Canadian Cancer Society
Société canadienne du cancer

PROCEEDINGS

EXPLORING THE CONNECTION

> A State of the Science Conference on Pesticides and Cancer

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Contributing Authors: Prithwish De (Canadian Cancer Society), Lalaine Lacuesta (formerly with Canadian Cancer Society), Heather Chappell (Canadian Cancer Society), Heather Logan (formerly with Canadian Cancer Society)

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LIST OF ACRONYMS

CDC	US Centers for Disease Control and Prevention
CEHAPE	Children's Environment and Health Action Plan for Europe
CFIA	Canadian Food Inspection Agency
CHMS	Canadian Health Measures Survey
EPA	US Environmental Protection Agency
FAO	Food and Agriculture Organization
HEAL	Health and Environment Alliance
IARC	International Agency for Research on Cancer
IPM	Integrated Pest Management
JMPR	Joint Meeting on Pesticide Residues
MIREC	Maternal-Infant Research on Environmental Chemicals
MRL	Maximum Residue Limit
NHANES	National Health and Nutrition Examination Survey
OECD	Organisation for Economic Cooperation and Development
PIC	Prior Informed Consent
PMRA	Pest Management and Regulatory Agency
POP	Persistent Organic Pollutants
WHO	World Health Organization

> PROCEEDINGS OF THE STATE OF THE SCIENCE CONFERENCE ON PESTICIDES AND CANCER

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I. INTRODUCTION

Pesticides are a group of chemicals that can be used for a variety of reasons. The *cosmetic* use of pesticides is aimed at improving the appearance of a lawn or garden, while *non-cosmetic* uses are for controlling pests that affect food, human health and safety. Pesticide use in agriculture is an example of non-cosmetic use and is intended to preserve the quality and quantity of crops by preventing damage by weeds, bacteria, fungi and other organisms. Pesticides are also sometimes used to protect farm products from pests during storage and transport. In addition to agricultural uses, non-cosmetic applications occur in the production of pressure-treated lumber and in the control of disease vectors such as West Nile virus. Despite their many applications, some research suggests the potential for harm from pesticide exposure as some studies have identified varying degrees of cancer risk associated with pesticide exposure.

Sources of contact with pesticides are from occupational exposure through pesticide production or application in agriculture and other industries, bystander exposure from pesticides carried into the home or as a result of pesticide drift from treated areas, and dietary exposure resulting from consumption of pesticide residues on vegetables and fruit. Populations with potential exposure include farm owners and operators as well as their families; golf course superintendents; pesticide applicators and manufacturers; residents who live in the vicinity of pesticides use; and consumers of food that have pesticide residues.

Given the complexity of the issue and the many differing points of view with regard to pesticides, the Canadian Cancer Society hosted the State of the Science Conference on Cancer and Pesticides on 12 and 13 November 2008 in Toronto, Canada, with the objective of engaging Canadian stakeholders in a discussion about the science and regulations on pesticides as well as practices around the non-cosmetic use of pesticides.[*] The overall goals of the conference were to i) exchange information about the science of pesticides as it relates to cancer in order to help inform policies on pesticides; ii) understand the regulations on pesticides that protect the health of Canadians; and ii) identify future research priorities. The panel of speakers included Canadian and other internationally recognized experts in research and policy as well as representatives from the occupational and farming sectors. The following sections capture the major discussions that took place over the two-day conference.

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[*] Prior to the Conference, the Canadian Cancer Society had adopted a strong stance on the cosmetic use of pesticides, calling for the ban of pesticides for such use. In November 2009, the Canadian Cancer Society made public its position on the non-cosmetic use of pesticides, based partly on learnings from the Conference. Both positions can be found on the CCS website: www.cancer.ca

II. PESTICIDES AND WORLD AGRICULTURE

Pesticides are a group of chemicals that include:

- insecticides for insect control
- herbicides for weed control
- fungicides for control of disease caused by fungi
- rodenticides for rodent control and
- fumigants (substances used in gaseous form to control insects).

The application of pesticides can prevent increases of natural substances in crops to toxic levels. For example, fungicides can prevent the production of carcinogenic mycotoxins such as corn ear mould that are harmful to human health. A person's contact with pesticides can occur in several ways, including absorption through the skin, by inhalation and ingestion. When a pesticide is sprayed, it can drift or run off and contaminate the nearby air, soil, groundwater and surface waters. It can collect on plants and other objects in the vicinity of the application area.

The importance of pesticides in industrialized and developing countries was discussed by **Dr Gerald Stephenson** from the University of Guelph. He stated that half of the world's use of pesticides, mostly herbicides, is in Europe and North America while developing countries account for most of the world's insecticide use. The goals of pesticide use can differ by region. Dr Stephenson explained that many people in developed countries want to reduce pesticide use and shift to organic growing as a means to avoid potential health risks of pesticides and maintain good health. Pesticide regulations are intended to ensure wide margins of safety and are complemented by requirements related to the application of pesticides. In developing countries, on the other hand, people want to use pesticides to improve food production in order to be healthier and have a higher standard of living. Stronger regulations and safety requirements are needed, especially since this is where most pesticides are still often applied by hand.

Some of the benefits associated with the use of pesticides were outlined:

- Some agriculturalists estimate that a ban on pesticides in the United States would reduce agricultural output by 30%.**(1)**
- The annual use of pesticides prevents a $26-billion crop loss in the United States.**(2)**
- When the costs and benefits of pesticide use are calculated, society receives a $2 return for every $1 used on pesticides.**(2)**
- Agricultural pesticides save fossil fuel energy and human energy. African women, on average, spend half their waking hours in the fields producing food – either planting, weeding or harvesting crops.**(3)**

- With pesticides as part of integrated pest management (IPM), 60% of the world's theoretical crop yield can be achieved as compared to only 30% without pesticides.(4)

According to Dr Stephenson, the correct approach to the use of pesticides is 100% reduction when pesticides are not needed. He explained that this is the principle behind IPM, which also provides a wider margin of safety than conventional pest control measures. IPM is one of the methods the Government of Ontario is promoting to achieve its Food Systems 2002 program goals.

Dr Stephenson claimed that with the expected growth in world population requiring an estimated 50% more people needing food as well as increasing amounts of agricultural land being used for biofuel production, IPM can increase the net yield of food on the same area of land.(4) He suggested that the theoretical yield could be increased from 60% to 90% with IPM along with genetic technology.

Mr Ronald Bonnett from the Canadian Federation of Agriculture provided a farmer's perspective on the issue of pesticide use and made a number of points for participants to consider. He stated that:

- Global competitiveness is important when considering the role of pesticides. If the cost of production goes up because of policies and regulations, farmers cannot be competitive against imports that do not have the same controls in place in the foreign country.
- Farmers use a whole suite of pest, disease and weed management tools before resorting to pesticides.
- Organic farming is considered less of a food safety option as conventional farming. Actually, organic and conventional farming have more in common than they used to have. In conventional agriculture, as in organic farming, a number of farming practices are used to reduce costs while optimizing yields.
- Farmers actively use new technologies to minimize pesticide use. For example, global positioning systems (GPS) for tractor spraying give more coverage per tank and limit overspraying of areas, spray nozzles with automatic sensors prevent repeat applications and wick technology eliminates broad application by simply touching the top of weeds in the application area.

III. THE LINK BETWEEN HUMAN CANCER AND PESTICIDES

The International Agency for Research on Cancer (IARC), which evaluates the carcinogenic risk of individual chemicals using laboratory, toxicological and epidemiological evidence, has concluded that some substances used in agricultural pesticides are known, probable or possible carcinogens. For example, IARC has determined ethylene oxide causes cancer, captafol as probably causing cancer and atrazine as possibly causing cancer.**(5, 6)**

Similarly, the US National Toxicology Program has classified a number of active ingredients in pesticides as "reasonably anticipated to be a human carcinogen".**(7)** The US Environmental Protection Agency (EPA) also conducts and reports on health and environmental risk assessments as part of its regulation of pesticides in the US.**(8)**

The epidemiological research to date has shown some links, albeit weak associations, between pesticides and Hodgkin lymphoma **(9)**, non-Hodgkin lymphoma **(10)**, leukemia **(11)**, prostate cancer **(12)**, kidney cancer **(13)**, brain cancer **(14)**, multiple myeloma **(15)** and lung cancer **(16)**. Research suggests that exposure to organochlorines possibly contributes to an increased risk for non-Hodgkin lymphoma, no risk for breast cancer, and unknown risk for testicular and pancreatic cancer.**(17)** However, most of the population-based research remains uncertain about the pesticide association with most cancers, particularly with regard to the specific role of pesticides.

> *Epidemiological evidence in adults*

The strongest evidence of cancer risk is from populations regularly exposed to pesticides, such as manufacturing workers, farmers and pesticide applicators. Studies since 1980 on cancer incidence and death among farmers suggest that this population, despite lower mortality for many causes of death including cancer overall has a slightly higher than average risk of developing Hodgkin lymphoma, non-Hodgkin lymphoma, leukemia, multiple myeloma, prostate and brain cancer.**(9-12, 14, 15)** For example, the Agricultural Health Study in the US followed pesticide applicators for nearly seven years and found an excess incidence of prostate and lung cancer in the group.**(16, 18)** A review of farmers and farm workers suggests that there is an increased risk of myeloid leukemia associated with occupational pesticide exposure in this group.**(11)** In a review of cancer among agricultural populations, Blair and Beane Freeman **(19)** note that the literature shows links between pesticides and several cancers in different agricultural populations. In agricultural communities, farmers and farm workers are likely to be exposed during the application of pesticides or when they re-enter a treated area. Families of farmers and farm workers can be exposed when pesticide residues on skin, clothes or equipment are brought into the home.**(20)**

Studies on migrant farm workers, gardeners, pesticide manufacturers, applicators and golf course superintendents also suggest that there may be a possible relationship between pesticides and cancer. Migrant and seasonal farm workers have been found to have a higher number of stomach cancer deaths **(21-23)**, while golf course superintendents have elevated mortality rates from non-Hodgkin lymphoma, brain and prostate cancer **(24)**. However, results of these occupational studies continue to be less convincing than studies on farmers.

The evidence regarding cancer risk in other populations is further limited. Studies on non-occupational exposures have examined farm workers' families and people living in agricultural communities, such as bystanders. Bystanders are individuals who live, work or play near areas where pesticides are used. As such, they can be exposed to pesticides through the air they breathe, water they drink, food they eat or objects they touch in the vicinity of treated areas. Higher levels of agricultural pesticides in farm homes suggests that exposure from farm workers can serve as a source of exposure for farm families.**(20)** Other non-occupational exposures can include indirect exposure in the community through pesticide drift **(25)**, consumption of pesticide residues on food and in water, and pesticides applied in the home or found in house dust.

Dr Aaron Blair from the National Cancer Institute in the US presented the evidence regarding the association between pesticides and cancer. Pesticides, he explained, may cause cancer in animals or humans in multiple ways, including genotoxicity, immunotoxicity and cell proliferation. An important finding from bioassays is that pesticides that have been shown to cause cancer in studies of laboratory animals do not fall into any one chemical class. This suggests that each pesticide needs to be carefully evaluated for cancer risk and that decisions cannot be made on chemical class.

Dr Blair stated that while there have been studies of cancer incidence and mortality in farmers since the early 1980s, most do not characterize exposure very precisely, let alone identify the types of pesticide used. Findings from two meta-analyses of cancer incidence and mortality among farmers show consistent higher risks for leukemia, lip and prostate cancers.**(26, 27)** Possible increased risks for non-Hodgkin lymphoma, myeloma, and cancers of the skin, stomach, brain and connective tissues have also been found.**(26)**

In meta-analyses of studies of individual cancers, there have been consistent elevated risks for the same cancers, although the relative risk estimates tend to be small. Migrant and seasonal farm workers have increased risks of some cancers, including stomach cancers.**(21-23)** According to Dr Blair, the total cancer picture for this group looks slightly different than that for farmers. Contrary to expectations, commercial pest applicators have no significantly elevated risks for many cancers compared to farmers.**(28, 29)** Dr Blair said that studies of non-farmers exposed to pesticides occupationally show elevated risk for leukemia, brain and prostate cancers (19), although the evidence is less consistent and compelling than what has been found for farmers.

He explained that there are numerous case-control studies that show some increased risk but the results are not consistent. For example, farmers' risk of non-Hodgkin lymphoma from exposure to 2,4-D has been found to increase when the pesticide is applied for more than 21 days per year.(30-32) However, a similar response to duration of application was not seen in an earlier study.(33) It is important to consider factors such as the frequency of changing clothes one or more days after handling pesticides because this behaviour has an impact on the exposure.

Dr Blair described the ongoing Agricultural Health Study (34) in the US, which is designed to evaluate exposure to pesticides and risk of various diseases, including cancer. The study of 90,000 participants includes farm operators and owners in addition to their families, and a small group of commercial pesticide applicators. The study categorizes private applicators by quartiles of exposure to different pesticides and examines the dose-response association. Thus far, the study shows a lack of association between cancer and atrazine but some excess risk for leukemia and myeloma with alachlor.(19)

Dr Mary Ward from the US National Cancer Institute discussed the evidence regarding non-occupational pesticide exposure and cancer risk in adults. This category of exposure includes bystander, dietary and indoor residential exposure to pesticides. To date, most studies of non-occupational exposure to pesticides have examined breast cancer and exposure to organochlorines. The category of organichlorines includes pesticides such as DDT (dichlorodiphenyltrichloroethane), dicofol, heptachlor, endosulfan, chlordane, mirex and pentachlorophenol.

Dr Ward explained that the main source of non-occupational exposure to organochlorines for the general population in developed countries is dietary intake of persistent residues, with fish being a major contributor.(35) For less persistent pesticides, the main routes of exposure are through pest control (in gardens or on lawns) as well as some exposure from the treatment of public lands and through agricultural drift.

According to Dr Ward, pesticides have also been detected in drinking water. A 1990 US EPA survey found that 10.4% of community water system wells and 4.2% of rural domestic wells contained one or more pesticides.(36) In one study, water samples from 27 of 29 cities were found to contain between two and nine different pesticides, while 14.1 million people were serviced by drinking water that was contaminated with five herbicides.(37) Nevertheless, the association between exposure to pesticides through drinking water and cancer risk has not been well-studied.

Like occupational exposure, most environmental exposure to pesticides is through the skin, although historically, dietary intake was an important route of exposure for organochlorine pesticides like DDT, which bioaccumulate through the food chain. Dr Ward presented the results of a 1990 EPA survey, which indicated that 82% of American households use pesticides; 66% treat their primary living areas once a year; and the application rate per acre for lawns is often greater than that for agricultural land.**(38)**

Dr Ward noted that the evidence for DDT and its breakdown product, DDE (dichlorodiphenyldichloroethylene), does not support the increased incidence of breast cancer, although the timing of exposure might be important (i.e. childhood exposure increases risk). For other organochlorines, the evidence is largely negative and inconsistent. She added that atrazine has been linked to hormonal changes in wildlife.**(39)**

She added that several studies have evaluated serum levels of persistent organochlorine pesticides and other cancer sites. Endometrial cancer was not associated with 10 different organochlorines **(40)**, while DDT showed a significantly elevated risk for pancreatic cancer.**(41)** Similarly, testicular cancer in servicemen has shown some positive associations with exposure to chlordane and DDE.**(42)**

Dr Ward described a study of self-reported pesticide use and breast cancer in which a modest increase in the risk of cancer was found for weed and insect treatments while indoor pest control was not associated with risk.**(43)** Elevated dust levels of 2,4-D and dicamba were not associated with cancer risk in a study of non-Hodgkin lymphoma.**(44)** Self-reported termite treatment of the home showed a 1.3 times increased risk. Risk was also elevated in homes with higher concentrations of chlordane in dust samples and was increased threefold among those whose homes had past termite treatments and had the highest chlordane concentrations. It was noted that chlordane was the major active ingredient in termite control products in the United States before it was banned in the 1980s.

Residential exposure to agricultural pesticides can occur through primary drift (the off-target site movement of spray droplets before deposition, also called *spray drift*) or secondary drift (the movement of a pesticide after deposition). Exposure can also occur through pesticide contamination of surface and groundwater. Unfortunately, very few cancers have been studied in the context of primary and secondary drift and through the drinking water route of exposure. Dr Ward claimed that the few studies that are available do not have detailed exposure information or do not identify specific pesticides. California’s Pesticide Use Reporting Database **(44)** has shown higher mortality from pancreatic cancer in zip codes where pesticides were used.**(45)**

Ongoing studies using California's unique pesticides database should provide further insights into non-occupational exposure to agricultural pesticides and cancer in the general population.

The Total Diet Study **(46)** is an ongoing collaborative effort since 1969 that examines the level of chemicals in foods prepared for consumption. **Dr Thea Rawn** from Health Canada's Health Products and Food Branch explained that while the study was originally aimed at detecting persistent organochlorine compounds, it has been expanded to look at other compounds, including levels of organophosphate pesticides as well as natural toxins and nutrients. The Total Diet Study provides data on concentrations of a variety of chemical classes that can be found in foods consumed by Canadians. These data are used for dietary exposure assessment and to establish whether concentrations are below maximum residue limits[†] (MRL).

As part of the Total Diet Study, imported and domestic foods that are raw, unprepared and prepared are collected by the Canadian Food Inspection Agency (CFIA) from four grocery stores and fast-food restaurants from a different city every year. The focus is on urban centres, and the type of foods collected changes over time as Canadian diets change. The data from the study can be used for trend analysis and for estimating the dietary intake of various chemicals. Prepared food samples are analyzed for approximately 70 pesticide compounds, including major insecticide classes and representative herbicides and fungicides. Dr Rawn presented some key results and observations of the Total Diet Study:

- While pesticides are detected in food, their concentration is quite low and varies with the type of food.
- MRLs are rarely exceeded; the annual variation in levels of pesticide residues in food is due to a number of contributing factors such as weather, control of active pest infestations and source of the food.
- Of the food composite samples reported in recent years, none were free of residues, only two had levels exceeding MRLs, nine had more than 30 pesticides present at low concentrations, and 13 had less than 10 pesticides detected.

Dr Rawn summarized that while pesticides are present in foods, particularly vegetables and fruit, not all samples have all pesticides. More importantly, most pesticide residues which are detected are in low concentrations (i.e. in the order of parts per billion), MRLs are rarely exceeded and the acceptable daily exposure amounts are not exceeded.

[†] the maximum amount of pesticide legally permitted to remain on food sold in Canada and established by Health Canada's Pest Management Regulatory Agency

> *Epidemiological evidence in children*

Childhood exposures to pesticides typically come from in and around the home and school, residues in food and water, airborne drift from agricultural and residential use, and residues brought into the home by parents exposed to pesticides at their workplace. Children may be more vulnerable to pesticide exposure than other people because of their rapidly growing and developing bodies as well as the unique ways they can be exposed.**(47)** Children are at risk of being exposed to higher levels of pesticides than adults from crawling and playing in grass or gardens that have been treated with pesticides. Greater amounts may be inhaled, absorbed directly through the skin and ingested from putting their hands in their mouths.

While the research is limited, reviews of pesticide and childhood cancers suggest a possible link with leukemia, brain cancer and non-Hodgkin lymphoma.**(48)** There is also evidence that children with parents who work with pesticides may have a small increase in their risk of non-Hodgkin lymphoma.**(49)**

Dr Peggy Reynolds from the Northern California Cancer Center discussed the evidence regarding pesticides and childhood cancer. She highlighted a number of case-control studies that suggest an association between childhood cancer and either household pesticide use or having a parent employed in the agricultural industry. She explained that these studies have a number of limitations, including limited information about residential proximity to pesticide application, non-specific pesticide information, and potential case-response bias as a result of variable recall of exposures.

California is an area of heavy pesticide use, and the state has legislated a comprehensive agricultural pesticide-use reporting system. Under the system, the active ingredient and amount of pesicide applied, the pesticide treatment location, date and method of application, type of crop, and number of acres treated must be reported.**(44)** The system is based on approximate square-mile reporting, which allows researchers to study the intensity of application at any point in time for a given pesticide within a defined geographic areas.

Using geographic information system (GIS) techniques, a statewide ecologic study of childhood cancer **(50)** in California was conducted along with a case-control study **(51)** that examined early childhood cancer and agricultural pesticide application. A follow-up large, multi-centre, case-control study of childhood leukemia is currently underway in Northern California.

The Northern California Childhood Leukemia Study, a case-control study between 1995 and 2009, includes household dust collection, in-home interviews and lifetime residential histories. The study has suggested higher leukemia risk with household pesticide use and also points to potential effects of in utero exposure.(52) Analyses are currently underway as part of this study to address the question of whether childhood leukemia risks are higher for children living in high agricultural pesticide-use areas at different points in their lives, based on the lifetime residential histories of participating families.

Dr Alex Lu from the Harvard School of Public Health described the Children's Pesticide Exposure Study (53), a longitudinal exposure assessment study that looked at dietary intake of urban and suburban school-age children in Seattle (Washington) and Atlanta (Georgia). Major findings were:

- Dietary intake of organophosphates contributes the majority of exposure in urban and suburban children. Levels of dietary intake vary with season, with higher urinary metabolite levels in the summer compared to the fall. Elevated levels observed in the winter could be attributable to imported food.
- Dietary intake contributes only a portion of the total pesticide intake, with another portion stemming from residential use of pesticides.
- Longitudinal studies that use biomarkers lend more confidence to conclusions drawn from cross-sectional measurements.

The study showed that an organic diet provides a substantial and immediate protection against exposures to organophosphorus pesticides that are commonly used in agriculture.

IV. REGULATION OF PESTICIDES IN CANADA

All three levels of government (federal, provincial/territorial and municipal) share the responsibility of regulating pesticides. Canada's federal legislation for pesticide regulations resides in Health Canada's Pest Management Regulatory Agency (PMRA), which regulates pesticides under the Pest Control Products Act and Regulations. The Agency is responsible for protecting human health and the environment from risks associated with pesticides. Its activities include:

- pre-market reviews through evaluation of the health, environmental, chemical and efficacy data for pesticides
- registering (approving) pesticides for import, sale and use
- re-evaluating registered pesticides
- setting MRLs under the Food and Drugs Act
- post-registration oversight

Other activities of the PMRA include:

- putting in place policy and programs that focus on alternatives to pesticides to reduce risk (e.g. integrated pest management) and minimize environmental contamination (e.g. identifying proper buffer zones) **(54)**
- working with other government departments (e.g. Canadian Food Inspection Agency, Environment Canada, Department of Fisheries and Oceans, Agriculture and Agri-food Canada), provinces and territories on pesticide-related issues (e.g. monitoring compliance with pesticide regulations)
- international initiatives that aim to ensure pesticide safety and reduce risk (e.g. through the North American Free Trade Agreement , the Organisation for Economic Cooperation and Development [OECD], and the international Persistent Organic Pollutants [POPs] and Prior Informed Consent [PIC] policies) **(55)**

When a pesticide is registered and approved for import, sale and use, the PMRA has determined that the product does not pose unacceptable health or environmental risks and that it serves a useful purpose. According to the PMRA, this means the product can be used safely if used according to its detailed instructions on the product label.

Dr Connie Moase from PMRA indicated that international pesticide testing protocols have been in place since the early 1980s. These protocols were developed and are periodically revised by member countries within the OECD.

She said that most of the toxicity information PMRA works with is on the active ingredient of the pesticide; only limited toxicity data are available on the mixtures in the end product. However, information to assess the amount of potential dietary and occupational exposure is based on the end products.

Dr Moase explained that for a new pesticide to be registered, PMRA examines more than 200 studies for its health, environment and value assessments. The onus is on the applicant to provide toxicological, occupational and other studies that follow international guidelines and are based on sound scientific principles. Evaluators also receive the raw data in order to conduct their own analyses.

PMRA looks for hazards, including acute effects, birth defects and neurotoxicity, and evaluates genotoxic and carcinogenic potential. When available, epidemiological data are also considered. In vivo and in vitro mutagenic tests are examined in addition to metabolic studies to understand how a chemical behaves in the body. PMRA also examines the potential for endocrine disruption in reproductive toxicity studies, which are regarded as one of the most comprehensive studies available to assess the potential for these effects. Animal toxicity studies compare effects across different mammalian species in order to assess similarity and consistency of effects. Other data that address relevance to human health are also considered.

Dr Moase stated that the non-toxic level in the most sensitive species is the basis for setting acceptable levels for human exposure. This no-effect level is divided by safety factors to set the acceptable exposure level. Safety factors are applied to non-toxic levels noted in animal toxicity testing in order to compensate for the extrapolation from animals to human health. The acceptable level of human exposure includes a hundredfold safety factor and a further tenfold factor when considering children. Thus, the acceptable level for human exposure is generally at least 100 to 1000 times lower than the non-toxic level in animals.

Risk is then determined by considering both toxicity and exposure. Potential exposure to a chemical, measured as the sum of dietary and non-dietary exposure, is estimated and compared to the acceptable level of human exposure[‡]. Pesticides are registered only if the level of human exposure is within the acceptable level of exposure, established as described above – i.e. the risk is “acceptable”.

[‡] exposure levels tend to be overestimated, particularly in the case of children and other sensitive populations, to be protective

In the case of a carcinogenic effect, if a threshold dose is not identified, animal toxicity data are statistically modelled to predict the likelihood of developing cancer over a lifetime. Generally a risk level of one in a hundred thousand up to one in a million is considered negligible for pesticide approval.

Dr Moase noted that, as of September 2008, 75% of the 401 pesticides registered prior to 1995 have been reviewed through the Re-evaluation of Pesticides Program, which re-evaluates registered pesticides on a 15-year cycle from when they were first registered.

The Canadian Food Inspection Agency (CFIA) monitors – through both random sampling and collection of data – pesticide levels on domestic and imported food to determine whether pesticide residues fall within the MRLs set by PMRA. The Agency also does targeted monitoring or directed sampling. This is done when certain shipments of vegetables or fruit are suspected to be non-compliant with set MRLs.

Dr Robert Charlebois from the Food Safety Division of the Canadian Food Inspection Agency spoke about how CFIA enforces the Food and Drugs Act. Published MRLs apply to both raw agricultural products and manufactured foods.

- MRLs are the maximum amount of pesticide residue legally permitted to remain on food sold in Canada. Dr Charlebois noted that because there is a large, built-in safety margin in the MRL, it does not necessarily mean that there is a potential health risk when there is non-compliance with MRLs.
- Dr Charlebois stated that monitoring of commodities over the years has shown a consistent compliance rate of up to 99.5% for domestic products, while the compliance rate of imports has hovered at 99% or above. The small number of non-compliant products was still well below the potential health risk, and in the vast majority of those, only one residue was detected.
- No residues are detected in 90% of Canadian and 89% of imported vegetables and fruit, he said.

CFIA conducts a significant amount of testing using different types of sampling approaches, such as:

- *Random monitoring*, the most common sampling approach, verifies compliance to the levels set by Health Canada in random samples chosen at different times of the year and from different locations as they are sold.

- *Targeted sampling* occurs if there are some indications of abnormal residue levels in some food (e.g. produce). For targeted samples, CFIA expects to find higher non-compliance rates.
- *Compliance and legal sampling* occurs when there is high suspicion of residues, and this approach usually confirms that suspicion.
- *Special* or *pilot surveys* are conducted to focus on certain produce.
- *Blitzes* are random sampling events over the short-term.

CFIA's monitoring activities are based on the principles of the Codex Alimentarius Commission **(56)**, which was created in 1963 by the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) to develop food standards, guidelines and related texts such as codes of practice under the Joint FAO/WHO Food Standards Programme. The main purposes of this joint effort are protecting health of the consumers and ensuring fair trade practices in the food trade, and promoting coordination of all food standards work undertaken by international governmental and non-governmental organizations.

Dr Charlebois noted that CFIA's National Chemical Residue Monitoring Program selects the sampling of specific foods and for particular types of residues based on their potential risk. CFIA tests all types of food, with no separate profile for organic food. The method of sampling is reviewed every year, using previous years' results to adapt the method whenever necessary. Every sample is statistically randomized, with the sampling schedule itself being random. CFIA's methods must be validated and are adapted to the purpose for both the residue and the type of food. Dr Charlebois indicated that a multi-residue methodology is preferred, whereby the measurement of up to 200 residues is possible within one sample. When necessary, single-residue testing can also be done. The Monitoring Program is audited regularly by other countries to ensure scientific rigour and valid results. CFIA regularly posts the results of the previous year's evaluation on its website.

V. MONITORING AND CONTROLLING THE HEALTH IMPACTS OF AGRICULTURAL PESTICIDES

Mr Douglas Haines from Health Canada's Risk Management Bureau discussed the biomonitoring of environmental chemicals as part of Health Canada's Chemicals Management Plan. Biomonitoring is the direct measurement of chemicals and their metabolites (their reaction products in people, usually in blood, urine or hair). Health Canada's biomonitoring activities fall under three general themes: national surveys and studies, targeted population studies and biomonitoring-supporting research.

Mr Haines described the Canadian Health Measures Survey (CHMS) **(57)** and the Maternal-Infant Research on Environmental Chemicals (MIREC) study **(58)**, which are two national biomonitoring initiatives.

- CHMS is a general health survey of Canadians to provide benchmark data on indicators of environmental exposures, chronic diseases, infectious diseases, fitness, and nutritional status, as well as related risk factors and protective characteristics.
  - Data are collected in a two-step process which includes a health questionnaire (administered during a home interview) and collection of direct measurements at a mobile clinic. The first cycle of the CHMS, conducted between March 2007 and March 2009, includes a biomonitoring component to measure human levels of environmental chemicals in a sample that represents the overall Canadian population.
  - Five thousand randomly selected Canadians between the ages of six and 79 years are tested at 15 collection sites.
  - Blood and urine specimens are collected from the participants and analyzed for approximately 91 different environmental chemicals or metabolites or both, including organochlorine, organophosphate, phenoxy herbicides, and pyrethroid pesticides and their metabolites.
  - Cycle 2 of the survey, to be conducted between 2009 and 2011, will include children ages three to five.
- MIREC is a national five-year study measuring the extent to which pregnant women and their babies are exposed to environmental chemicals, assessing what pregnancy health risks, if any, are associated with exposure to heavy metals (lead, mercury, cadmium, arsenic and manganese), and measuring the levels of environmental chemicals and some of the beneficial components (nutritional and immune constituents) of breast milk.
  - Taking place between 2007-2012, it is recruiting approximately 2,000 pregnant women (from 10 collection sites) during their first trimester of pregnancy, and then following them through pregnancy and up to eight weeks after birth.

- Data are collected through a questionnaire, along with samples of maternal urine and blood, cord blood at delivery, and maternal hair and milk post-partum.
- Organochlorine and organophosphate pesticides are among the many chemicals to be analyzed.
- Initial MIREC results are expected in 2012.

Targeted population studies, Mr Haines said, include the Northern Contaminants Program and the Canada-USA-Mexico Maternal Blood Contaminant Study. The Northern Contaminants Program's biomonitoring research has tracked Northerners' exposure to environmental chemicals, particularly POPs and metals, since the early 1990s. Two Northern Contaminants Program reports have been published (1997 and 2003) and the next report (due in spring 2009)again focuses on persistent organic pollutants and metals. Biomonitoring supporting research is undertaken to advance biomonitoring scientific methods and techniques and to develop tools to better understand, interpret and communicate biomonitoring results.

While pesticide biomonitoring provides general population exposure data integrated from all sources and can track trends over time, it does not target specific exposure scenarios or high-exposure populations. Biomonitoring is also limited by high laboratory costs. However, Mr Haiens noted these national-level surveys will be the first comprehensive national biomonitoring studies in Canada and will provide important baseline data for comparison with subpopulations and with other countries.

> Occupational health and safety policies

Mr Rex Eaton, who has served with WorkSafeBC, discussed the program's initiatives as a means to address pesticide safety on the farm. He outlined occupational health and safety policies aimed at reducing pesticide exposure to farm workers. WorkSafeBC developed a pesticide exposure index from its determination of pesticide application and labour intensity factors for each of eight study regions in the province of British Columbia. WorkSafeBC has a special occupational disease unit that can draw on occupational health physician and hygienist expertise to assist with health claims. Among other things, they may conduct exposure assessments at the workplace as well as literature searches to try to resolve claims.

Mr Eaton described six common pesticide application techniques, ranging from handheld units to aerial spraying, each with varying levels of exposure risk. Operating pressure and the position of the spray pattern relative to the worker are just two of the risk factors considered when assessing exposure potential, he said. For pesticides that meet criteria in the WorkSafeBC regulation for carcinogenicity, sensitization or reproductive toxicity, employers are required, where practical, to substitute a material that reduces the risk to workers, for example, by using a less toxic pesticide or eliminating pesticide use. This requirement applies to about 16 pesticides. Mr Eaton explained that WorkSafeBC relies on the employer to search out available information on a product as part of a worker's right to know about pesticide hazards and protective measures.

The occupational health and safety regulation in British Columbia provides three levels of protection to address risk of exposure:

i) core requirements that address responsibilities and programs for employers, suppliers and workers
ii) chemical and biological safety requirements that cover all hazardous materials, and
iii) a set of requirements specific to pesticides not addressed by the previous requirements.

Mr Eaton stated that WorkSafeBC requires applicators, including farmers, to be certified if they apply moderately or very toxic pesticides, and to use applicable re-entry intervals for pesticide-treated areas.

VI. INTERNATIONAL EXPERIENCE WITH PESTICIDES AND CANCER

Dr Angelo Moretto from the International Centre for Pesticides and Health Prevention and the University of Milano briefly recounted the history of the Joint Meeting on Pesticide Residues (JMPR) of the FAO and WHO. The JMPR acts in an advisory capacity to the FAO, specifically with regard to the Codex Alimentarius. The Codex Alimentarius is a collection of internationally recognized standards, codes of practice, guidelines and other recommendations relating to foods, food production and food safety.

Officially convened in 1961, the JMPR is a committee of experts that meets yearly to assess all available data on pesticide residues. The JMPR's members belong to regulatory bodies, research institutions and academia from around the world. The group does not work within a fixed region, is not governed by international laws and makes decisions based on the best available science.

The JMPR is similar to national regulatory bodies such as Canada's PMRA in that it examines the scientific literature as well as biochemical and toxicological data from product manufacturers in order to characterize the toxicological hazard and assess the risk of a pesticide. In its characterization of an active substance, the JMPR first determines the critical toxicity end points. It then determines the *no-observed-adverse-effect level* for such an end point, and subsequently applies an appropriate safety factor to arrive at an *accepted daily intake* and the more recently defined *acute reference dose*.

In 1990, the JMPR published *Principles for the Toxicological Assessment of Pesticide Residues in Food*, which is currently being updated. The JMPR also produces three books annually that detail its findings – a summary report presents basic conclusions, another report provides pesticide residue assessments and definitions, and another one details the toxicological evaluations as a monograph for each active substance. Dr Moretto stated that in the last 10 years, the JMPR has examined more than 80 active substances and found that all were unlikely to pose a cancer risk to humans.

> Biomonitoring of pesticide exposure in the US

Dr Bryan Williams from the Centers for Disease Control and Prevention (CDC) described the major biomonitoring initiatives of the CDC, which include the National Report on Human Exposure to Environmental Chemicals **(59)**, large-scale cohort studies and smaller hypothesis-generating studies. Data for the biennial National Report is collected through the National Health and Nutrition Examination Survey (NHANES). He said that the National Report is an assessment of the exposure and prevalence of the US population to 75 out of 250 selected environmental chemicals.

Dr Williams explained that the NHANES did not initially monitor environmental chemicals in 1971 when the survey was first started, but currently examines approximately 250 chemical agents, including organophosphates, herbicides, repellents, fungicides and fumigants, in its annual surveys of about 5,000 people including children under the age of three. The survey also looks at organophosphate metabolite detection frequency over time.

Results from NHANES suggest overall exposures to organophosphate pesticides have declined over time, but the most vulnerable populations, including children and elderly adults, appear to be increasingly exposed. Dr Williams said that although NHANES biomonitoring data are useful for following trends in exposure, they must be regarded critically.

> *Policies and practices for reducing pesticide exposure in Europe*

Dr Nathalie Röbbel from the WHO Regional Office for Europe described the Children's Environment and Health Action Plan for Europe (CEHAPE) as a science-based political commitment that defines four regional priority goals. The fourth goal, which is the most relevant for pesticides and also covers a wide range of hazardous chemicals and physical agents, addresses concerns around exposure in the occupational setting as well as during pregnancy, childhood and adolescence.

Dr Röbbel described the risk assessment tools which include the Environment and Health Performance Reviews that determine who is doing what in terms of regulation and monitoring in member states. The risk management tools CEHAPE uses include WHO norms and standards (e.g. Codex Alimentarius food standards) and the CEHAPE "action pack", which details the actions that policy-makers can implement. The action pack provides scientific evidence for actions as well as a collection of case studies.

The WHO is also partnering with the International Union of Pure and Applied Chemistry in a project to educate school children about safety and protecting themselves from pesticides and hazardous chemicals. Thus, Dr Röbbel underlined the importance of working with new stakeholders, including youth, and strengthening intersectoral collaboration.

Ms Genon Jensen from Health and Environment Alliance (HEAL) addressed European approaches to promoting precautionary policies for reducing pesticide exposure. Created in 2003 out of the European Public Health Alliance, she explained that HEAL has a broad and diverse membership of more than 60 organizations from 22 countries. Most of its work is done through working groups that review policies and make recommendations. One of HEAL's key missions is to monitor environmental health concerns and advocate for those concerns and evidence to be put at the centre of European environmental policy.

One such issue is the cut-off criteria to prohibit the sale and use of pesticides that are potentially carcinogenic, cause mutation or reproductive damage, or are endocrine disruptors, immunotoxins or developmental neurotoxins. Ms Jensen said that the precautionary approach towards this cut-off in the European Union's pesticide reform has been criticized, yet a European Parliament study estimated that 26 billion euros could be saved in health costs by eliminating some of the currently used pesticides, such as chlorpyrifos and 2,4-D.

She presented examples of pesticides policies from several European countries. Following widespread government and public support for pesticide reduction, Denmark has adopted a precautionary approach since the 1980s. The country achieved dramatic reductions through farmer training programs and by implementing a pesticide tax, establishing indicators for monitoring and reporting on success. France, the largest pesticide consumer in the European Union, has a goal to reduce pesticide use by 50% by 2018 and remove 53 pesticides from its market by the end of 2008. Another example is the Co-operative Group in the United Kingdom, which prohibits and restricts the use of certain pesticides but provides farmers with alternatives and training. Finally, the German grocery chain, Lidl, has policies in place that encourage suppliers to reduce pesticide use.

Ms Jensen also highlighted work by public interest and community groups to involve the scientific field in the policy-making process and increase public participation in regulating pesticides. The HEAL pesticides and cancer campaign is part of a European initiative to raise awareness of links between pesticides and cancer, with most activities in France and in the UK.

VII. ALTERNATIVES TO PESTICIDES IN AGRICULTURE

> *Biological control*

Dr Rene Van Acker from the University of Guelph explained that one alternative to chemical pesticides is classical, or inundative, biological control. Classical biocontrol can be effective – for example, flea beetles are used to control leafy spurge – but this alternative pest control practice is about establishing a new balance between pests and the biological control rather than eliminating the pest. Specific biocontrol agents exist for specific weeds; while this can work in non-crop areas, it is not a good solution for agricultural fields that have multiple weed species.

He outlined the benefits of using biocontrol agents and threshold levels for insect pests and disease, but he said biocontrol is not practical for weeds, since weed seed banks tend not to fluctuate. He suggested that biocontrol options are greater for vegetable and fruit crops (especially greenhouse production) compared to field crops, which are often grown on large acreages. Inundative biocontrol, such as the use of biological pesticides and mycoherbicides, is designed for high and rapid efficacy, year after year, to avoid yield losses, but there really are no effective broad spectrum inundative biocontrols available for weed control in field crops.

Dr Van Acker highlighted the work of the Pesticide Action Network, an international organization that focuses on sharing knowledge on pesticides. As an information clearinghouse, it provides information on pest species biology, critical control points, competitive crops and crop genetic resistance. He noted that farmers sometimes try to address genetic resistance of pests by using multiple tools, including crop rotation and the use of different pest control products from year to year. He suggested that the current low-dose chemical pesticides should be included in alternatives.

Dr Van Acker claimed that present-day agriculture developed out of a “seed, spray and harvest” philosophy of old. He emphasized that crop rotations are a key practice in reducing pesticides, while also reducing energy use and carbon emissions. He stated that the barriers to adoption of crop rotations include a lack of knowledge, suitable equipment, cash flow and time. Furthermore, he said that the current farm support system does not reward innovation. Dr Van Acker emphasized that the agriculture system that we see is the system that society drives through its choices and policies. He stressed that we cannot simply eliminate pesticides as pest management tools for farmers the way we have done for cosmetic purposes in home lawns and gardens. Our agricultural system is designed to depend to some extent on pesticide use, he said. There are ways and means of reducing pesticide use and there are choices of pesticides that are safer to use, but elimination would require fundamental and massive changes in the way we live, he claimed. Dr Van Acker stated that it would take big changes and significant costs on society's part to eliminate pesticides from agriculture.

> *Organic farming*

Some of the reasons why farmers farm organically are land stewardship and ecological sustainability, chemical avoidance for farm workers and their families, economic considerations (e.g. reduction of input costs) and improved market access. A review by Badgley et al **(60)** found that yield ratios are comparable for organic and conventional agriculture in developed countries and higher for organic food categories in the developing world.

In speaking about organic farming, **Dr Andrew Hammermeister** from the Organic Agriculture Centre of Canada at the Nova Scotia Agricultural College stated that nature is efficient in terms of nutrient use, with low levels of inputs, natural nutrient inputs and higher diversity relative to monoculture cropping systems. These conditions, combined with the evolution of uncultivated species, have led to relatively high resistance to pest pressure. In contrast, agricultural systems are generally high-input monoculture systems, which allow rapid spread and evolution of pests, and potentially more lush plant growth, which can be more susceptible to pest pressure. Among agricultural systems, he said that organic agricultural systems tend to have lower fertility levels (especially nitrogen) and higher biodiversity (longer and more diverse rotations accompanied by some intercropping), creating a condition of lower risk to pest pressure than in conventional agriculture (in the absence of pesticide use).

Dr Hammermeister explained that the principles of organic agriculture are not that dissimilar from conventional agriculture – the difference is in how those principles are applied. Organic farming is not about what not to use but about what farmers should be doing to ensure healthy soil and crops. Features of organic farming include:

- the prohibition of the use of synthetic pesticides, instead requiring a pest management plan including cultural controls (such as rotations, resistant crop selection, planting density, planting timing), mechanical controls or substances permitted for use in organic agriculture
- a proactive and prescriptive approach to building soil fertility, which prohibits synthetic fertilizers and promotes practices such as rotations with legumes, composts and manures to build soil fertility
- the prohibition of the use of antibiotics, genetic engineering and nanotechnology
- the use of only 30 of the 500 food additives permitted in non-organic processing

Dr Hammermeister explained that farmers who convert to organic farming have a three-year transition period before they can be certified organic. Independent inspectors ensure compliance and make recommendations to certifying bodies. Certifying bodies may be regional, national or international in scope and are accredited by independent organizations.

He further highlighted that the concentration and frequency of single or multiple pesticide residues are lower on organic produce than on conventional produce. However, the absence of pesticides cannot be guaranteed because there may be residues in the soil prior to an organic farming transition and chemical spray drift from conventional farm operations and atmospheric deposition cannot be controlled for.

Dr Hammermeister concluded by saying that recent global analysis has shown that organic farming systems can sustainably feed the world population.

VIII. GAINING A BETTER UNDERSTANDING OF THE LINK BETWEEN CANCER AND PESTICIDES

Dr Barnett Kramer from US National Institutes of Health spoke about weighing evidence. He said that five questions are typically asked in every risk assessment study:

- What is the exposure and the outcome of that exposure?
- How certain is it that the exposure causes the outcome?
- How important is the outcome?
- How big is the effect?
- To whom does it apply?

An analytical framework frames the questions and helps determine the target population. But since there is limited evidence linking target populations to the outcome, end points that are linked to health outcomes are considered. End points can supplant the outcome to infer the same conclusions but require stringent criteria for acceptance.

The public responds differently upon hearing the same information presented in relative versus absolute terms. Health authorities sometimes present relative risk ratios even though absolute risk is more indicative of the real risk. Dr Kramer also said that sometimes regulators have to make decisions without all the evidence. He emphasized that how much evidence there is and where it is coming from are important to know.

> Limitations of current research on pesticides and cancer

While the research on pesticides and cancer is growing and helping us better understand this relation, there are methodological limitations to the research. **Dr Aaron Blair** explained that, in general, epidemiological studies of cancer and pesticides are limited by confounding factors and misclassification. Although confounding is a concern, misclassification may be a greater problem. Misclassification can be differential or non-differential in case-control studies, but it is largely non-differential in cohort studies. Non-differential misclassification of exposure would tend to bias estimates of relative risk toward the null value and result in false-negative findings. Additionally, many occupational studies have limited sample size and short follow-up of cohorts. He said that most studies have not looked at particular chemicals in relation to specific cancers because doing so would dilute observed effects.

Dr Blair said that while having information on the delivered dose is one strength of animal experiments, it is rarely available for epidemiological studies, except when measured for organochlorines and other fat-soluble pesticides. Differences between humans and experimental animals complicate extrapolation of findings from bioassays and experimental studies to humans.

He noted that animal and human epidemiologic studies complement each other and both make important contributions to our understanding on pesticide risks in humans.

Timing of exposure in relation to age may be crucial for risk. For example, childhood cancer risk is higher despite lower exposure levels. It was agreed that most exposure for farm owner-operators comes at a young age but knowledge of its impact at later stages of life is unknown. Dr Blair said that biomonitoring surveys can be an indicator of what population exposure levels might be and can provide direction for more targeted research, especially in vulnerable populations.

Dr Vincent Cogliano from IARC further elaborated on the fact that childhood cancer risk can mean an effect manifested during childhood or early life exposure that can contribute to effects later in life. The EPA has determined that cancer risks can be 10 times higher for children under the age of two and three times higher for children between the ages of two and 16.

He said that differences in children's capacity to metabolize and clear chemicals, more frequent cell division during development and children's lower ability to repair DNA damage compared to adults could account for the higher cancer risk observed. Furthermore, children's immune systems are not fully functional and their hormonal systems operate at different levels.

Risk characterization considers the various dimensions of risk, such as hazard, dose-response and exposure. Exposure can occur through multiple pathways that differ from urban to rural environments. A safe level of exposure for food alone may not be protective of cancer when there is exposure through other pathways. Dr Cogliano suggested that it is important to consider other chemicals with common mechanisms that may have additive effects. In bioassays, chemicals are administered one at a time, as this is most practical. People, however, are exposed to multiple chemicals that act through similar mechanisms. Furthermore, inert ingredients, such as solvents and dispersants, that are contained in pesticides may be toxic chemicals in their own right, he said.

In general, only aggregate exposure is estimated to determine levels of exposure. Dr Cogliano explained that the average consumption of a full range of foods is considered, but few people actually fit that pattern of consumption. For instance, some people may eat certain items far more than the average and thus get 10 to 100 times the exposure. Since consumption habits change over time, there are also problems in estimating consumption levels across seasons and over a lifetime. With toxicological data, risk estimates are derived for the average response, and there are individuals of higher and lower susceptibility. Finally, exposure during early life stages is generally not studied in lifetime bioassays. In other words, exposure levels which focus on average pesticide residues can hide some peak exposure periods. Dr Cogliano suggested considering some maximal exposure scenarios to address this issue.

IX. CONCLUSIONS

The information presented by speakers generated much discussion around current research, policies and regulations on pesticides. With regard to research, a number of priorities were identified including:

- the need to look at cumulative, or synergistic, effects of multiple environmental contaminants on cancer, especially given that low-level exposures have become part of our background environment
- the consideration of health risks from pesticides in addition to cancer
- the trade-off between bigger economic gains in agricultural production and the impact on population health from the use of agricultural pesticides
- qualitative and quantitative risk assessments (e.g. in-home interviews and biomonitoring) to provide a more complete picture of cancer risk from pesticides
- the effects of climate change on the use of pesticides and the possible emergence of new pests and diseases in the residential environment

With regard to policies, efforts to reduce agricultural pesticide use need to be balanced with efforts to protect food security, food safety, human health, the environment and the economic stability of farmers and other food producers. Policies must therefore be thoughtful as well as targeted and must address the gaps while keeping in mind the broader picture.

In terms of regulations, it will be important to determine whether pesticide residue levels allowed on domestic and imported foods are low enough and if currently available methods to test for residues are adequate to detect harmful levels. It was clear that regulations need to be based on quality science and should include both hazard and risk assessments. Moreover:

- Information on monitoring results has to be accessible and made understandable, particularly with regard to products with high levels of pesticide residues.
- Information on ways to minimize exposure to agricultural pesticides should be made more widely available to the public and especially to workers. For example, better safety facilities and procedures (e.g. a water source to wash hands after pesticide handling) and modification of behaviour (e.g. changing clothes immediately after handling) are needed.
- Medical doctors should be educated about the potential risks of pesticide exposure and be able to articulate these to their patients
- Medical journalists should appropriately convey the benefits and risks of pesticides use to the public
- Pesticide product labelling and best practices programs for occupational settings should be expanded.

- Farming methods that minimize pesticide use should be developed, including adopting new technologies and promoting innovation.

Ultimately, protecting the health of Canadians is about multiple issues, including cancer prevention, nutrition, as well as food safety, quantity and affordability.

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