests.

The biologic activity of pesticides implies that they may, if the dose is sufficiently high and if there is a means of sufficient exposure, exert toxic effects on humans. Therefore in using such chemicals, the overall risk is a function of both the intrinsic hazard of the chemical and the frequency and duration of exposure.

The general population may be exposed to pesticides through ingestion of residues in or on treated foods (including meat, fish, dairy products, fruits, and vegetables), by skin exposure after applications in the home or on lawns, gardens, and public spaces, or inadvertently by inhalation during the application of sprays.

## Regulation of Pesticides

To protect both human health and the environment, pesticides generally must undergo rigorous testing and evaluation prior to their registration for use. In terms of human safety (the focus of this report), the pesticide approval process involves the intensive evaluation of important toxicologic data for the pesticide (most notably carcinogenicity, chronic toxicity, reproductive and developmental toxicity, environmental impact, and residue data) and is intended to ensure that only those products that can be used safely and do not result in the presence of hazardous residues in food are approved for sale.

Of necessity, the health hazard evaluation of potentially toxic pesticides has focused primarily on research in laboratory animals that have served as experimental models for the biochemical, physiologic, and pathologic responses of humans. Prior to the registration and commercial production of a new pesticide, epidemiologic studies of the direct effects on humans, exposed occupationally or nonoccupationally, are available only rarely.

Ideally, the pesticidal activity of these chemicals would be highly selective, but in practice, many are nonspecific in both target and nontarget species. The nature and impact of this nonspecific toxicity, and the increased awareness and concern for ecologic implications of the use of pesticides, have begun to attract the attention of toxicologists, epidemiologists, and environmentalists toward studies in humans under realistic conditions of field use.

The toxicologic evaluation process related to human safety is complex and involves a determination of the intrinsic hazard of the pesticide. This evaluation results in the establishment of a ''no observed effect level'' (NOEL), the highest dose level tested experimentally that did not produce any adverse effects. This dose level then is divided by a ''safety factor'' to establish an acceptable daily intake (ADI). Safety factors are selected based on judgment and experience, follow international convention, and typically range between 100–1000, depending on the biologic relevance and severity of the observed effect.

Mathematically, the relationship can be expressed as:

$$\text{ADI} = \frac{\text{NOEL}}{\text{SF (safety factor)}}$$

Once the ADI has been established, it can be compared with the expected exposure to the pesticide from all sources (including food residues) to ensure that exposure by humans will never exceed levels determined to be acceptable. In other words, let us assume that potatoes are to be treated with a pesticide that would result in a maximum residue of 10 mg of pesticide per 100 g of potatoes. Let us also assume that Canadians, on average, can be expected to consume 500 g of potatoes per day. Therefore, Canadians would be exposed to 50 mg of the residue ($10 \times 5$) per day. If the ADI is $\geq 50$ and if potatoes were the only source of exposure to this pesticide, the proposed use would be considered safe and approved for use; otherwise the proposal would likely be rejected and use would not be permitted.

Because many pesticides are used on more than one crop, a similar calculation is performed for each proposed application to ensure that the total residues consumed never exceed the ADI established for the pesticide in question.[13] Indeed, in most cases, total dietary exposure to pesticides falls well below the permitted limits.[14]

It already will be apparent that the calculation allows for a substantial measure of safety. First, in the determination of the ADI, the NOEL is subjected to a large safety factor, even though the NOEL is in itself a dose level that did not produce any adverse effects. Second, the calculation of residue intake assumes that all crops are treated all the time, always at the maximum permitted levels, and that the foods consumed always contain these maximum residue levels. In fact, food quality surveys conducted by Agriculture and Health Canada suggest that most foods do not contain any detectable residue at all and that those that do contain residues usually fall well below permitted levels.[15]

In most cases, exposure to pesticides in the general population occurs largely through ingestion of residues in food and through home and garden use. Therefore, exposure almost always is of a chronic nature occurring over a period of years. Chronic toxicity and carcinogenicity are toxicologic endpoints of considerable study and research in the overall assessment of the safety of pesticide residues. Similarly, immunotoxicity also is evaluated, albeit indirectly, as a component of carcinogenicity, chronic toxicity, and developmental toxicity assessment. Finally, when reviewing the safety of pesticides to the general public, it is also important to evaluate potential risks associated with pesticide residues in food in relation to the well established benefits of an abundant, wholesome, and low cost supply of fresh fruits and vegetables.[16] It should be noted that individuals who manufacture or apply pesticides commercially may experience different risks than the general public, and this should be taken into consideration as well.

## Pesticides in General: Epidemiologic and Laboratory Evidence

The International Agency for Research on Cancer has reviewed the potential carcinogenicity of a wide range of insecticides, fungicides, herbicides, and other pesticide-type compounds.[17] The Agency noted that of the 56 chemicals evaluated, only 1 had sufficient human data, 2 had limited human data, and the remainder had either insufficient or no human data available. In addition, 26 of the chemicals had inadequate animal carcinogenicity data available, 29 had either limited or sufficient evidence of animal carcinogenicity, and only 1, methyl parathion, had evidence suggesting a lack of carcinogenicity. In its overall evaluation, the Agency concluded that it was not possible to classify the potential carcinogenic risk to humans of 35 of these pesticides whereas another 16 were considered to be either probably or possibly carcinogenic to humans, largely on the basis of animal studies; only 1, arsenic and arsenic compounds, had sufficient evidence to conclude that these substances are carcinogenic to humans.

### *Phenoxy herbicides: Epidemiologic and laboratory evidence*

As noted earlier, due to the widespread use of agricultural herbicides in North America, cancer risks associated with this type of pesticide use have figured prominently in reported studies, and hence form the main focus of this review.

Phenoxy herbicides in general, and 2,4-dichlorophenoxyacetic acid (2,4-D) specifically, are among the most widely used chemicals in contemporary agriculture. 2,4-D has been commercially available throughout the world, including Canada, for approximately 50 years. It is also one of the most intensively studied of all pesticides, with many published articles and technical reports addressing the issue of its safety and efficacy.

Epidemiologic studies of phenoxy herbicides and human cancer have employed both case-control and cohort designs. The following review highlights those studies considered most relevant to an assessment of the overall weight of evidence.

### *Non-Hodgkin's lymphoma*

The most convincing evidence suggesting that phenoxy herbicides may be human carcinogens arises from epidemiologic studies of NHL.[4,5,18–21] A number of epidemiologic studies of NHL and phenoxy herbicides have revealed elevated risks; those studies that have examined dose-response relationships usually have reported statistically significant findings.

A case-control study conducted by Hoar et al. in Kansas reported a significant dose-response relationship between the annual number of days on which a farmer applied herbicides and the risk of NHL.[4] Farmers exposed on $\geq$ 20 days per year had a 6-fold increase in the risk of NHL relative to nonfarmers. A case-control study of NHL in eastern Nebraska noted an increased risk odds ratio (OR) (OR = 1.5) for men reporting mixing or applying 2,4-D. This risk increased to 3.1 for men who reported exposure for $\geq$20 days per year.[21]

A Swedish case-control study revealed an OR of 4.9 associated with occupational exposure to phenoxy acids for at least 1 year.[20] An analysis of Saskatchewan

farmers noted a dose- response relationship between risk of NHL and numbers of acres sprayed with herbicides.[5] However, several related case-control studies in New Zealand observed no association between phenoxy herbicides and risk of NHL.[22-24] Lynge also reported no significant excess risk associated with exposure to phenoxy herbicides.[2] More recently, investigators have reported excess rearrangements and chromosomal breaks in chromosome band 18q21 in herbicide applicators and band 14q32 in fumigant applicators.[25] Although the pathobiologic relevance of these observations requires further study, it is noteworthy that translocations linking 14q32 and 18q21 are the most common rearrangements observed in patients with NHL. Similarly, significant increases in the incidence of lymphoproliferative cancers also have been recently reported in a rural farming community in Michigan.[26] The authors postulated that the expression of risk resulting from sustained environmental exposures to agricultural chemicals may occur in conjunction with familial or genetic factors.

### *Soft Tissue sarcomas*

The role of herbicides in the etiology of soft tissue sarcomas is unclear. A number of Scandinavian case-control studies have found a significantly increased risk of soft tissue sarcoma after exposure to phenoxy herbicides.[2,27–29] An increased risk of soft tissue sarcoma was observed among female, but not male, rice weeders exposed to phenoxy herbicides. However, in a recent review of North American, New Zealand, and Swedish case-control studies, either very small increased risks or no increased risk of soft tissue sarcoma were observed among persons exposed to herbicides.[30] In addition, in the positive Scandinavian studies, evidence of an exposure-risk relationship was lacking. In this regard, a cohort mortality study of forestry workers exposed to phenoxy herbicides recently has been reported.[31] The author reported that in a cohort of 1222 men with 25,274 years at risk, no deaths were observed due to cancers such as soft tissue sarcoma and NHL that have been cited by other authors as being associated with exposure to phenoxy acid herbicides. However, it is important to note that the cohort may have been too small and followed for too brief a period to allow identification of a relatively rare disease outcome.

One possible explanation for the different findings of phenoxy herbicide effects in Scandinavia, New Zealand, and North America is the difference in relative exposures to specific phenoxy herbicides or their contaminants. The predominant phenoxy herbicide used in Scandinavia was MCPA, whereas 2,4-D was used primarily in North America and 2,4,5-trichlorophenoxyacetic acid was used principally in New Zealand. Furthermore, Scandinavian use of phenoxy herbicides principally is in forestry, whereas use in North America primarily is in agriculture; application techniques and exposures in agriculture and forestry are likely to differ.[32]

### *All cancers*

Although there have been too few studies of an appropriate nature to properly assess other cancer sites, there is a report linking phenoxy herbicide exposure to cancer of the prostate.[33]

### *Laboratory evidence*

2,4-D has been the subject of animal lifetime cancer bioassays using rats, mice, and dogs; in general these studies have concluded a lack of evidence of carcinogenicity, at least under experimental conditions. Specifically, a rat study performed according to Good Laboratory Practice standards and reported in 1986 included lifetime dietary administration of 2,4-D for 2 years at doses up to 45 mg/kg/day.[34] The authors of this study concluded that treatment did not affect any of the usual clinical parameters, and tumor incidence was not reported to be increased relative to controls, with the exception of brain astrocytomas, which showed a statistically elevated incidence in males receiving the highest treatment level. However, on review, the study authors argued that a lack of a plausible mechanism of tumorigenesis taken together with the fact that astrocytomas (brain tumors) are not characteristic of chemically induced tumors led to the conclusion that this brain tumor was unlikely to have been caused by exposure to 2,4-D. Similarly, a lifetime cancer study performed in mice receiving dietary doses of up to 45 mg/kg/day concluded that exposure to 2,4-D did not alter tumor frequency in any treated group. The mutagenicity of 2,4-D also has been investigated; although the majority of studies did not provide evidence of mutagenicity, some indicated equivocal results.[35,36]

### *Review panels*

In 1989, the Harvard School of Public Health convened an expert panel of scientists to examine the weight of evidence on the potential carcinogenicity of 2,4-D.[36] In its report, the Panel of experts concluded that ''In assessing all of the evidence on 2,4-D, workshop participants were not convinced that a cause and effect relationship between exposure to 2,4-D and human cancer exists.'' However, the Panel did recognize that although a cause and effect relationship for NHL and 2,4-D exposure, the endpoint of greatest debate in the 2,4-D controversy, is far from being established, the

evidence for an association is suggestive and most certainly merits further investigation. Limited additional support for this conclusion also is derived from a report in which investigators observed a modest association (OR = 1.3) between malignant lymphoma in dogs and their owner's use of 2,4-D on their lawns.[37] Although this latter study is consistent with increased risks of NHL among farmers using phenoxy herbicides, the canine study provided only very poor exposure quantification, and the increased overall risks were very small (OR = 1.3).[38]

Similarly, the U.S. Environmental Protection Agency (EPA) directed its Science Advisory Board and Science Advisory Panel to review the epidemiologic studies and other relevant data relating to the carcinogenicity of 2,4-D. In its 1994 Report,[39] the Panel concluded that epidemiologic studies relating to 2,4-D generally have shown no increased risk of cancer. The Panel did note that although some studies have shown a risk of NHL, this risk invariably has been in association with the occupation of farming and not related to a specific exposure to 2,4-D or to other agents. The Panel did caution that available data should be interpreted with caution because population studies generally have been small and the follow-up period usually short.

Although a number of cytogenetic studies have been published in which conflicting results have been reported,[35,36,40] the U.S. EPA Special Panel, recognizing the paucity of adequate genotoxicity data, did conclude that the available evidence suggests that 2,4-D is nongenotoxic.

### *Environmental persistence and occupational exposure*

Potential occupational and bystander exposure to 2,4-D has received considerable attention. Respiratory exposure to 2,4-D during agricultural application has been reported to be very low.[41] Similarly, a typical internal dose after agricultural application of 2,4-D was estimated at approximately 5.78 $\mu$g/kg/spray operation.[41] Forestry workers applying 2,4-D had exposure that was estimated to reflect an internal dose as low as 3–4 $\mu$g/kg/day and as high as 100 $\mu$g/kg/day, depending on the nature of the application equipment, frequency of use, etc.[42] It is noteworthy that these estimated internal doses are 500–10,000 times lower than doses utilized in the rodent studies, which did not produce any biologically relevant effects.

In two separate studies, Harris et al. reported on the environmental persistence and human exposure to 2,4-D and other turfgrass pesticides during home and garden use.[43,44] In these studies, the authors reported that when turfgrass is treated with pesticides for weed or insect control, only very low percentages (1–6%) can be dislodged physically by vigorous scuffling with cloth covered boots immediately after treatment. Dislodgeable residues decline rapidly to well below 1% of the applied dose within 1 day for the insecticides diazinon, chlorpyrifos, or isofenphos and within 4–5 days for 2,4-D or related herbicides. Mowing the turfgrass did not influence the disappearance of dislodgeable residues markedly. At equivalent rates of active ingredient, granular herbicides or insecticides are less dislodgeable than liquid formulations of the same chemicals applied as sprays. However, at the high rates usually recommended for 2,4-D applied as a fertilizer formulation, the dislodgeable residues were not lower. Irrigation or rainfall immediately reduced dislodgeable pesticide residues to negligible levels ($<$0.01%) even on the day of application. The authors also reported that there were no detectable exposures for passive bystanders who resided in homes of treated lawns or for barefoot, barelegged bystanders who actively walked or sat on turfgrass for 1 hour on the day after spraying.[43,44]

## Triazine Herbicides: Epidemiology and Laboratory Evidence

### *Ovarian carcinoma*

Two Italian case-control studies have linked an increased risk of ovarian carcinoma with exposure to herbicides. One study by Donna et al. revealed a significantly increased risk of mesothelial ovarian tumors corresponding to reported herbicide exposure.[1] In a similar study by the same investigators,[45] a significantly increased risk of epithelial ovarian tumors was associated with triazene herbicides.

### *Toxicology of triazene herbicides*

Herbicides used for corn production, including alachlor and atrazine, have tested positive in various mutagenicity assays.[17,46] The International Agency for Research on Cancer has concluded that there is limited evidence that atrazine is carcinogenic in animals, and that atrazine is a possible human carcinogen.[17]

## Chlorine Containing Pesticides

Organochlorines or chlorinated hydrocarbons represent a very broad range of organic chemicals based on the element chlorine. Some of these, such as dichlorodiphenyltrichloroethane (DDT) are now known to have done much damage to the environment, whereas others, such as polyvinyl chloride, have greatly enhanced the quality of human life. Chlorine itself has had an immeasurable positive impact on human health, preventing disease both in the developing and developed nations by providing a means to produce inexpensive, safe drinking water.

Compounds of chlorine, whether organic or inorganic, have extremely diverse toxicity. Consequently, there is no characteristic chlorine toxicity. The effects of one member of the class of organochlorine compounds may be entirely different from that of another member of the group.

Chlorine and its compounds are a component of many pesticides, including insecticides and herbicides. The organochlorine insecticides have been used widely in agricultural and vector control programs for $>$ 50 years with dramatic beneficial effects in terms of both life and health, particularly in the control of diseases such as malaria in developing countries. More recently, these organochlorine compounds have come into disfavor because of their propensity for environmental persistence and concern regarding potential adverse human health effects. However, the relatively low cost of many chlorine containing pesticides, coupled with their effectiveness and the unavailability of substitutes for some uses, suggests that their use will likely continue in many countries for many years to come.

Insecticides are the best known of the organochlorine pesticides although several well known chlorine-containing herbicides also have been in use for many years. The organochlorine insecticides include the chlorinated ethane derivatives such as DDT, which has been banned in Canada since the early 1970s; the cyclodienes that include aldrin, dieldrin, heptachlor, endrin, and toxaphene; and the hexachlorocyclohexanes, such as lindane. These organochlorine insecticides enjoyed wide use throughout the world from the mid-1940s to the mid-1960s, after which time they fell into disfavor and declining use due to their environmental persistence and tendency to bioaccumulate.

Methoxychlor, a chlorinated ethane derivative, enjoyed increasing use which mirrored the decline in use in DDT. Methoxychlor is less toxic to mammals and also is less persistent in the environment than DDT.[47]

The organochlorine pesticides, such as DDT, as well as the polychlorinated and polybrominated biphenyls have been tested extensively experimentally and have produced predominantly or exclusively liver tumors in rodents.[48] However, it is interesting to note that DDT, which has been widely tested under different test conditions, has not been found to be carcinogenic in either the hamster or in nonhuman primates. Doll and Peto noted that there has not been an increase in the incidence of liver tumors in the developed countries since the time of the introduction of DDT and other persistent pesticides.[6] (Liver tumors in individuals in developing countries are considered to be predominantly caused by viral infections).

The contribution that compounds such as DDT may make to the etiology of human breast carcinoma currently is a topic of intense research interest. Breast carcinoma is a highly heterogeneous disease with an extremely complex and multifactorial etiology. Known etiologic factors have been established to account for only approximately 30% of breast carcinomas.[49] Many studies are suggestive of an increasing incidence of breast carcinoma, and there are important geographic differences in the incidence of the disease. A much lower incidence prevails in Japan and Asia than in Western countries.

Although DDT was banned in the U. S. in 1972, and shortly thereafter in Canada, it is ubiquitous in the food chain. Recently, new concerns regarding DDT have been raised because it appears to have estrogen-like effects that may be related to breast carcinoma. A study by Falck et al. compared concentrations of organochlorines in breast tissue from 20 Connecticut women with breast carcinoma and observed higher concentrations of polychlorinated biphenyl (PCB) and ppDDE, a metabolite of DDT, than in controls with benign breast disease.[50] The differences in concentrations of DDE and PCB were significant when age, smoking history, and body mass index were considered. However, the population size was small and other important confounding variables were not assessed. Wolff et al. conducted a nested case-control study in a large population of women in New York. PCB and ppDDE concentrations were compared in 58 breast carcinoma patients and 171 matched controls. A statistically significant increase of DDE levels but not PCB was noted.[3] In Canada, a pilot study in Quebec City by Dewailly et al. found only small differences between organochlorine levels in breast carcinoma cases and controls, with a statistically significant difference being reported for concentrations of ppDDE for cases that were identified as being estrogen receptor positive.[51] This research currently is being supported by the Canadian Breast Cancer Research Initiative.

In what we believe to be the most comprehensive study published to date, Krieger et al. reported that no association could be found between serum DDT and PCB levels and risk of human breast carcinoma.[52] Similarly, other investigators have noted that contemporary human exposure to organochlorine contaminants such as DDT is very limited and may be biologically insignificant compared with other exogenous sources of estrogenic compounds such as oral contraceptives, estrogen replacement regimens, and phytoestrogens in common foods such as cabbage.[49] Although re-exposure attributable to atmospheric recycling may still provide limited opportunity for exposure in Canadian populations, a recent report

suggests that exposure to organochlorines such as DDT is only of historic relevance in North America.[49]

### Pesticides: Exposure

Pesticide exposure to the general population may occur via the application of pesticide products in and around the home, inhalation of vapors, ingestion, or dermal contact with residues on surfaces, and dust. As discussed earlier, exposure to pesticides used in lawncare is minimal.[43,44] The U.S. EPA's Non-Occupational Pesticide Exposure Study (NOPES) assessed various routes of pesticide exposure to the general population for 32 select pesticides and pesticide residues, including inhalation and dermal and dietary exposures.[53] The results of this study found that for most of the pesticides tested, dietary exposure appeared to be greater than inhalation exposure. The exceptions to this were the cyclodiene termiticides, for which exposure via inhalation was greater. Pesticide residues in carpet dust also could contribute to human exposure, especially in small children; however, the extent of this exposure was unknown.[53]

From the NOPES study, it appears that pesticide exposure is greatest by the dietary route.[53] Dietary exposure occurs through consumption of food commodities, both domestic and imported, containing pesticide residues, as well as through ingestion of contaminated drinking water. Although pesticide residues have been detected in drinking water,[54] this was not found to be an important route of exposure in the NOPES study.[53] Therefore, only dietary exposure via food consumption will be discussed in this article.

In both Canada and the U.S., the maximum residues that may be present, the maximum residue limit(MRL), is strictly regulated by legislation and regulation.[55] Regulations are established to ensure that residue levels are maintained as low as possible, recognizing that certain subsets of the population, such as children and the elderly, may have increased susceptibility and noting that any given pesticide may be used on more than one crop at any time. It also is noteworthy that regulations respecting the establishment of MRLs equally apply to both imported as well as domestic commodities, assuring Canadians that residue limits permitted in or on imported commodities must meet identical safety requirements to those imposed on commodities produced in Canada.

In Canada, Agriculture Canada has been routinely monitoring agri-food products since 1970 for all contaminants, including pesticides in plant products and veterinary drug residues in meat, eggs, and cheese.[15] Monitoring of the food supply over a period of approximately 25 years has shown that chemical residues in excess of official tolerances rarely are found. Agriculture Canada reported that during the 1991–1992 fiscal year, a total of 303,038 samples were analyzed in various monitoring and surveillance programs. Monitoring of imported commodities included 20,484 shipments, and sampling of imported commodities covered 55 foreign countries. Overall, $>$ 99.33% of all samples tested did not contain residues in excess of permitted limits, representing a compliance rate of 99.30% for domestic and 98.56% for imported foods. Indeed, fully 84.52% of all domestic foods and 73.4% of all imported foods did not contain any detectable residue levels whatsoever whereas another 14.81% of domestic foods and 25.1% of imported foods had residue levels below permitted limits. Only 0.67% of domestic foods and 1.44% of imported foods contained residue levels in excess of permitted levels. When residues in excess of lawful limits did occur, they often were associated with a single chemical entity in or on a very limited range of food commodities.

In the U.S., the Food and Drug Administration has responsibility for the enforcement and monitoring of residue limits established by the EPA. Domestic food samples are collected as close as possible to the point of production to maximize residue levels, and many commodities, especially fresh produce, are analyzed as the unwashed whole commodity with peel or skin intact. In its 1991 monitoring program, there was compliance with standards in 99% of the 8281 domestic surveillance samples. Indeed, 64% had no detectable residues at all and no violative residues were found in any of the 155 baby food samples tested.[56] More recently, the state of California has reported on its residue monitoring of fresh fruits and vegetables in 1996.[57] In its report, California noted that the monitoring program, which covered 5588 samples and included 161 different commodities, did not detect any residues in 66% of the samples, whereas another 32% were below allowable limits. Only 1.5% (84 samples) had an illegal residue level.

In interpreting this data, it is useful to consider how MRLs are established in Canada and the U.S. MRLs are established utilizing essentially three assumptions: 1) that the residue level at the time of consumption is maximum, 2) that all of the crop has been treated with the pesticide, and 3) that exposure only is to treated crops containing the maximum residue established in regulation. However, experience has taught that such assumptions invariably overestimate the likely dietary intake of pesticide residues. Indeed, levels at the time of consumption may be only 20–40% of the permitted levels established at harvest, largely due to the effects of processing, washing, and cooking.[58] Surveys of actual dietary exposure in the U.S. have demonstrated that typical intake averaged

<1% of the acceptable daily intake,[59] in itself a very conservative measure of safety. Furthermore, the effect of shipping, washing, trimming, and cooking actually may reduce residue levels an additional 14–100%, depending on the commodity and the degree of processing. In addition, pesticide use reduction programs, such as those in Ontario, Canada,[60] further demonstrate the continuing decline in pesticide use. In Ontario alone, the overall decline reported from 1983–1988 went from 8700 tonnes of pesticide active ingredient to 7200 tonnes; this further declined by 1993 to 6200 tonnes. Overall, from 1983 to 1993, the decline was reported to be 28.3%.[60] Noteworthy as well is that such declines in pesticide use rarely are reflected in established residue limits but nevertheless result in dietary intake that is often far below MRLs.

Despite these improvements, it is important to note that the MRLs for foods consumed by infants and children should be strictly controlled. The Committee on Pesticides in the Diets of Infants and Children of the U.S. National Research Council recognized that pesticide use has increased crop yield, thereby increasing the quantity of fresh fruits and vegetables in the diet and contributing to improvements in public health.[61] However, it concluded that certain regulatory changes should be considered. Most important, the Committee noted that total exposure (dietary) to pesticide residues should reflect the unique characteristics of the diets of infants and children, and also should consider all potential nondietary sources of exposure.

### Pesticides: Benefits

The potential risks of pesticide use with regard to cancer needs to be considered in parallel with the potential benefits of pesticide use. Pesticide use leads to direct benefits including improved crop yields and lower food costs, and indirect benefits associated with increased consumption, particularly of fresh fruits, vegetables, and other dietary components rich in fiber. There is strong evidence that such a diet is associated with a reduced risk of chronic disease, including many cancers.

The economic benefits of pesticide use have been widely published. Some authors have argued that the absence of pesticides would result in substantial reductions in the domestic supply (both in Canada and the U.S.) of fresh and processed fruits and vegetables.[62] Reports suggest that if man-made pesticides were entirely eliminated, average yields would be reduced by up to 70%, and a reduction in pesticide use of 50% might result in a decline in yield of 37%.[62] However, impacts are variable and will depend on crop, climate, integrated pest management programs, and application of the principles of sustainable agriculture.[63] In the U.S., yield reductions associated with the elimination of pesticides have been estimated to be as high as 100% for potato production in Maine to a 30% decline in apple production associated with a 50% reduction in pesticide use in Washington State.[62] Utilizing 1990 data, the economic benefits of pesticide use in the U. S. were estimated to be $10,900 million per year, balanced against direct costs of approximately $2800 million attributable largely to resistance and loss of natural enemies.[64] This 3-fold return to the producer is supported by other estimates that indicate a $3–5 direct return to the farmer for every dollar spent.[64] Use of nonchemical control measures and integrated pest management programs further enhance this return for farmers.[63] However, the impact of curtailing pesticide use is controversial and not all authors agree on the extent of the impact. Nobel prize winner Norman Borlaug has reported that crop losses would increase by 50% and food prices would increase 4–5-fold,[65] whereas Pimentel and Hanson suggested that crop losses might be only 7%, although they did point out that losses for some crops might be much greater than for others.[64] Pimentel and Hanson also noted that in addition to the direct costs of using pesticides, indirect costs also might include human and animal poisonings, reduction in the populations of natural enemies and honey bees, losses to other vegetation and wildlife, and costs of pollution control programs.[64] Alternatively, one can consider the additional land that would be required for cultivation to compensate for estimated crop losses. One source has estimated that the land required to make up the yield deficit for 16 common U.S. crops produced without pesticides would be a land mass equivalent to Minnesota, Iowa, Missouri, Arkansas, South Dakota, Nebraska, Oklahoma, and Louisiana.[66] In addition, declines in food production through curtailment of pesticide use potentially would have dramatic implications for the proportion of income that consumers would have to devote to food. It is estimated this would double in North America and Europe from its current range of 15–30%.[62] Furthermore, declines in pesticide use also might lead to consumer rejection of products with poor appearance and quality, more perishability, return to more seasonal availability of fruits and vegetables, potentially increased soil erosion resulting from increased cultivation to control weeds, and a host of other adverse impacts otherwise difficult or impossible to measure.[62]

As noted earlier, diet is popularly perceived as an important source of exposure to pesticides. However, it is generally agreed that the use of pesticides in food production has improved crop yields and has increased the quantity of fresh fruits and vegetables in the diet, thereby contributing to significant improve-

ments in public health. Indeed, the Committee on Diet and Health of the U.S. National Research Council noted that there is no evidence that pesticides or natural toxins in food contribute significantly to cancer risk in the U.S.[67] In its report, the Committee also noted that increased consumption of diets high in plant foods such as fruits, vegetables, legumes, and whole grain cereals (invariably related to an increase in availability and a decline in cost) are associated with a lower occurrence of coronary heart disease and, more specifically, malignancies of the lung, colon, esophagus, and stomach. Although the pathophysiology underlying these effects is not completely understood, the decreased cancer risk may reflect the fact that diets rich in plant foods also tend to be low in total fats. A high fat diet has been associated directly with the risk of certain cancers. Indeed, of all dietary factors, fat has attracted the most interest.[16] Similarly, diets rich in fruits and vegetables that contain complex carbohydrates such as starches and fiber, vitamins, minerals, and trace elements also confer protection against certain cancers and coronary heart disease. Epidemiologic studies have suggested that consumption of carotenoid-rich foods are associated inversely with the risk of lung carcinoma whereas animal laboratory studies consistently provide strong evidence that certain retinoids prevent, suppress, or retard the growth of chemically induced cancers at a number of anatomic sites, including the esophagus, pancreas, colon, skin, breast, and bladder. The Committee did note the important link between frequent consumption of vegetables and fruits, especially green and yellow vegetables and citrus fruits, and the decreased susceptibility to cancers of the lung, stomach, and large intestine. Most important, the Committee considered the impact of potential increases in exposure to pesticides through increased consumption of fruits and vegetables and concluded that despite consideration of worst-case hypothetic scenarios, the benefit of dietary modification to include more fruits and vegetables far outweigh the potential for adverse effects ''which is minimal, if any.''[67]

The European School of Oncology Task Force on Diet, Nutrition and Cancer also has reviewed the issue of diet in the etiology of cancer.[68] The Task Force reported that in a combined analysis of 13 case- control studies of colorectal carcinoma, dietary fiber was found to be protective, with increasing protection as a function of increases in estimated consumption of dietary fiber.[69] Similarly, the Canadian National Breast Screening Cohort Study reported that dietary fiber was found to be protective.[70] Overall, the U.S. National Research Council also noted the accumulating evidence that suggests that risk of colorectal and other cancers is reduced in consumers of vegetables and fruits.[67]

Overall, the European Task Force has estimated that increased fruit and vegetable consumption may contribute to as much as an 80% decrease in potentially preventable cancers.[16] The Task Force specifically noted that potentially preventable cancers were largely associated with reduction in alcohol intake, reduction in smoking, reduction in fat consumption, and increased intake of fruits and vegetables (Table 1).

## Ongoing Research

There is a considerable amount of research under way in North America and other parts of the world to determine any causal link between environmental exposures and cancer, particularly breast carcinoma.

Cancer maps of the U.S. reveal that breast carcinoma rates are higher in the northeastern and mid-Atlantic parts of the U.S. compared with the rest of the country. Although much of this regional variation can be attributed to differences in the prevalence of known risk factors[6], there remains the concern that environmental contaminants may play a role. Two National Cancer Institute (NCI)-sponsored studies currently are underway to address the question of environmental and other risk factors for breast carcinoma in high risk areas. The Long Island Breast Cancer Study Project has initiated a number of cooperative studies and protocols that are being developed to address the measurement of environmental exposures and historic reconstruction of exposures in the Long Island population. Environmental factors being investigated include airplane emissions and exposures associated with contaminated water, soil, and air. Pesticide exposure, including DDT, will be considered as will hydrocarbons and metals in vehicle exhaust, solvents, PCB and polybromated biphenyl (PBB), heterocyclic amines in diet, and electromagnetic fields. A similar study in the northeast/mid-Atlantic states also is currently underway.

The NCI also has initiated a series of case-control studies aimed at correlating breast carcinoma risk and exposure to organochlorine compounds outside of the northeastern part of the U.S.

In Michigan, PBB was accidentally introduced into cattle feed in 1974. The farming families in the regions were heavily exposed to varying degrees and currently are the subject of an ongoing study to determine whether they suffered adverse health effects. Approximately 3000 men, women, and children from those who lived on the 600 most heavily contaminated farms or received produce from these farms are being followed.[71]

NCI scientists also are examining a cohort of indi-

**TABLE 1**
**Estimates of Potential Effects of Dietary Change on the Incidence of Various Cancers**

| Site | Recommended action | Population attributable risk[a] | Potential preventable[b] |
|---|---|---|---|
| Oropharynx, esophagus, larynx | Reduce alcohol, increase fruits and vegetables | 90% | 86% |
| Colon and rectum | Reduce fat and increase vegetables | 50% | 79% |
| Breast | Reduce fat and increase vegetables | 27% | 75% |
| Lung | Eliminate smoking, reduce fat, increase vegetables | 80% | 76% |
| Pancreas | Eliminate smoking, reduce calories, dietary cholesterol and increase vegetables | 50% | 70% |

[a] Proportion of the cancer considered to be attributable to the factors listed under action.

[b] Proportion of the population attributable risk of cancer that could be prevented if the recommended action was taken.

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viduals exposed to high concentrations of DDT in Triana, Alabama, a small rural town downstream from a major military/industrial site at which DDT was manufactured between 1937 and 1971. They are planning a study to compare DDE residues in cases and controls and a community mammography screening program has been established to monitor breast carcinoma rates.[72]

The largest study ever undertaken (to the authors' knowledge) to explore the possible relationship between exposure to various pesticides and the risk for various cancers is currently underway. Known as the NCI Agricultural Health Study, it will evaluate the relationship between exposure characteristics of an agricultural lifestyle and risk of cancer for any site. The study will involve 75,000 farmers, their spouses, and children from Iowa and North Carolina and will assess a variety of exposures such as to pesticides, fertilizers, diesel exhaust, solvents, animal viruses, sunlight, and other agents characteristic of farming. The main part of the study is a prospective cohort study in which the exposed persons will be followed for $\geq$10 years. Cases of the cancers of interest, such as prostate carcinoma, NHL, lung, skin, and breast malignancies, that are identified over the first 5 years will be included in case-control studies that will obtain even more detailed information on possible exposures and risk factors.[69]

A variety of other studies of pesticide exposure and breast carcinoma are in progress in the U.S., several of which are being funded by the U.S. Army's Breast Cancer Research Program. One such study is assessing breast carcinoma incidence in occupational cohorts exposed to ethylene oxide and polychlorinated biphenyls; other studies are evaluating organochlorines in occupationally exposed populations. The National Action Plan on Breast Cancer also is funding studies assessing a possible relationship between organochlorine exposure and breast carcinoma in Alaskan natives and in women in North Carolina, and the NCI is launching such a study in Mexico. In addition, the NCI and/or the National Institute for Environmental Health Sciences are supporting a series of projects on breast carcinoma risk as a consequence of exposure to organochlorines that are being performed by scientists around the U.S.

In Canada, Health Canada is planning an epidemiologic study that will focus on the role of organochlorines and other risk factors in breast carcinoma. The National Cancer Institute of Canada (NCIC) and the CCS also are committed to advancing knowledge regarding important risk factors in the etiology of breast carcinoma. To this end, NCIC and CCS currently are supporting studies examining the association between exposure to organochlorines and breast carcinoma risk.

Opportunities also are being explored to study a unique population in Kurdistan, Turkey. In the 1950s, in response to a major famine, the U. S. shipped grain intended for planting. This grain had a protective coating of hexachlorobenzene. Regrettably, the grain was used for direct human consumption and the chemical was transmitted through breast milk, resulting in widespread death in the neonatal population. Further study of survivors of this highly exposed population may yield extremely useful information regarding the long term effects of pesticide exposure.

## Recommendations with Respect to Research

Research performed to date suggests that at high occupational exposures (as would be observed in farming populations and among pesticide applicators), there is evidence of an increased incidence of NHL. However further studies suggest that the general population, through food residues, is not exposed to any appreciable risk. Notwithstanding, the Panel recognized that epidemiology studies often do not provide definitive

evidence of causality and that continued vigilance and monitoring of research must be maintained and enhanced to ensure that NCIC, CCS, and regulatory agencies are cognizant of research developments of relevance to the assessment of human cancer risks and exposure to pesticides. Difficulties in defining exposures and exposure pathways, as well as incomplete understanding of potential biologic mechanisms, require strong support of ongoing research and frequent reassessment of existing scientific knowledge and risk management strategies.

During its deliberations, the Panel noted the anxiety and concern on the part of many Canadians regarding pesticide use and the safety of the food supply. The Panel stressed the importance of public education in understanding the concept of risk as a natural aspect of life. The Panel encourages the development of programs to foster better understanding of the concept of cancer risk assessment and its role in identifying the causes of cancer, their impact on human populations, and the development of practical programs for cancer prevention and control. Such an approach will certainly help us all, both individually and as a society, to make informed decisions about our own health, and of the consequences of inappropriate decisions. A view held by some is that it is more acceptable to be outraged by exposures that are caused by others, rather than by exposures over which we may have direct control. However, this view may raise concerns that are not appropriate to the level of risk and also may have the undesirable effect of diverting public attention from areas that present significant public health risks and that are modifiable by individual choice. There is a strong need for behavioral studies to improve our understanding of how educators and those in the communications industries can better present a balanced view of the hazards and benefits that are faced in everyday life. It is most important that we find the ways to put hazards into perspective for the public, to provide a credible source of factual information to encourage a thoughtful and balanced assessment of both risks and benefits, and to ensure that the public is aware of, understand, and implement the simple avoidance procedures that can reduce their risk greatly.

## Conclusions

1. Concerns have been raised that pesticide exposure may be an important cause of cancer. The Panel was unaware of any direct evidence developed since the Doll and Peto assessment in 1981[6] to suggest any major revision of their view that synthetic sources of chemicals are responsible for only a small percentage of all cancer mortality. However, that estimate continues to rest on incomplete understanding of potentially complex exposures and biologic mechanisms. Further research and continuous reassessment clearly are necessary.
2. Phenoxy herbicides have been implicated in causing an excess of some cancers in farming populations and among pesticide applicators. With respect to NHL, the Panel concluded that the evidence was suggestive with high occupational exposure. The Panel found no evidence to suggest increased risk in the general population; however, they noted the absence of studies specifically designed to investigate the risk of herbicide exposure in the general population.
3. Some studies have implicated DDT, and its metabolite DDE, in the etiology of breast carcinoma. Although a causal relationship remains far from established, and although DDT is no longer produced or used in Canada, the Panel encourages the support of studies to further explore the relationship between organochlorines in general, and DDT specifically, and breast carcinoma.
4. The Panel noted that in Canada at least 30% of all cancers and numerous other health effects are attributable to tobacco use directly, making it the single most important preventable cause of cancer and premature mortality.
5. The Panel agrees with the many published reports suggesting that a diet rich in fruits and vegetables is important in the reduction of cancer risk at various anatomic sites.
6. The Panel does not believe that any increase in intake of pesticide residues associated with increased intake of fruits and vegetables poses any increased risk of cancer and, in any case, believes that any risks, however small, are outweighed greatly by the benefits of such a diet.
7. The Panel recognizes the importance of pesticide use toward enhanced crop production and food quality and the associated impact on declining costs of fruits and vegetables, concomitant increase in consumption, and resulting positive effect on declining cancer risks.
8. The Panel did not find any existing evidence to suggest that crop protection chemicals and lawn and garden products are likely to be a major cause of cancer.
9. The Panel has concluded that exposure of the general population to pesticide residues is minimal and below those levels already deemed to be safe by government regulatory agencies. The Panel notes that in Canada, fully 85% of all food commodities monitored in 1991–1992 had no detectable residues.
10. The Panel has noted that although current regulatory requirements provide reasonable assurance of the safety of pesticides, many older pesticides were regis-

tered prior to the introduction of contemporary requirements and thus may have escaped appropriate scrutiny. The Panel urges regulatory authorities to regularly review the status of older products and to ensure that their continuing use is supported by adequate data and that the results of new research has been considered.

11. The Panel recognizes the general paucity of appropriate studies regarding pesticide exposure and cancer, particularly for pesticides other than phenoxy herbicides, and encourages support for further research in this area.

12. The Panel notes that its review of the issue of pesticides and cancer is a work in transition that must be updated as new knowledge emerges and whose conclusions must be reviewed and amended, when appropriate.

13. The Panel believes that the current priority to reduction and elimination of tobacco use is appropriate for cancer control and prevention and did not find any evidence to support the view that this priority should be modified.

14. The Panel encourages the CCS to promote research into improving the ways in which ''risk'' is communicated to the public.

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