Lawn and Garden Pesticides: A Review of Human Exposure & Health Effects Research

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PREFACE

This report summarizes the evidence concerning how people may be exposed to lawn and garden pesticides and the potential for health effects from that exposure.

As a relatively brief review (despite consulting nearly 300 separate references and reports) of an already highly complex area of scientific evidence, and given resource and time constraints, this research had to be rather precisely circumscribed. An attempt was made to report on studies that investigate the effects from specific lawn and garden pesticides identified as commonly available in Canada. It focuses largely on summarizing the epidemiological literature citing review articles and primary references to case-control and cohort studies found in peer-reviewed scientific journals.

A balance of information is presented to the extent possible, acknowledging that publication and reporting of scientific evidence tends to be inclined towards the reporting of positive results rather than negative results.

It should be noted that the report focuses on health effects of pesticides themselves and leaves for another discussion the questions of the health effects of pest plants and insects (e.g. poison ivy, ragweed, stinging insects). It also leaves for future discussion any risk-benefit analysis of lawn and garden pesticides.

This report updates the information on human health and ecological effects that was summarized in the 1998 report of the Environmental Protection Office of Toronto Public Health, entitled, "Pesticides: A Public Health Perspective" (Toronto Public Health, 1998). The current report therefore updates information and conclusions that were previously published by this office on the issue of lawn and garden pesticides.

In addition, this report is intended as one companion piece to Toronto Public Health's public discussion document, "Playing it Safe: Healthy Choices about Lawn Care Pesticides". The present report provides an expanded discussion of the health effects literature which is only briefly summarized for a lay audience in "Playing it Safe". At its July 16th, 2001 meeting, the Toronto Board of Health requested that the Medical Officer of Health prepare these documents to inform a larger process of public consultation on the issue of pesticide use in Toronto. At its November 6th meeting, Toronto City Council endorsed a plan to engage in a public consultation process on the issue of pesticide reduction on private property in the City of Toronto. Public input is being sought on "strategies to phase out the non-essential[1], outdoor uses of pesticides on private property" in the city. (City of Toronto Council Motion November 6, 2001).

[1] The term "non-essential is used to accord with its use by the Supreme Court of Canada in the recent decision surrounding the municipal pesticide by-law for the town of Hudson, Quebec [114957 Canada Ltée (Spraytech, Société d'arrosage) *v.* Hudson (Town) [2001] SCC 40, File No.: 26937]. We acknowledge that the term is undefined here and that its use and definition are controversial.

EXECUTIVE SUMMARY

Scientific knowledge regarding exposure and the potential for health effects from residential use pesticides is a highly complex area of study that draws on evidence and expertise from a number of different disciplines, including toxicology and epidemiology.

Health Canada's Pest Management Regulatory Agency (PMRA) applies risk assessment methods to evaluate the chance of harm to people and to the environment from all pesticide products for use in Canada. The PMRA follows standards that accord with internationally accepted and available scientific and regulatory approaches and it states that it has adopted many of the advances in the health risk assessment aimed at improving consideration of child-specific vulnerabilities. The PMRA aims to minimize the risks from residential pesticides such that, under intended conditions of use, exposures to non-target living organisms (including humans) will be well below the levels determined to cause no adverse effects in studies on test animals. Risk management is the decision-making or policy step that defines the conditions of a product's registration. The PMRA also specifies the instructions that must be included on a pesticide label and that people (both professional applicators and homeowners) must follow, by law, in order to avoid undue exposure and risk to themselves, to others and to the environment.

The PMRA is conducting priority re-evaluations of the most common active ingredients found in lawn-care pesticides (four insecticides and four herbicides) that incorporate currently accepted evaluation methods. Voluntary phase-outs are already in place for most residential use products containing two insecticides, chlorpyrifos and diazinon. Re-evaluation decisions on the remaining lawn pesticides are expected by the end of 2002.

There is concern that all the potential risks posed by pesticides are not fully predicted by risk assessment approaches. For some health effects or mechanisms of effect (such as immune and endocrine modulation) testing is dependent on scientific methods that are under continual evolution, since these potential health effects have not been thoroughly studied or are newly recognized. It is also the case that some phenomena, such as from exposure to mixtures of different pesticides and other environmental and occupational chemicals, have not been well studied and methods are not yet available to adequately test for effects. The PMRA states that where science is uncertain their standard practice is to incorporate additional safety (or uncertainty) factors to ensure that exposure levels will not pose unreasonable risk to health of people or the environment.

Recent biomonitoring studies in U.S. samples of both adults and children, indicate that exposure to some home-use pesticides is very low. However, for some insecticides, this exposure appears to have been relatively widespread. Exposure does not equate to adverse health effects. Indeed these low exposures have not been associated with health effects in individuals and toxicological studies would predict there should be no observable effects given the very low doses involved. However, there is still some degree of uncertainty about the potential for subtle, long-term effects when children are exposed at sensitive periods of development. Preliminary methods for assessing the potential for cumulative effects from compounds with common mechanisms of toxicity have only recently been developed but are not yet validated and available to regulators.

Toxicological studies are an important foundation for our understanding of the potential for health effects from exposure to pesticides and for establishing reference doses. It has been argued however, that they cannot fully predict the nature and magnitude of the health effects from the real world circumstances of our environmental exposures. These involve long-term, complex exposures to pesticides and other chemicals. The means by which these effects are best assessed is by epidemiological studies, another important tool.

Most studies in humans (epidemiological studies) have sought to examine the risks of long-term health effects associated with pesticide exposures in occupationally exposed groups. It is understood that people who work with pesticides typically have much higher exposure than the general public. As such, the results of occupational studies are not directly reflective of health risks from the general public's use of lawn and garden pesticides. With some exceptions, most epidemiological studies are unable to ascertain the degree to which specific lawn and garden pesticides are linked with the health effects under study.

These studies have assessed the risks of three categories of health effect including, 1) some cancers (especially leukemias, and lymphomas), 2) reproductive effects (including fertility problems, birth defects, adverse pregnancy outcomes such as spontaneous abortions and perinatal mortality) and 3) neurological effects (manifest as polyneuropathy, neuropsychological effects, or neurodegenerative conditions such as Parkinson's disease). Researchers are also examining the possible role of pesticides in immune system suppression and endocrine alterations, although there are relatively limited data from epidemiological studies and most is known from studies in animals and tissue cultures. Epidemiological studies of those exposed occupationally are suggestive that there are moderately increased risks for some health effects in each of these categories that may be associated with exposure to pesticides.

Occupational studies do not adequately inform knowledge of the risks to the young. Limited epidemiological research has also assessed the associations between early exposure to pesticides and long-term effects in children. These studies have shown apparent moderately increased risks of some cancers (leukemia, non-Hodgkin's lymphoma and neuroblastoma) and some birth defects with pesticide exposure around conception, *in utero* and in early postnatal life.

The methodological and theoretical issues surrounding the human health effects evidence are frequently cited as limiting the ability to draw firm inferences about causality. Acknowledging the weaknesses of epidemiological studies does not detract, however, from the suggestiveness of their findings. The evidence is persuasive that the greater susceptibility of pregnant women and foetuses, infants, children and the elderly justifies prudent avoidance and precautionary measures to limit unnecessary exposures to pesticides for these vulnerable subpopulations.

Toronto Public Health supports strategies that will enhance public awareness, improve understanding of the risks from pesticides and avoid or minimally reduce, unnecessary exposures, especially for vulnerable groups.

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1.0 INTRODUCTION

Pesticide use on lawns, and the potential health effects arising from exposure to these commonly used chemicals, has raised the attention of the scientific community and the general public. This report addresses the possible implications for public health from the use of lawn and garden pesticides.

Among the voices that have been raised on the issue of pesticides, the public health perspective is distinct in how it considers the risks and benefits of a given pesticide use. The use of pesticides undeniably comes with some risks. These substances are intended to be harmful to living organisms and because they are released into the environment, they pose an exposure and potential health risk to other organisms, including humans. On the other hand, society has benefited from the use of pesticides. Current conventional agricultural practices rely on the use of chemical pesticide technology. Pesticides have also played a role in preventing the spread of major infectious illnesses and in controlling noxious pests. The issue for this report, however, is to evaluate the potential for health risks from pesticide use by the urban population for the purpose of lawn and garden maintenance.

Toxicological studies are a cornerstone of the testing that aims to ensure the risks posed by pesticides when they are used as intended, are not unacceptable. However, even the rigourous and thorough testing of products used in Canada cannot fully predict the real-life effects of these products on the population. This report describes some of the limits to what toxicological scientific methods can tell us, in particular, with respect to the possible future effects on people of long-term, complex exposures to pesticides. The means by which these effects are measured - by epidemiological studies – is the best tool we have available. It must also be noted however, that epidemiological science has a limited capacity to explain the apparent effects of low-level chronic exposure to lawn and garden pesticides as well.

There is however, in our opinion, as discussions below shall show, sufficient suggestive evidence to warrant precaution with the use of these substances. Epidemiological studies of occupational groups such as farmers and pesticide applicators have shown (although not always with consistency) associations with a variety of chronic health effects. These include some cancers, neurobehavioural, neurodegenerative and reproductive effects. As well, experts find the evidence persuasive that pre-conception, foetal and childhood exposure to pesticides should be limited to the extent possible because of the potential harm to children’s developing reproductive, nervous and immune systems.

2.0 PESTICIDES IN GENERAL

The term "pesticide" as used throughout this report refers to chemical substances (i.e. conventional pesticides) that are biologically active and interfere with the normal biological processes of living organisms deemed to be pests, whether these are noxious plants or weeds, insects, mould or fungi. Pesticides used to maintain lawns and gardens are frequently similar to those used in agriculture, although they may be applied in different concentrations and in a different manner.

Pesticides can be broadly classified according to their intended target pest (i.e. herbicide for weeds, insecticide for insects, fungicides for plant diseases, fungi and molds and so on). Pesticides are also categorized by their chemical structure and properties. Chemical structure is a key to the action of the pesticide and hence, its intended functions. Pesticides are designed and intended to be biologically harmful to living organisms deemed to be pests. The biological activity of pesticides is achieved by different modes of action.

Although there are several hundred different pesticide active ingredients and many thousands of pest control products registered for use in Canada only a relatively small number of them are used with great frequency in lawn and green space management. It is the intention of this report to highlight those compounds that are most commonly used (and available to consumers for use) in the management of pests on lawns, green spaces and in gardens and hence, those to which there is the greatest possibility of general population exposure.

Table 1 in Appendix 1 provides summary information on some of the major types and classes of pesticides that can be used for lawn and garden maintenance and their regulatory status in Canada. These will be referred to throughout this report.

2.1 Pesticide Use in Canada

Canadian data on pesticide use and sales are not readily available, although the Pest Management Regulatory Agency (PMRA) reports that it is currently developing a national pesticide sales database (Smith, 2001). The data that are available, from the province of Quebec, from Crop Life Canada (formerly the Crop Protection Institute) and the Urban Pest Management Council primarily, shed some light on how pesticides are used in Canada.

A 1997 inventory by the Quebec Government indicates that of the approximately 3.3 million kilograms of pesticides sold annually in that province, more than 80% (by volume of sales) are used in agriculture. Domestic uses (which include both indoor and outdoor applications) and ornamental horticulture respectively constitute the second (8.5%) and third (3.0%) largest sectors for annual pesticide sales in Quebec, (Gouvernement du Quebec, 2000). Products used specifically for lawn and garden maintenance in these two sectors combined (domestic and ornamental horticulture) represent just over 4% of the total annual sales of pesticides in Quebec. In both cases, herbicides are the most commonly purchased pesticide products for lawn and garden care. It is interesting to note however, the differences in the types of pesticides used by homeowners versus trained professionals as shown below in Table 1. According to the Quebec figures, homeowners purchase relatively and absolutely far more insecticides at about 3.7 times the figure of insecticide sales recorded for the ornamental horticulture sector. In contrast, the ornamental horticulture sector in Quebec is much more likely to use fungicides, primarily in maintaining fruit trees, lawns and vegetable gardens.

Table 1. Pesticide sales* attributed to lawn-care in Quebec for 1997 (Source: Gouvernement du Quebec, 2000)

Sector	Herbicides	Insecticides	Fungicides	Total
Domestic	18,978	9,388	5,422	33,788
Ornamental horticulture	76,994	2,562	22,418	101,974
TOTALS	95,972	11,950	27,840	135,762

* Figures expressed in kilograms of active ingredients

Data from a 1999 member sales survey by Crop Life Canada and the Urban Pest Management Council of Canada show that 96% of pesticides by weight sold in Canada are for non-urban use, while 3.2% represent use by urban professional applicators (including golf course attendants) and 0.8% is for homeowner uses (as cited by Canadian Consumer Specialty Products Association, 2002).

Data most relevant to understanding the use of pesticides by residents of Toronto come from a recent survey by Toronto Public Health, which indicates that approximately 45% of Toronto homeowners with lawns had treated their yards with pesticides in the past two years (Toronto Public Health, 2002). This figure reflects both homeowner application and those performed by a professional lawn care company. These figures are higher than those presented by Statistics Canada suggesting that 31% of Canadian homeowners with a yard or garden had used pesticides outdoors in 1994 (Statistics Canada, 1995).

2.2 Common Lawn & Garden Use Pesticides

Regularly collected data on pesticide sales and usage from the U.S. Environmental Protection Agency's (U.S. EPA) Office of Pesticide Programs indicates the variety of active ingredients that are most commonly used in non-agricultural sectors, although these figures do not separate home (or indoor) from yard and garden applications. Nonetheless, given that the top four homeowner-applied pesticides are herbicides (i.e. not typically used indoors), it suggests this list of active ingredients is reflective of those used for lawn maintenance.[2]

[2] Differences between Canadian and American climate, growing seasons, variety of species and hence, relevant pests, mean that U.S. data are likely not directly comparable to Canadian pesticide use patterns but the figures are instructive nevertheless.

Table 2. Pesticide active ingredients and quantities most common in homeowner applications (From Aspelin & Grube, 2000).

Pesticide	Type	Millions of Pounds
1. 2,4-dichlorophenoxyacetic acid (2,4-D)	Herbicide	7 - 9
2. Glyphosate	Herbicide	5 - 7
3. Dicamba	Herbicide	3 – 5
4. Mecoprop (MCPP)	Herbicide	3 – 5
5. Diazinon	Insecticide	2 - 4
6. Chlorpyrifos	Insecticide	2 - 4
7. Carbaryl	Insecticide	1 - 3
8. Benefin [3]	Pre-emergence herbicide	1 - 3
9. DCPA	Herbicide	1 - 3

The above list (Table 2) is largely similar to that produced by Health Canada's Pest Management Regulatory Agency (PMRA) which has identified the eight most common lawn-care chemicals in Canada as part of its *Action Plan on Urban Use Pesticides* (PMRA, 2000c) from a search of their pesticide labels database. The most common pesticides are those with the largest number of end-use products for a given active ingredient (Smith, 2001) and include the insecticides diazinon, carbaryl and malathion, and the herbicides, 2,4-D, mecoprop, dicamba and 4-chloro-2-methylphenoxyacetic acid (MCPA) (PMRA, 2000a). This list does not however, reflect the full range of lawn and garden pesticides available to the consumer.

[3] Benefin, also known as benfluralin, is a pre-emergence herbicide that is not registered for use in Canada.

3.0 REGULATION OF PESTICIDES IN CANADA

In order to adequately explore the issue of exposure and potential health effects from pesticides, it is useful to briefly discuss the regulation of pesticides in Canada. The Pest Management Regulatory Agency (PMRA) is tasked with the evaluation of all pesticide products proposed for use in Canada. Its mission is:

> …to protect human health and the environment by minimizing the risks associated with pest control products, while enabling access to pest management tools, namely, these products and sustainable pest management strategies. (PMRA, n.d.)

3.1 Risk Assessment

In its decision-making about pesticides, PMRA relies primarily upon a scientific process called risk assessment (RA). RA is the overall procedure that identifies, analyses and evaluates the chance of harm or injury to people and to the environment from a given substance.

The risk to human health and the environment from the use of a pesticide depends on 1) the toxicity of the pesticide and 2) the amount and degree to which humans and the environment are exposed as a result. An adequate RA process will therefore require data on toxicity, human exposure and environmental fate. The PMRA requires that the registrants, the manufacturers, of pesticides provide extensive data from experimental studies (laboratory animal, cell culture and field tests) conducted by independent laboratories. These laboratories must adhere to an internationally recognized standard protocol for testing practices and conditions known as Good Laboratory Practice (GLP). GLP was first established by the Organisation for Economic Co-operation and Development (OECD) in 1978 (OECD, 1998). OECD publishes Test Guidelines that detail the methods used to assess the hazards of individual chemicals. Data from these tests along with data from published, peer-reviewed scientific literature (both toxicological and epidemiological studies) are evaluated together in the RA process.

PMRA scientists conduct the RA and it involves several stages where the body of scientific studies is analyzed. The first of these is to identify and assess the hazard associated with the pesticide (the Hazard Identification stage). This step involves an evaluation of available animal toxicity studies that have been conducted using a range of dose[4] levels several times higher than doses to which humans would be exposed. The evaluation also determines the dose that causes no adverse effects on the health of animal, which is referred to as the "No Adverse Effect Level" or NOAEL. Wherever possible, evidence from human studies is used as well.

[4] Toxicology is founded on the assumption that there is a proportionate relationship between dose received and response measured (health effect). Generally the higher the dose, the greater the potential for effects. Toxicologists traditionally assume that for any given chemical there is usually a dose below which no response occurs or can be measured (Kamrin, 1997) although evidence for health effects from some environmental exposures such as lead, ozone and particulate matter challenges this assumption. (See for example, Landrigan, 2000; Burnett et al, 1994; Health Canada & Environment Canada, 1998).

The dose-response assessment is an important step in determining the NOAELs. It uses data, primarily from animal studies, to try to predict the health effects for each given dose. This usually results in a numerical estimate of effects in terms of rates of disease or death. In the case of threshold chemicals, PMRA scientists utilize the NOAEL to calculate the level of exposure at which they predict that there will likely be no harmful effects to humans, known as the Reference Dose (RfD). The RfD is calculated by applying a safety factor[5], typically ranging from 100-1000 fold, to the NOAEL to account for differences between species (since the hazard information is based on animal studies), and differences within species (accounting for variable sensitivities among humans at different developmental stages, including infants, children, and the elderly). Selecting a safety factor is based on scientific judgement and the factor increases as the hazard profile increases.

In the case of cancer however, scientists generally assume that there is no "threshold" (i.e., a level of exposure below which there will be no effects) and therefore, they must calculate minimal or "acceptable" levels of risk.[6] With cancer, the acceptable (or *de minimus*) risk is an exposure level that will not produce more than one extra case of cancer in a million people.

Exposure assessment attempts to predict the degree to which people will be exposed to pesticides according to how they will be used. In the case of pesticides not intended for food use, play habits of children and their unique behaviours that might increase pesticide exposure are considered. Exposure estimates are determined for various occupational, residential and bystander scenarios (referring to those that do not apply pesticides, including children). The NOAEL is then divided by the exposure estimate for each exposure scenario to yield a Margin of Exposure (MOE). If an unacceptable MOE is calculated, mitigation measures such as changes to product packaging, application methods and application rates, are imposed to reduce exposure. If these measures fail to result in an acceptable MOE then registration is not permitted.

An Environmental Risk Assessment (ERA) is a parallel part of the overall RA process. The ERA assesses information on the behaviour of the pesticide once it is released in the environment (environmental fate) as well as the likelihood and the degree to which other (non-target) organisms will be harmed by the pesticide (environmental toxicology). (The reader is referred to a brief discussion of research on the environmental fate and ecotoxicity of lawn and garden pesticides found in Appendix 2.)

The PMRA has standards of risk assessment that are, many would agree, among the most up to date in the world. When a pesticide manufacturer proposes a new chemical for use as a pesticide it must provide PMRA with the information that allows PMRA to judge the safety, merit and value of the product. To allow PMRA to assess safety, pesticide manufacturers must provide results from at least six categories of animal studies testing for toxicity. These categories include tests of:

1. acute toxicity
2. short-term toxicity
3. long-term toxicity and carcinogenicity

[5] Regulatory agencies use the term "safety factor", however, others prefer the term "uncertainty factor" as better reflecting the intent of these multipliers

[6] It is recognized that non-genotoxic carcinogens, that is, agents that contribute to the development of cancer other than by direct effects on nuclear DNA may operate differently from genotoxic carcinogens, in the sense that a threshold of effect can be determined.

4. reproductive and developmental toxicity
5. genotoxicity
6. metabolism and toxicokinetics (PMRA, 2001d)

Within each category of tests there are multiple types of tests required. Neurotoxicity tests are not mandatory in all cases but are required only for chemicals that act by affecting the nervous tissue (PMRA, 2001d) or, when the animal studies above indicate neurological effects or that the young are more sensitive to any effect (Government of Canada, 2000). If the results of the battery of standard toxicity studies indicate the potential for effects on the immune or hormonal systems, further tests for immunotoxicity and endocrine disrupting potential may be required as well (PMRA, 2001d).

The requirements are extensive and rigourous. Although this battery of tests has been required in the law only since 1994, PMRA submits that the testing requirements were in place in the form of Trade Memoranda since the early 1980s. Most, if not all, of the pesticides commonly used in lawn maintenance were originally registered for use in Canada prior to December 31, 1994.[7] However, the PMRA reports that the majority of older registered pesticides do have a complete toxicology database (PMRA, 2002b).

In addition to assessing risk to health and to the environment, PMRA's established RA process evaluates a pesticide's value, merit and effectiveness (also called a Value Assessment). All of this information factors into the Risk Management Strategy phase, which identifies allowable uses, restrictions and labeling requirements of a given product. It is beyond the scope of this report to adequately discuss this component of the process.

3.2 Harmonizing "Old" and "New" Standards

The PMRA has formally recognized the need for re-evaluation of the many older pesticides registered before the newer, more stringent standards were required (PMRA, 2001c). This is a formidable task given that over 400 pesticide active ingredients (out of a total of 550 active ingredients currently allowed) were registered prior to December 31, 1994 (PMRA 2001c). Although there was a stated commitment to re-evaluate all before 2006[8], progress has been generally slow and hampered by inadequate resources (Standing Committee on Environment & Sustainable Development, 2000).

Recently, the commitment to re-evaluate some of the older pesticides has seen some prioritizing that has resulted in relatively greater progress. For example, new scientific evidence of the potential for irreversible effects on nervous system development in test animals, and concern for the greater vulnerability of children to neurotoxic pesticides, prompted the PMRA (and other regulatory

[7] This does not imply that the tests required for pesticides registration prior to 1994 were inadequate, nor that the regulatory decisions made prior to the current regulatory context were incorrect. Registrations of the lawn care pesticide active ingredients were considered acceptable and reasonable at the time and were based on then accepted and available scientific and regulatory approaches (PMRA 2000 as cited in Ogilvie 2001). This is simply to highlight the fact that changes to the regulatory regime are relatively recent.

[8] Re-evaluation of older active ingredients by 2006 is in keeping with the targets of the U.S. EPA and reflects efforts to harmonize pesticide regulation in Canada with that in the U.S.

agencies such as the U.S. EPA) to begin re-evaluation of the organophosphate class[9] of insecticides in June 1999 (PMRA, 1999b). The PMRA subsequently revised its risk assessments of both chlorpyrifos and diazinon. Ultimately this led the PMRA to announce voluntary phase-outs (agreed to by the manufacturer) of most residential-use products that contain either chlorpyrifos or diazinon. In the case of chlorpyrifos, the phase-out was complete as of December 31, 2001 and for diazinon it will be in full effect as of December 31, 2002 (PMRA, 2000b; PMRA, 2001b).

As stated earlier, in November 2000 the PMRA also announced that as part of its *Action Plan on Urban Use Pesticides* (PMRA, 2000c), it would conduct priority re-evaluations of the eight most common active ingredients in lawn-care pesticides, including chlorpyrifos and diazinon (PMRA, 2000a). In this plan, the PMRA committed to applying current risk assessment techniques, including additional safety factors to protect children where appropriate, in their re-evaluations of these eight chemicals. The PMRA is likely to complete the re-evaluation of the herbicides by the spring of 2002 and of the insecticides by the end of 2002 (Aucoin R., 2002). The re-evaluation of the organophosphates chlorpyrifos and diazinon, as mentioned above, are already complete.

It should be noted that the governments of many industrialized nations have been co-operating to harmonize toxicity testing regimes and regulatory approaches for pesticides and other chemical substances for several years. Regional and international harmonization of pesticide regulation is intended to maximize the ongoing efforts to incorporate newer science, improve health protection and share the work associated with chemical evaluation. This cooperation amongst governments will also reduce and possibly eliminate any trade issues associated with use of a product.

3.3 Consideration for Children's Vulnerability

These changes to the regulatory decision-making process and the resultant actions reflect the influence of both changing public and scientific opinion over the last five to ten years in Canada, the U.S. and Europe. PMRA acknowledges that their 2000 Action Plan itself was a response to public concern about the use of pesticides in the urban environment. Prior to this however, the U.S. National Academy of Sciences' report entitled, *Pesticides in the Diet of Infants and Children* (National Research Council, 1993) brought to the fore a key scientific paradigm shift that has helped formally alter regulatory approaches in the U.S. and elsewhere, including Canada, to better account for the distinct vulnerabilities of children to pesticides.

The recommendations of the National Academy of Sciences' report provided the basis for amendments to the U.S. legal framework that, in turn, directed the U.S. EPA to formally address issues of children's developmental susceptibilities.[10] Specifically, in 1996, the implementation of the Food Quality Protection Act (FQPA) required by law, that the U.S. EPA consider incorporating three key refinements to the RA process. The first was to consider applying an additional safety factor (up to ten-fold) when setting regulatory limits for pesticides. The extra safety factor was intended to account for the differences between adults and the young in susceptibility to harm from chemicals (where animal data indicate this is necessary) or to compensate for lack of scientific data

[9] The organophosphates include chemicals used commonly in the treatment of lawn pest infestations, such as chlorpyrifos, diazinon and malathion.

[10] While these issues were already under consideration by regulatory agencies, the NAS recommendations and the FQPA served to enshrine them in U.S. law.

on developmental effects. This safety factor would be in addition to the compound safety factor that is already applied to the NOAEL to account for inter- and intra-species differences as described above.

In addition to requiring consideration of an extra safety factor to account for children's vulnerabilities, the FQPA also recommended that risk assessment incorporate methodologies to assess aggregate exposures and to account for possible cumulative effects from chemicals of common mechanisms of toxicity. In the past, RA has been criticized for its single pollutant, single medium of exposure approach to assessing chemicals. This situation appears to be improving. Aggregate exposure assessment protocols[11] are now being incorporated especially for specific pesticides that are intended for use on food crops (U.S. EPA, 2001c; PMRA, 2002). In addition, techniques for assessing the cumulative risks from pesticides with a common mechanism of toxicity have been developed and are under validation but are not yet available for full regulatory implementation. For example, the U.S. EPA's Office of Pesticide Programs recently released a preliminary cumulative RA for the organophosphorous pesticides for open comment on December 3, 2001 (U.S. EPA, 2001e).

The PMRA states that it can adopt (and in some cases is adopting) many of the advances in the health risk assessment that are embodied in the U.S. under the FQPA (Government of Canada, 2000). In particular, the PMRA states it is already applying an additional safety factor where warranted and has adopted enhancements to previously existing protocols for examining effects on fetal development as well as more recently developed protocols for assess neurological development in the fetus and neonate (PMRA, 2002b). The PMRA recently published a Science Policy Notice describing how they incorporate consideration of child-specific vulnerabilities in their regulation of pesticides (PMRA, 2002a). Their stated commitment to child health as a priority is merited in light of the scientific uncertainty.

3.4 Additional Areas of Uncertainty

There is concern that despite the improvements described above, RA itself cannot adequately address all the potential risks posed by pesticides because it is fundamentally constrained by the limits of current scientific understanding and methodology. Specific shortcomings in the ability of the current procedures to adequately assess the potential for health effects have been identified.

RA relies largely on information derived from studies of animals where exposures are generally much higher than would be expected for humans. However, the exposure conditions in animal studies are also highly controlled and specific in each type of study. The researchers' control over experimental conditions in animal studies is very different from real-life exposure conditions, which are difficult to approximate in animal tests (National Toxicology Program, 2001a). (The reader is referred to section 5.3 for further discussion of the role of toxicological studies in assessing health risks from pesticides.)

For example, there are few studies that have assessed multiple exposures to a variety of different chemicals that are commonly present in our environment and in human tissues. Reviewers have noted that the uncertainty increases when considering the interactions with other classes of chemicals such as therapeutic drugs and many persistent environmental contaminants, which have been

[11] Aggregate exposure assessment methods attempt to estimate the exposure to a single chemical by all potential pathways and routes of exposure.

measured in human tissues, including amniotic fluid and breast milk (Foster et al., 2000; Health Canada, 1998a).

Although an additive effect is most commonly observed when two chemicals are given together, it is suspected that in some cases, different chemicals may have synergistic or interactive effects that make them more toxic in a mixture than any of the chemicals on their own. For example, Marinovich and colleagues (1996) showed in an *in vitro* study using human neuroblastoma cells, that the effects of pesticide mixtures cannot be predicted from the known effects of the individual pesticides. In experimental studies on adult mice, Porter and co-workers (1999) indicated that there were synergistic effects and greater variety of biological responses from exposure to mixtures of pesticides and other contaminants. The mixes of two agricultural pesticides (aldicarb and atrazine) and nitrate (from fertilizers) were administered at levels within the range of concentrations commonly found in rural groundwater (Porter et al., 1999). Relyea and Mills (2001) showed substantially higher than predicted rates of mortality among tree frog tadpoles exposed to both low levels of carbaryl (3 to 4% of the LC50[12]) and stress induced by predatory cues. Although this is a field of expanding research, the effects of mixtures have not been well studied despite the realization that people are routinely exposed to mixtures of different pesticides and other chemicals. (See the discussions on exposure, sections 4.1 and 4.2 below). In addition, there are currently no methods available to estimate the effects from exposure to mixtures of diverse chemicals at different times during development.

It should be noted that the concept of synergistic effects is not uniformly supported by the published research. Some studies have indicated that similar mixed exposures produce no increase in effects or reduced effects, suggesting that some combinations of chemicals may interact antagonistically.

Testing for important health effects such as developmental neurotoxicity, immunotoxicity and endocrine disrupting ability of chemicals is not mandatory for all pesticides. Toxicological data requirements are assessed for "triggers" that are suggestive of developmental neurotoxicity, immunotoxicity or endocrine disrupting potential. Assessment for these effects is highly dependent on scientific testing methods, which continue to be refined. However, the PMRA (2002a) states that they are (and have) committed to implementation of these methods as they become available. In addition, scientists in the U.S. have raised concerns about the adequacy of the current guidelines for evaluation of carcinogenic risk in children (U.S. EPA, 2000c).

It should be noted that the PMRA states that they acknowledge the existence of these uncertainties and, where applicable, the limitations of available methods to adequately address these uncertainties. They submit that their default response to such uncertainty is to consider applying additional safety factors to calculate reference doses and margins of exposure where warranted (PMRA, 2002b).

[12] LC50 is the concentration of a substance that is predicted to kill approximately half of a study sample under prescribed exposure duration and conditions.

4.0 EXPOSURE TO PESTICIDES

Pesticides are intentionally introduced into the environment and depending on their volatility, persistence and solubility, they can cycle through environmental media such as air, soil and groundwater (Kamrin, 1997) and from these points, can find their way to people. Exposure assessment is an important aspect of estimating the likelihood of an identified hazard actually posing a risk to human health when conducting a risk assessment. Exposure assessments aim to identify the potentially exposed people, the potential pathways of exposure and to quantify the potential dose or chemical intake (U.S. EPA, 1997b).

The scientific paradigm used to define risks from environmental exposures can be expressed as "risk = hazard + exposure". Regulatory agencies evaluate risks on the basis of both the inherent hazard to health (or to the environment) and the probability (and degree) of exposure (to people or to the environment).

Exposure depends on the intensity, frequency and duration of contact between the body's "portals of entry" (i.e. the mouth, nostrils or skin surface) and any given chemical agent. The routes of exposure therefore, include ingestion, inhalation or dermal absorption. The extent to which such contact is important in a toxicological sense depends on the relative concentration of the contaminant in environmental media, the availability from and the rate of contact with these media. It will also depend on the characteristics of the individual who is exposed.

In light of this important context, it should be stated at the outset that exposure is not synonymous with the advent of health effects.

Non-occupational exposure assessments may use either direct or indirect approaches to estimating exposure. Relatively few published studies exist where there has been personal monitoring for specific exposure scenarios, thereby yielding direct data. Therefore, most often exposure assessments must rely on information available on the concentrations of chemicals in exposure media and modelling techniques about the nature of human contact with these media.

Generally speaking, there is often considerable uncertainty around exposure estimates. Exposure assessment has been described as the "weak link" in risk assessments (American Chemical Society, 1994). The following quote from the U.S. Environmental Protection Agency's Office of Pesticide Programs clearly states the limitations in this phase of risk assessment:

> In estimating exposure, as in other phases of its work, OPP (Office of Pesticide Programs) is constantly hampered by lack of adequate data, and is forced to resort to indirect and inaccurate methods in its effort to make plausible estimates. (U.S. EPA, 1996: 2)

The PMRA states that they typically take a "worst case", conservative approach is taken to generate a high-end estimate of exposure (PMRA, 2000d).

The focus of this report is potential exposure to and health effects of lawn and garden pesticides. However, the potential sources of exposure to pesticides for a given person are multiple and diverse. They include indoor applications, outdoor applications, personal applications (on people and family pets) and dietary pesticide residues (minute concentrations of pesticides) on a small proportion of

agricultural produce (National Research Council, 1993; Niedert et al., 1994; Niedert & Saschenbrecker, 1996; Neidert & Havelock, 1998).[13]

It is apparent that exposure to lawn and garden pesticides represents one portion of the total exposure. Given that exposure to pesticides is multi-route and from multiple sources, it is difficult to predict the effects from exposure to lawn and garden pesticides alone. In other words, because we cannot be certain of the extent of exposure from lawn and garden pesticides, we can also not be certain to what degree or if, this exposure is contributing to health outcomes. Regulators in Canada and the U.S. now use methods that assess risk on the basis of aggregate exposure from all scenarios and all routes for a given pesticide. In addition, for those types of pesticides that produce biological effects through common mechanisms of toxicity, (such as the organophosphates), new methods to estimate the cumulative exposure and risk for all pesticides in that group have recently been adopted.

The majority of studies of human exposure to pesticides have focused on workers involved in the manufacture of pesticides, agricultural workers, and professional pesticide applicators. This is because occupational exposures are considered to represent the "worst-case scenario" and therefore most appropriate for assessing potential effects (PMRA, 2002b). Extensive information on occupational exposure is required for regulatory approval of pesticides. Studies examining exposure to pesticides in the general population have been relatively less common, although PMRA notes that it does account for exposures to bystanders in its occupational exposure assessment (PMRA, 2001f).

4.1 Exposure to Lawn and Garden Pesticides

Researchers at the U.S. EPA were among the first to publish studies of nonoccupational exposure of the general population to common pesticides used around the home, in the Nonoccupational Pesticide Exposure Study (NOPES) conducted from 1986 to 1988 (Immerman & Schaum, 1990a). This study measured concentrations of 32 household pesticides in a variety of indoor and outdoor media as well as providing proxy measures for exposure via inhalation and skin absorption.[14]

EPA researchers evaluated the air exposure data for potential chronic health risks, concluding that risks were generally low (for non-cancer outcomes) or within the range that the EPA considers negligible (for cancer) (Immerman & Schaum, 1990b: 58). They focussed on inhalation exposures, concluding that 85% of adult exposure to airborne pesticides was from indoor air, which had on average higher concentrations than outdoor air (Immerman & Schaum, 1990b). However, dermal exposure was determined to be a potentially important source of exposure as well with pesticide residues in household dust substantially higher than levels[15] in air (Immerman & Schaum, 1990b). Although this study did not address the potential for health effects from chronic dermal exposure,

[13] It should be noted also that some persistent organochlorine pesticides, no longer in use in Canada continue to be measured in the environment and in the food chain because of the phenomenon of biomagnification. This represents an additional source of exposure to pesticides as corroborated by biological monitoring studies (Health Canada, 1998a).

[14] NOPES applied the Total Exposure Assessment Methodology, an approach which combines multi-media sampling procedures and questionnaire data collection with personal monitoring techniques "to obtain statistically defensible estimates of exposure levels in the general population" (Immerman & Schaum, 1990a: 1).

[15] The levels of pesticide residues that had settled in carpet dust were assessed as being an order of magnitude higher than the levels in indoor air (carpet dust concentrations from 1 to 100 μg/g versus air levels of 0.1 to 0.5μg/m^3) (Lewis et al, 1994).

researchers recommended that there was need to further explore the role of exposure to pesticides via household dust (which could be comprised of tracked-in yard soil), particularly for infants and toddlers, recognizing that hand to mouth transfer enhances exposure via ingestion (Budd et al, 1990).

The U.S. EPA's National Human Exposure Assessment Survey (NHEXAS) is a comprehensive study currently underway to assess human exposure to various environmental pollutants through multiple media[16]. Pesticides represent one among a number of classes of environmental pollutants being measured. Again, this study has not focused solely on exposure from lawn use of pesticides, although some of the media and the pesticides examined likely reflect exposures from treatment of lawns and gardens. Preliminary results[17] indicate that there are generally low levels of chlorpyrifos in environmental media analysed (Robertson et al., 1999). Notably however, indoor air has relatively higher median levels of chlorpyrifos and diazinon compared to outdoor air. (Note: it is not the case that exposure to these levels would be associated with risks of chronic health effects.)

Direct experimental evidence has shown that adult exposure during application of lawn and garden pesticides will depend on a number of factors. These factors include the pesticide's chemical properties and formulations, the mode of application, the type of protective gear worn during handling, application and clean-up, the amount absorbed through skin, anatomical location of skin contact and the weather conditions. Generally, the less clothing worn and the more direct skin contact with the pesticide, closer to the time of treatment, the greater the chance of exposure (Gold et al., 1982; Harris & Solomon, 1992; Harris et al., 1992). These aspects of user/bystander practice and exposure will be further addressed below.

The modes of applying a pesticide are diverse and vary according to the product and the targeted pest. Broadcast pesticide spraying can be associated with the significant airborne dispersal and provides a potentially important route of exposure via inhalation. The Standard Operating Procedures of the U.S. EPA emphasise that this route is only relevant however, for pesticides handlers (U.S. EPA, 1997b). Although some studies indicate that the potential for bystander exposure to sprayed lawn care pesticides is low (see below), inhalation of fine droplet spray can be important as a route of exposure to the pesticide handler during applications on lawns and in gardens (U.S. EPA, 1997b). Skin absorption, however, is usually the more important route of exposure for handlers. This route is also more important for post-application exposure to handlers and others as there may be amounts remaining on treated surfaces (i.e. dislodgeable residues) for some period of time, depending on the chemical properties of the individual pesticide (U.S. EPA, 1997b).

A recent study by researchers at Lincoln University in New Zealand (Brown et al., 2000) experimentally assessed the degree of exposure to four phenoxy herbicides in a simulated aerial application. Brown and colleagues state that for these specific herbicides, odour is not considered to be a good indication of exposure as the active ingredients themselves are odourless. Spray odour is attributed to trace manufacturing additives or impurities in the pesticide formulation. The authors determined that the actual amount of active ingredient generated in their odour "clouds" was below threshold limits and therefore of little toxicological significance.

Researchers at the University of Guelph conducted experiments in the early 1990s of exposure to the herbicide 2,4-D. It should be noted that the authors did not report any health effects associated with the exposure conditions among study subjects. Their results showed that residues in urine were

[16] Media studied include yard soil, foundation soil, house dust, indoor and outdoor air, drinking water, food and beverages.

[17] Results have been published only for chlorpyrifos and diazinon thus far.

detectable (in small amounts) only when individual adult volunteers, had direct contact with treated turf (within one hour of treatment), wore minimal clothing or had accidental direct skin contact with the pesticide during mixing or application (Harris & Solomon, 1992; Harris et al., 1992).[18] Their results also indicated that the urine of adult bystanders[19] did not carry detectable residues of pesticides (Harris et al., 1992). It is important to note that urinary excretion is used since it captures exposure from all possible routes (i.e. dermal, inhalation or ingestion). The fact that the major feature distinguishing the two groups of volunteers in the first study was degree of skin contact with the treated turf suggests that the dermal route largely accounts for this (small) exposure to turf use pesticides.[20] (Harris & Solomon, 1992)

4.2 Assessing Children's Exposures

There are few direct studies of the specific mechanisms of exposure for children from use of lawn and garden pesticides. In one experimental study testing the potential for children's exposure to the insecticide chlorpyrifos from contact with treated grass, Black (1993) determined that hand to mouth transfer (i.e. dermal contact and subsequent ingestion) contributed about 50% of the estimated systemic dose. Dermal absorption and inhalation contributed 30 and 20 per cent respectively, of the estimated total dose of chlorpyrifos received. Black determined that the children in the study were not exposed to doses high enough to cause clinical symptoms through such a lawn application.[21]

Research indicates that people, especially children, can be secondarily exposed to lawn-care pesticide residues indoors. Experimental studies by the National Exposure Research Laboratory of the U.S. EPA using the phenoxy acid herbicide 2,4-D have shown that turf applications can be inadvertently transported indoors on shoes and feet. 2,4-D was subsequently measured in indoor air, carpets and on other interior surfaces (Nishioka et al., 1996; Nishioka et al., 1999; Nishioka et al., 2001). The estimated exposure to 2,4-D was about ten times higher indoors after such a turf application (Nishioka et al., 2001). Pesticides found in the indoor environment persist longer than they would outdoors because they are not subject to the external elements that promote degradation. A small amount of the tracked-in pesticide is available for dermal contact and in young children this can entail an important contribution to total pesticide exposure, depending on the amount absorbed

[18] In one study to assess exposure after turf was treated, detectable levels of 2,4-D were measured one hour following exposure in three of five volunteers wearing tee shirts, shorts and open footwear. None of the volunteers in a group of five wearing tee shirts, long pants, socks and closed footwear had detectable levels. The highest levels detected after one hour (5.36 μg/kg) were found in one volunteer who removed his shirt for the last 30 minutes of the one hour exposure session. (Volunteers were instructed to alternate at five minute intervals between walking, sitting or lying on the treated turf for a total of 60 minutes) (Harris & Solomon, 1992).

[19] Bystanders were people living in homes where the herbicide 2,4-D had been sprayed, but were not actually doing the spraying themselves.

[20] The results of these experimental studies notwithstanding, inhalation exposure of people and non-target organisms to pesticide drift from spray and dust applications is a concern that the U.S EPA is currently addressing (U.S. EPA 2001a).

[21] It is noteworthy that experiments with indoor application of chlorpyrifos determined that despite following the product instructions, there could still be exposure to significant amounts (between 20 and 120 times the recommended reference dose) of chlorpyrifos, measured on toys and other absorbent surfaces, well after the recommended safe period for re-entry (Gurunathan et al, 1998).

through the skin and the amount obtained from hand-to-mouth transfer.[22] Others have shown that pesticide residues found on children's hands correspond to the type and concentration of pesticides found in household and carpet dust (Lewis et al., 1994; Bradman et al., 1997). These data are incorporated into standard exposure scenarios as discussed below.

On average, people - especially children - spend a much greater proportion of their time indoors. Young children and infants spend much more of their time in contact with the floor and are more likely to have hand-to-mouth transfer of residues found on surfaces they touch. Therefore, these indirect exposures from the use of lawn pesticides are important to consider.

It has been recognized that children can also be exposed to pesticides in the womb and through breast milk, although neither of these routes has been well studied directly (i.e. in people) for lawn and garden pesticides in current use. A recent pilot study conducted by researchers of Columbia University's Center for Children's Environmental Health detected metabolites of two organophosphate insecticides (diazinon and chlorpyrifos) in the meconium (the first feces or stool) of 95 to 100% of a small sample[23] of newborn babies (Whyatt & Barr, 2001). These findings were consistent with general reports of extensive residential use of these pesticides[24], although the authors did not report on the pesticide use practices of the parents in the study. Evidence suggests that the presence of pesticide metabolites in meconium may reflect fetal exposure to pesticides from the second trimester through to delivery. It should be noted that this study did not report adverse health effects in these infants although the authors recommend that further research is required to evaluate the dose-response relationship in this context (Whyatt & Barr, 2001: 419).

Fat-soluble pesticides are those most likely to appear in breast milk, providing an additional potential route of exposure to nursing infants. Pyrethroids are highly fat-soluble and can be transferred through breast milk (Hunt & Gilbert, 1977; Gaughan, et al., 1978). A recent experimental study by Argentinian researchers showed that 2,4-D administered in high doses to mother rats was transferred to neonatal rats through milk (Sturtz et al., 2000). 2,4-D has also been detected in cow's milk (Dogheim et al., 1990). The toxicological significance of these exposures is not known. As will be discussed below, we have uncertain knowledge of the effects of exposures at such vulnerable periods in an individual's development. As stated earlier, if standard toxicity tests on a specific pesticide indicate that young animals demonstrate unique susceptibility, it is the PMRA's current practice to add an additional safety factor in the risk assessment to further protect this population (PMRA, 2002b)

The U.S. EPA applies 25 hypothetical[25] residential exposure scenarios relevant to children to estimate exposure. Of these, ten reflect exposure scenarios specific to outdoor residential use of pesticides. These include additional situations not discussed here such as ingestion of soil that contains pesticide residues, direct ingestion of pesticide granules or pellets, ingestion of pesticide-

[22] The authors conclude that at the high end of their estimated exposure levels, nondietary ingestion of 2,4-D from contact with dust on hard surfaces could approach the reference dose limits of 10µg/kg/day for 2,4-D as defined by the U.S. EPA IRIS database (Nishioka et al., 1999; Nishioka et al., 2001).

[23] Meconium samples were collected opportunistically, but without knowledge of parents' prenatal pesticide use (Whyatt & Barr, 2001).

[24] The reader is reminded again that diazinon and chlorpyrifos are in a program of phase-out in Canada and the U.S.

[25] These scenarios are hypothetical only insofar as there are no direct studies that have examined children's exposure to pesticides in these ways, but based on studies of child behaviour, they represent plausible means of exposure nonetheless.

treated foliage and direct hand-to-mouth transfer (U.S. EPA, 1999). It should be noted that the PMRA utilizes the Standard Operating Procedures (SOPs) outlined by the U.S. EPA for its exposure assessment. In addition, it states in its recent Science Policy Notice that in the residential risk assessment "infants' and children's exposures from all routes and pathways are considered, as well as their unique behavioural and activity patterns" (PMRA, 2002a: 5).

4.3 Population Biomonitoring Studies

Biological monitoring provides another source of direct information on human exposure and pesticide pharmacokinetics (the absorption, distribution, metabolism and excretion in the human body). This area of study is still evolving. The pharmacokinetics of any given pesticide in humans are complex and not entirely understood for most pesticides (Lewalter & Leng, 1999; U.S. EPA, 1999a) although PMRA require data submissions on pesticide phamacokinetics in laboratory animals (PMRA, 2002b). Levels of pesticides and their metabolites in urine are the most common measures used in biomonitoring studies since, as stated earlier, they allow for estimation of internal dose from all routes or exposure.

For some pesticides such as 2,4-D, the toxicokinetics in humans are reasonably well understood. Research has shown that when human volunteers ingest a single dose of 5 mg/kg of the herbicide 2,4-D, it is excreted in the urine largely unchanged (12.8% is found as a 2,4-D conjugate) (Sauerhoff et al., 1977). Half the amount of 2,4-D ingested is eliminated within about 18 hours on average with total elimination in about five days (Sauerhoff et al., 1977; Feldmann & Maibach, 1974). U.S. EPA documents state however, that, "the quantitative relationship between a measurement of a metabolite in one urine sample to an exposure level of the parent compound is not well established for most pesticides, especially for children" (U.S. EPA, 1999: 24).

A number of population biomonitoring studies in the U.S. demonstrate that urinary levels of pesticides are relatively very low[26] [measured as micrograms (μg) per litre or parts per billion[27]]. None of these studies, including those of the occupationally exposed, has been able to clearly demonstrate that these exposure levels are associated with acute health effects or symptoms in the individual subjects. The reader is reminded that while these biomonitoring studies are indicative of exposure, exposure is not necessarily indicative of a health effect. Although the required toxicological tests assess for a range of health effects across a substantial portion of the life cycle, some researchers caution that we cannot fully predict the potential long-term effects from such chronic, low-level exposure, particularly if exposure occurs at sensitive developmental periods (Loewenherz et al., 1997; Steenland et al., 2000; Lu et al., 2001). Research on the potential for low-dose effects from hormonally active substances, discussed in section 8.4 below, provides useful clarification of the reasons for concerns about the scientific certainty. The PMRA reports that it considers application of extra safety factors in the risk assessment to account for the uncertainty associated with exposure to vulnerable populations (PMRA, 2002b).

[26] Steenland and colleagues (2000) contrast the average urinary TCPy level of 629.5 μg/L for professional applicators with recent exposure to chlorpyrifos (and no significant measured adverse health effects) with figures on the order of 4.5 μg/L for the general population.

[27] One part per billion (ppb) and one microgram per litre (or per kilogram for solid measures) are equivalent measures of concentration. A ppb corresponds to about one drop of pesticide in 500 barrels of water (Kamrin, 1997).

Data from the U.S. National Health and Nutrition Examination Survey (NHANES) found low levels of 2,4-D in 12% of a sample of 1000 adults (Hill et al., 1995). The same study found levels of a chlorpyrifos metabolite [3,5,6-trichloro-2-pyridinol (TCPy)], in 82% of the sample and concluded that exposure to chlorpyrifos was apparently increasing (Hill et al., 1995). The human biomonitoring studies of NHEXAS report that two of the pesticide metabolites tested for (1NAP a metabolite of carbaryl, and TCPy a major metabolite of chlorpyrifos) were present in over 80% of the samples of adult urine (MacIntosh et al., 1999).

Only a very small number of biomonitoring studies of children exist for general population samples and these are for the U.S. Their findings suggest that there is, as described by the researchers, "widespread" and continuing[28] exposure of children to some common household pesticides and their breakdown products (Adgate et al., 2001: 589). Specifically, these researchers reveal that a large proportion of the individuals in their studies (up to over 90% in some cases) had detectable residues of certain pesticides (or their metabolites) in urine samples (Lu et al., 2001; Adgate et al., 2001).

In the Minnesota Children's Pesticide Exposure Study (MNCPES), Adgate and colleagues (2001) tested the urine of 102 children (ages 3 to 13 years) for concentrations of 4 metabolites representing four different organophosphate insecticides. They detected TCPy[29], a metabolite of chlorpyrifos and related compounds, in 93% of their sample. Metabolites of carbaryl and malathion were detected in 45% and 37% of samples, respectively.

Lu and colleagues (2001) from the University of Washington analysed urine samples from 110 children ages 2 to 5 years from Seattle for six dialkylphosphate compounds (different breakdown products of organophosphate insecticides). At least one of the metabolites was measured in 99% percent of children, with two main metabolites measured in 70 to 75% of children. Only one child had no detectable levels of pesticide metabolites. This was also the only child whose parents reported using no pesticides and buying only organic food.

The latter two studies yield contrasting conclusions on the degree to which lawn and garden pesticide use contributed to metabolite levels in the urine of individual children. Adgate and colleagues (2001) observed that metabolite levels were not significantly higher for subjects from homes where pesticide use was reportedly higher. Lu and co-workers (2001) on the other hand, determined that there were significantly higher concentrations in children whose parents used garden insecticides such as chlorpyrifos and diazinon (despite these pesticides not having been applied for months). However, contrary to expectations, urinary metabolite concentrations were not significantly higher where parents reported using pesticides (herbicides and insecticides) on the lawn (as opposed to the garden) or in the home.

Adgate and colleagues state "children's (urinary) metabolite levels of these organophosphate pesticides were greater than in recent (U.S.) populations based studies of adults" (Adgate et al., 2001: 589). This agrees with suggestions that children's exposures to pesticides may be higher than those of adults in the general population due to the behavioural and activity differences that increase their intake (see below). A study measuring metabolites of pyrethroid pesticides in an urban sample

[28] Researchers point out that because the organophosphate pesticide metabolites measured in these studies are typically eliminated from the body after a short period of time, their widespread detection suggests "continual" exposure in these samples (Eskenazi et al., 1999: 410).

[29] The metabolite TCPy is both a urinary and an environmental breakdown product of chlorpyrifos and related pesticides. It has a half-life of 27 hours in urine, but is highly stable in the environment, persisting for up to a year in soil (MacIntosh, et al, 1999). Levels in urine therefore reflect the intake of both environmental TCPy and of the parent compounds, including chlorpyrifos.

of Germans concluded that urinary pyrethroid metabolite levels in children did not differ from those in adults (Heudorf & Angerer, 2001). Clearly, the unique pharmacokinetics of different chemical pesticides does not allow for generalisations in this regard.

In most of the above studies it is not possible to assess to what degree lawn and garden care use of pesticides contributes to the measured levels in urine. The NHEXAS researchers have estimated that dietary intake of chlorpyrifos contributes only 7% of the TCPy in urine from their study sample (MacIntosh et al., 2001). It is not possible to determine however, whether the measure of urine TCPy reflects exposure to intact pesticide or to the breakdown product that persists in the environment (Koch et al., 2001). It is equally difficult to say, in the case of chorpyrifos, whether these exposures were due to indoor or outdoor use of this pesticide. The reader is reminded that both chlorpyrifos and diazinon are currently under a program of phasing out most residential-use products containing these insecticides. As of December 2001, chlorpyrifos is no longer available to consumers for home use and will soon be unavailable for residential use by professional applicators as well.

4.4 Vulnerable Subpopulations

When determining the risks from exposure to substances like pesticides it is important to acknowledge that children are not “little adults". Children and infants exhibit both qualitative and quantitative differences that influence their exposure and susceptibility to pesticides compared to adults (National Research Council, 1993; U.S. EPA, 2000a). Children’s behaviour and activity patterns bring them into greater contact with pesticides found in their environment. Greater hand-to-mouth activity and mouthing of items as well as the time they spend close to surfaces where pesticides may accumulate (lawns and carpets) mean that they are more likely to directly ingest ambient pesticide residues. Studies have shown that exposure varies inversely with age and this fits with the model that the greater hand-to-mouth activity of the very young enhances oral ingestion of contaminants including pesticides (Freeman et al., 2001; Eskenazi et al., 1999; Bradman et al., 1997).

A child’s breathing zone is lower and some pesticides will be found in greater concentration closer to the ground. This has been demonstrated with experimental studies of indoor pesticide applications (Fenske et al., 1990). Children’s smaller size and physiological differences mean that they are proportionately more exposed. They breathe in, ingest and absorb more air, water, food and soil per unit body weight and consequently, more of the contaminants found in these media (National Research Council, 1993; Selevan et al., 2000).

The fetus, infant and toddler have potentially the greatest susceptibility to adverse effects from pesticides due to biological differences.[30] Immature organs and tissues (especially the brain, nervous system and lungs) are vulnerable to harm from toxic exposures for a long period of time. Adverse effects in these vulnerable tissues may be permanent and irreversible (Selevan et al., 2000). The neurotoxicity of some pesticides (particularly some insecticides, as will be discussed below) to the developing nervous system is recognized as an area of research that is inadequately understood but

[30] The U.S. National Research Council reported that “differences in toxicity between young and mature animals may be in either direction but are generally modest” (1993: 105). In other words, depending on the specific compound under consideration (and its pharmacokinetics and metabolism) the young may be more, less or equally sensitive to a given substance compared to adults. The U.S. NRC also noted at the time, that they found very few data on the relative toxicity of pesticides in young versus adult humans and that “data on age-dependent pharmacokinetics of pesticides are lacking for most animals” (1993: 106).

of prime importance in assessing the potential for effects from these pesticides (Eskenazi et al., 1999).

In general, their immature metabolic and physiological systems protect children less effectively from toxic exposure and effects. Large-scale accidental pesticide poisonings have demonstrated that children often suffer more extreme effects from exposure and that the dose-response relationship for children is different from that for adults. For example, in Jamaica, accidental poisoning by parathion in contaminated flour indicated that the estimated fatal dose in children was substantially lower than that for adults (Diggory et al., 1977).

Children rely on the protection of adults to avoid undue and unnecessary exposure to substances like pesticides. Children may also be accidentally poisoned from exposure to pesticides that are improperly stored or where appropriate precautions are not taken after use. Symptoms of pesticide poisoning in children are non-specific and can easily be missed (Jackson, 1995). Most pesticide poisonings result from home uses and children are at greatest risk of such accidental exposures. Of the 1,026 suspected pesticide-poisoning reports to the regional Poison Control Centre at Toronto's Hospital for Sick Children in 1990, almost 60% occurred in children less than six years of age (Ferguson et al., 1991).

Children also have a longer "shelf-life" (Goldman, 2000). In other words, they have much more of their life ahead of them and a longer period of time during which exposures can occur and for health problems to manifest. Some research suggests that early low-dose exposure to neurotoxic pesticides, such as bioallethrin, may modify the response to contaminant exposures in adulthood and subsequently hasten age-related degenerative changes (Eriksson & Talts, 2000).

While it is beyond the scope of this report to adequately discuss this topic, the concept, raised above, that early exposures (particularly "adaptive" changes in fetal life that affect fetal nutrient supply) can bring about life long consequences has been studied by Barker and colleagues for more than a decade (see e.g. Barker et al, 2001; Godfrey & Barker, 2001). These researchers have found that altered fetal growth and development (as indicated by low birthweight) is associated with notably higher risk in adulthood of several chronic health problems, such as coronary heart disease (Godfrey & Barker, 2001). They propose that these associations may occur due to a sort of fetal "programming"; the permanent structural and functional result of an "environmental" insult at a critical window of exposure. The notion of critical windows of exposure and developmental effects from environmental exposures has received attention of late from scientists internationally.[31] The potential for adult consequences from early environmental exposures is not well understood but requires further investigation (Selevan et al., 2000). It has been a particular concern of researchers studying the toxicologic effects of low-dose[32] exposures to hormonally active substances, including some pesticides (Foster, 1998). (See further discussion of research into the effects of hormonally active substances in section 8.4 below.)

[31] For example, see Environmental Health Perspectives June 2000 issue (Volume 107, Supplement 3) entitled, "Identifying Critical Windows of Exposure for Children's Health". This monograph publishes multiple papers by numerous international scientific experts developed from the 1999 "Workshop to Identify Critical Windows of Exposure for Children's Health".

[32] We acknowledge that the definition of "low-dose" is important, yet not easily defined in a general manner. A precise definition of "low-dose" would be compound specific and would incorporate data generated from animal toxicity testing. In the context of hormonally active substances, "low-dose effects" (biological changes that result from environmentally relevant exposure levels) are currently an important though controversial, environmental health issue (National Toxicology Program, 2001b). (See discussion on the National Toxicology Program's scientific peer review in section 8.4 below).

Researchers also speculate that the elderly may be at greater vulnerability from exposure to pesticides as well (Weiss, 2000). It is clear that the elderly react differently to medications. There is evidence too of a diminished capacity to compensate for impairments caused by toxic exposures in the aging nervous system (Weiss, 2000). Weiss speculates that such greater susceptibility may reflect in part the impact of early exposures to pesticides or other substances.

Each individual has varying degrees of sensitization to the effects of pesticides and studies indicate that comparable exposures to pesticides can cause significantly different biological effects (Lewalter & Leng, 1999). There are a number of different polymorphisms of genes encoding for enzymes involved in pesticide metabolism that are linked to heightened vulnerability to the toxic effects of pesticides. For example, Lewalter & Leng (1999) cite studies indicating workers with low levels of one transferase enzyme most often reported symptoms of impaired well-being from exposure to the carbamate insecticide, propoxur. McGill University researchers have shown that children who carry certain genetic mutations in the P450 cytochrome enzyme system that is involved in carcinogen metabolism had higher odds of developing acute lymphoblastic leukemia (ALL) with exposure to certain insecticides used indoors (Infante-Rivard, et al., 1999). Relatively new research on increased risk for Parkinson's disease in those exposed to pesticides implicates an underlying genetic susceptibility (see the neurodegenerative effects summary, section 7.4) (Hubble et al., 1998).

The PMRA submits that it is their standard practice to consider additional safety factors in the risk assessment to account for either 1) toxicological evidence of differential susceptibility (whether in the young, the adult or the sick) or 2) uncertainty associated with the exposures for such vulnerable populations (PMRA, 2002b).

5.0 HEALTH EFFECTS RESEARCH

5.1 Introduction

Current knowledge of the health effects from pesticides is largely based on experimental studies in animals and cell cultures as well as from clinical and epidemiological data from people who are exposed to higher than average doses either by accident or through their work.

Acute toxicity of pesticides is best characterized. We know from cases of accidental pesticide poisoning that pesticides can be harmful and are potentially fatal in high[33] doses. Some pesticides can cause various immediate reactions like burning, stinging or itching of eyes, nose, throat and skin. Acute effects can also include nausea, vomiting, diarrhea, wheezing, coughing and headache, symptoms that are non-specific and liable to misdiagnosis. This is especially the case with exposure in children, where symptoms may mimic those of common conditions such as influenza or allergic responses (Jackson, 1995). Therefore, even though our understanding of acute effects from pesticides is relatively more complete, accurate information on diagnoses of pesticide related poisoning might not always be detected due to the potential for clinical misdiagnosis and underreporting.

While we acknowledge that acute exposures to lawn and garden pesticides (i.e. from accidental poisoning) are not uncommon and can represent an important health problem (particularly when users of pesticides do not follow all appropriate precautions and instructions) they are not directly the focus of this report. An emerging area of concern in the last decade has been to better characterize the effects on the general population of chronic exposure to low-levels[34] of pesticides in the environment (Fleming & Herzstein, 1997). Lawn and garden pesticides represent one ambient source of these exposures to pesticides.

Based on the results of recent U.S. biomonitoring studies discussed above, it is reasonable to assume that chronic, low-level exposure to some pesticides is more prevalent among the general population than previously believed.[35] Given that the exposure levels are low and below established Reference Doses, it is not likely that people will manifest immediate health effects from such exposures. It should be noted that regulators describe the Reference Dose, as "the amount of pesticide that is considered safe for human consumption or exposure for each day for a lifetime" (PMRA, 2002b).

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[33] According to the classification by the Ontario Ministry of Agriculture Food and Rural Affairs, most lawn care pesticides commonly used in Canada are deemed to be of slight to moderate acute toxicity by the oral route (OMAFRA, 1999). This reflects that in general, they will only be harmful (fatally or acutely) in high doses as defined in toxicological terms. A high dose exposure (i.e. one that is potentially fatal) can be defined as from 3 to 30 ml (approximately half a teaspoon to two tablespoons) for pesticides of moderate toxicity or greater than 30 ml for those of slight toxicity (OMAFRA, 1999).

[34] The reader is referred to footnote 32 for a definition of "low" doses or levels, as they are understood in the context of this report.

[35] Since these data reflect exposures based on samples from across the U.S., it is not clear whether we can extrapolate these results to make similar statements about exposure in Canadians. Similar population-based exposure studies have not been performed in Canada except among agricultural families (see Bruce et al, 1998; Ritter et al, 1998).

Although the standard battery of toxicity tests assesses chronic, low-level exposure over a good portion of the life cycle, some researchers caution that we lack definitive knowledge from humans of all the potential cumulative and long-term effects of such exposures over an individual's lifetime.

Exposure to pesticides has been positively associated[36] with a range of chronic health effects in humans. The long-term health effects studied fall into three main categories. These include 1) cancer (especially leukemias and lymphomas), 2) reproductive effects (including fertility problems, birth defects, adverse pregnancy outcomes such as spontaneous abortions and perinatal mortality) and 3) neurological effects (manifest as polyneuropathy, neuro-behavioral effects, or neurodegenerative conditions such as Parkinson's disease) (Baldi et al., 1998). Research is also examining the possible role of pesticides in immune system suppression, endocrine alterations, and respiratory effects, although data are not as well developed for these areas. In addition, researchers are addressing the possible links between early exposure to pesticides and long-term effects in children such as cancer and neurobehavioural deficits. The remainder of this section will summarize the research on the potential for health effects in humans by category of effect, focussing primarily on epidemiological data.[37] Fundamental issues that influence interpretation of the human health effects evidence must first be addressed.

5.2 Methodological and Theoretical Considerations

It must be stated clearly and emphatically that the scientific literature examining the health effects associated with pesticides is not conclusive, nor is it uniformly positive. Both methodological and theoretical issues affect the certainty with which we can translate the relevance of existing scientific findings to predict health effects in the general population. These issues also limit our ability to clearly establish the relationship between pesticides and long-term human health. Scientists who study this problem from all perspectives generally agree that, for many reasons, rarely (if ever) is there absolute certainty in interpretation of scientific results (Solomon, 2001; Kamrin, 1997).

There are relatively very few chemical substances for which we can say our knowledge of precisely how they may affect health is certain. For the majority of substances, including many pesticides, the health effects in humans are not fully known and under constant assessment. What we do know about pesticides, from both positive and negative findings, represents only a small portion of a larger, somewhat indistinct picture. In some cases (for certain health effects and for some pesticides) there is relatively much greater uncertainty and gaps in information. For example, the potential for effects from some pesticides on the immune system or on neurological development is not well studied in animals or humans. More science usually does establish greater certainty in the long-term, however, because of the extreme complexities of human diseases, research often yields conflicting results prior to that point. Discussion of the research that has examined the role of phenoxy

[36] The term "association" or "link" is used in epidemiology to denote that there is a relationship (in a statistical sense) between a given exposure and disease outcome, without implying that the relationship is necessarily one of cause and effect (Weisenberger, 1993). Epidemiological principles of causation will be discussed briefly in section 5.4 below.

[37] A focus on epidemiological data is taken mainly for practical reasons. The volume of toxicological data on specific lawn care pesticides is considerable, probably numbers in the thousands of studies and is not readily available in journal publications. For example, in fulfillment of the re-registration requirements of PMRA, the chemical manufacturers of the herbicide 2,4-D submitted results for nearly 300 toxicological studies (mainly unpublished) commissioned since the mid-1980s alone (Page, 2001).

herbicides in the etiology of some human cancers provides a clear example of conflicting results and uncertain conclusions despite a relative wealth of scientific data.

Assessing the health risks from exposure to pesticides is an enormously complicated task. That task is affected by the types of studies, the nature of human biology and development and by the conditions of our exposure to pesticides. Two different sources of information are used to determine risks of adverse chronic health effects from pesticides; 1) data from toxicological experiments using laboratory animals and cell cultures and 2) epidemiological data derived from humans exposed to pesticides. Both types of data have different inherent advantages and limitations.

5.3 Toxicological Studies

Most research on health effects from pesticides has come from experimental studies using animals and cell cultures that are exposed to progressively increasing exposure levels, including very high doses. In the realm of toxicological experiments, high doses refer to doses that are several orders of magnitude higher (several thousand times greater) than the levels to which it is generally expected most people will be exposed. Toxicological studies are currently an accepted methodology for investigating the potential effects from substances like pesticides and for regulatory decisions concerning acceptable uses as discussed earlier in section 3.1. Test animals provide a convenient, cost-effective means of assessing the inherent toxicity for a particular chemical.

As discussed earlier, toxicity testing assesses the potential for adverse effects such as reproductive problems, behavioural abnormalities and cancer, among others. In some cases, for some types of health effects (e.g. harmful effects on the developing nervous system or on the immune system) it is primarily observations from toxicological studies that are available to assess the potential for human health effects. Different samples of test animals are typically exposed to relatively large doses of a given substance under specific test conditions and examined to ascertain the effects of chronic dosing. The test conditions include periods that capture exposure throughout much of the life span (from *in utero* to adulthood). The toxicological data are evaluated to determine the NOAEL[38]. For threshold effects, the NOAEL is then divided by a safety factor (which is between 100 to 1000) that is intended to increase the margins of safety. This yields a measure called the chronic Reference Dose, the level of daily exposure over a human lifetime that it is predicted will be without adverse effects. Safety factor selection[39] is intended to account for the uncertainty in extrapolating from animal data to humans and for the variable sensitivity among human sub-populations according to age. For carcinogenic (non-threshold) effects, rather than application of safety factors, linear extrapolation (mathematical modeling) is used.

Toxicological studies, therefore, are an important foundation for our understanding of the potential for health effects from exposure to pesticides. It can be argued however, that these toxicological studies provide only a prediction of the nature and magnitude of the health effects in humans. As one authority suggests, while "the techniques available for assessment of chronic toxicity, especially carcinogenicity, provide rather clear evidence as to whether or not a particular chemical causes a particular effect in animals … there is great uncertainty about the amounts needed to produce small changes in human cancer incidence" (Kamrin, 1997: 606). Similarly, U.S. National Toxicology

[38] The "no-observed-adverse-effect-level".

[39] According to PMRA, safety factor selection is based on scientific judgement and experience and follows internationally accepted conventions and may be increased if the toxicological data suggest a greater inherent hazard (PMRA, 2002b).

Program (2001a: I-2) documents state that "it is not possible to predict with complete certainty from animal studies alone which agents, substances, mixtures, or exposure circumstances will be carcinogenic in humans." It is beyond the scope of this report to adequately discuss the limitations of toxicological data sources for assessing potential human health effects from pesticides.

5.4 Epidemiological Studies

Because the responses of laboratory animals to chemicals do not always correspond precisely to human responses, additional information is used to evaluate health risks to humans (National Toxicology Program, 2001a). In order to fully characterize the nature of the risks from exposure to pesticides then, data on health effects in humans who are exposed to pesticides are highly desired. Human evidence is typically opportunistic and observational. Human evidence is rarely experimental in the strict sense.[40] It generally comes from either the case reports of people accidentally poisoned by pesticides or from epidemiological studies of people exposed occupationally. Overall, there are relatively fewer studies that have explored the health risks in the general population, from non-occupational exposures to lawn and garden pesticides. This observation is explained in part for reasons that will be discussed below.

Given that most people are exposed to relatively lower doses of pesticides compared to workers (or those with accidental poisoning), the epidemiological evidence therefore also represents an extrapolation. However, unlike the experimental animals (and perhaps more like those exposed through their work) the general population is also potentially and typically exposed to mixtures of pesticides and other chemicals with unknown interactive effects. The utility of the findings from occupational studies for estimating the risks relevant to the general population are limited, given that occupational exposures are typically several orders of magnitude higher than those for the public (Ritter, 1997). Others suggest however, that the results of occupational studies are indicative of where concern should also extend to the residential uses of pesticides (Mao et al., 2000).

As stated earlier, epidemiological studies provide information on associations, which denote that there is a relationship (in a statistical sense) between an exposure and disease outcome, without implying that the relationship is necessarily one of cause and effect (Weisenberger, 1993). Establishing causality in epidemiology involves assessment of all available evidence according to guidelines originally established by Sir Austin Bradford Hill (Hill, 1964). It is extraordinarily difficult to prove causation and often, one can only increase the confidence in the hypothesis that an association between two factors is real (appreciating of course, that with newer information, that hypothesis is subject to modification).

While it is beyond the scope of this report to thoroughly discuss the principles for drawing inferences about causality and how such principles are applied, it is worthwhile drawing attention to some

[40] For some organophosphate and carbamate insecticides there do exist experimental data gathered from studies using human volunteers. (See references to 14 studies cited in SAB/SAP Joint Subcommittee on Data from Human Subjects, 1999). Although the EPA under the Clinton administration had voiced a policy that opposed the use of information from such human tests, under the Bush administration the EPA appeared to be reversing that policy. There is great controversy about the ethics and scientific validity of accepting such results. Recently, the EPA requested guidance from the National Academy of Sciences on the complex scientific and ethical issues posed by the use of human toxicity studies before it formulates any official policy (U.S EPA, 2001d).

elements of Hill's scheme. Among the nine criteria that Hill identifies as important for inferring causality, some key concepts relevant to the present discussion include:[41]

- Strength of the association – that the chance of observing the health effect is significantly greater in the exposed versus the unexposed populations, thereby reducing the possibility that the differences are occurring by chance alone
- Consistency – that similar associations are observed by other researchers studying other populations
- Biological gradient – that a dose-response curve or dose dependent response is observed
- Biological plausibility – that the effects observed are consistent with current understanding of biological mechanisms (informed from multiple perspectives including toxicology, genetics, phamacokinetics, endocrinology, among others)

The epidemiological evidence for health effects from exposure to most pesticides is currently inadequate to draw firm inferences about causality. However, it is instructive to be mindful of these principles when assessing what evidence does exist.

Studying health effects from pesticides is a challenge because of limits to our understanding of the biology of the associated chronic health effects in humans. With some rare exceptions[42], there are no known "signature" health effects specific to pesticide exposure. The chronic health effects most often associated with exposure to pesticides are complex and multifactorial in etiology. Current understanding of the etiology of conditions such as different cancers, various birth defects, reproductive problems, neurological degeneration and asthma, for example, is that these are influenced by a combination of environmental factors (in the broad sense) and aspects of individual biology and lifestyle. It is a significant challenge to determine all the relevant environmental exposures that may play a part in the etiology of these conditions for any given individual. In addition, by definition these chronic health effects do not happen until many months, years, sometimes decades, after the contributory exposures. All of these factors complicate interpretation of research on the potential for health effects from exposure to pesticides.

Central problems in studying human health effects from pesticides stem from the acknowledged limitations of current epidemiological studies for assessing actual risks. Myers and Schettler (2001) point out that only through well-designed prospective studies will we expand our understanding of the range of health effects associated with exposure to pesticides. Such studies would need to carefully monitor the health of large samples of people through time and have adequate characterization of exposures (through study of biological markers of exposure) in order to substantially improve knowledge. A further improvement on this ideal study would be to study populations that provide "natural experiments" in that they allow for assessing the health effects of an intervention that removes the risk factor of interest. However, because we are a long-lived species with considerable genetic diversity and a complex development and physiology, long-term prospective studies in humans are quite difficult and generally less feasible. Because of the latency and the rarity (in epidemiological terms) of many of the chronic health effects of interest, prospective studies take a long time, require very large sample sizes to detect health effects of interest, and therefore they are expensive. (They also lack the control of important factors that comes with an experiment on small samples of animals or cultures of cells.)

[41] The entire Hill scheme includes additional criteria that will not be discussed here, including specificity of the association, temporality, coherence, reversibility and analogy.

[42] The clinical syndrome "organophosphate induced delayed neuropathy" (OPIDN), is a delayed effect of acute exposure to these neurotoxic insecticides (Keifer & Mahurin, 1997).

In the absence of such ideal studies, epidemiologists must turn to alternate study designs. A suitable way to study the relationship between pesticides and chronic health effects in humans is through retrospective data gathered from either cohort studies or case-control studies.[43]

Cohort studies are considered the strongest epidemiological studies, methodologically speaking. They document the health of groups of people who have been exposed historically to pesticides through their work and examine whether they have increased risks for specific health effects or for mortality from specific diseases. The advantage in using exposed workers, is that if there is an elevated risk of a given chronic health outcome it will be easier to detect in those with higher exposure than in samples of the general population with presumably lower levels of exposure. For this reason, researchers may also conduct a case-control[44] study nested within the cohort. Such nested case-control studies are an equivalently strong design. Farmers and agricultural workers are among the most frequently studied occupational cohorts for assessing effects from pesticide exposure because they generally represent the most highly exposed population of pesticide users.

A common methodological criticism of epidemiological studies is insufficient sample size. In order to detect increased risks of rare conditions such as cancer, researchers require large sample sizes. Sample size has direct influence on the power of a study to detect differences that are real as opposed to artifactual. The International Agency for Research on Cancer (IARC) has coordinated a large cohort study of nearly 27,000 workers employed in herbicide manufacturing plants from eight countries (Kogevinas et al., 1997). Cohort studies of this sort, with large sample sizes, are the exception rather than the rule in epidemiological evidence (Munro et al., 1992).

An alternative to large cohort studies is the case-control study design. Case-control studies determine whether people who manifest a certain type of rare disease (for example, non-Hodgkin's lymphoma or Parkinson's disease) are more likely to have been exposed to pesticides than people who do not have that condition but are otherwise similar to them for other influential characteristics. Cases refer to the people who have the health outcome of interest and controls represent those who do not. The case-control study design has the advantage of being able to concentrate the study on a smaller sample of people. Case-control studies have the disadvantage that the self-reported exposures of those with rare conditions such as cancer can be differentially greater (engendering what is known as recall bias) compared to those for control subjects. Differential recall bias is often assumed to exist in case-control studies, but has apparently rarely been documented by validation studies (Infante-Rivard & Jacques, 2000).

The primary, consistent limitation of any retrospective studies examining the risks of chronic health effects, however, is the difficulty obtaining accurate and specific information on pesticide exposure. This has been the case especially with population-based case-control studies (Olshan & Daniels, 2000). Typically only indirect means of determining exposure are available or feasible, rather than

[43] A third type of epidemiological study is the ecological study, which represents the weakest design, statistically speaking. Ecological studies statistically describe the patterns of health problems in a community, correlating these to available exposure data. Data are assessed for correlations between disease and various risk factors. Data on health effects and exposure are typically cross-sectional in nature and derived from pre-existing sources such as mortality records, cancer registry data, regional pesticide spraying patterns, and so on. Most ecological studies assessing pesticide exposure and effects have focused on agricultural regions. While these studies are methodologically less rigourous they are important for hypothesis generation and initial investigations of the associations between environmental exposure and health effects.

[44] See discussion below for a description of case-control studies.

direct means such as through biological measures.[45] Indirect means of assessing exposure have included for example, report of employment in a specific occupation, such as "farmer", or proximity of subject's residence to areas of documented agricultural pesticide application. Some studies gather data from interview of subjects, whereas other studies collect data from birth or death certificates or disease registries. The level of detail of indirect measures of exposure can vary considerably from study to study and is largely dependent on study design and objectives.

Many of the studies examining the associations between pesticides and chronic health effects have been exploratory, trying to assess the role of a variety of exposures to environmental chemicals, including pesticides. Such exploratory studies typically have only asked case subjects whether they were exposed to "pesticides" or general categories of pesticides such as "herbicides", "insecticides" or "fungicides" (Daniels et al., 1997). In a review of over thirty studies of pesticides and childhood cancers, Daniels and co-workers (1997) cite that over three-quarters of these studies were only able to present exposure as a dichotomous variable, separating subjects into "ever" versus "never-exposed" categories. Only recently has there been collection of greater detail of specific pesticide exposure in some population-based retrospective studies (see for example, McDuffie et al., 2001; Arbuckle et al., 2001).

Indirect data on exposure derive generally from questions asked of the subject or a proxy respondent such as parents, next-of-kin or neighbours. This method of inferring exposure (i.e. from self-reported data that cannot be independently verified) is subject to other problems aside from lack of detail, problems such as recall or reporting bias. Recall bias can manifest as either overreporting or underreporting depending on the type of respondent. Overreporting is a more common problem with case subjects in case-control studies. It is generally observed that those who have had a particular rare health effect such as cancer, (or the parents of children with such a health effect) have enhanced recall of many different exposures, whether they are relevant or not. This occurs because it is assumed that sick people look for reasons for their illness (or the parents of sick children are motivated to report a wider range of exposures). In theory, recall bias or overreporting can lead to overestimation of the influence of that exposure as a risk factor.[46]

Inaccurate or inadequate recall can occur due to the fallibility of memory and leads to inaccurate reporting of pesticide exposure. In addition, it has been observed that recall is generally poor for the frequency of use and types of pesticides used when subjects are asked to recall the specifics of their exposure to pesticides many years or even decades earlier as is frequently the case in epidemiological studies (Olshan & Daniels, 2000).

Existing studies show that indirect or surrogate assessment of exposure can often be inadequate. The adequacy of exposure determination will directly influence the strength of an association and therefore the interpretation of the evidence. Statistical power will be lower and results generally biased toward the null when assessment of exposure is inadequate (Landrigan & Goldman, 1998). In a recent commentary on studies examining the potential risks of childhood cancers from exposure to pesticides, Olshan and Daniels (2000) suggest that those studies with an *a priori* interest in assessing

[45] Biological measures generally only reflect recent exposures because current use pesticides are generally relatively non-persistent. Therefore, biomarkers are of limited use for determining individual dose when studying long-term effects.

[46] It is noteworthy that where tests for heterogeneity of study design were included in recent meta-analyses of cancer risk in farmers (e.g. Acquavella et al, 1998c; Khuder et al, 1998a) researchers showed that this had an important influence on the strength of the reported findings. Cohort studies typically showed lower relative risks for cancer than case-control studies. Acquavella and colleagues (1998c) interpret this as an overestimation of risks in the case-control studies.

the role of pesticides were more likely to have greater detail in exposure ascertainment and were also more likely to show positive associations in their data.

Studies of workers exposed to pesticides generally provide better data on exposure although they may not be immune to systematic errors in exposure ascertainment. Again, much depends on the study design and aims. Use of occupational title rather than self-reported details of pesticide use can mean less bias, but no greater certainty of when, how much, or indeed if, exposure occurred. For example, in the U.S., "licensed pesticide applicators" can include private applicators (generally considered "farmers", but including ranchers, floriculturists or orchardists) or they can be commercial or public applicators, people who are licensed to apply restricted-use pesticides in non-private, non-agricultural contexts (Fleming et al., 1999). The combined group of commercial and public applicators are considered pesticide applicators but includes both those who apply pesticides and those who supervise others in the application of pesticides but may not necessarily have comparable exposures (Fleming et al., 1999).

Occupational exposure data are generally best for those who work in pesticide manufacturing plants as exposure can be inferred from job records or from questionnaires designed to elicit detailed information on work-related activities that influence exposure (Kogevinas et al., 1997; Burns et al., 2001). However, these types of studies have been comparatively rare in the epidemiological literature.

A final key methodological limitation is that even where exposure ascertainment is more rigourous, seldom are researchers able to appropriately control for confounding factors. In other words, most epidemiological studies, even the most carefully designed, are unable to adequately control for all the other exposures that might independently explain any increased risk of health effects attributed to pesticides. There is also no way to tease out whether observed positive associations between pesticides and health effects are indicative of other factors that interact with pesticides to heighten risk. Studies examining health risks in agricultural workers are often exemplified as those with inadequate control over confounding factors. These subjects are often exposed to other environmental factors, both biological, chemical and physical that may also account for some observed increased risks. Some suggest also that where increased health effects are observed for agricultural workers it may be a phenomenon of pesticides interacting with some unknown, other aspect of the agricultural environment (Ritter, 1997; Infante-Rivard & Sinnett, 1999; Mao et al., 2000).

Confounding exposure may occur because pesticides themselves are complex chemical formulations. Beyond the active ingredient, pesticides also include formulants[47] (substances added to aid the effectiveness of the active ingredient) and may contain contaminants that are the unavoidable product of the manufacturing process.[48] It was determined from cohort studies that dioxin contamination of the phenoxy herbicide 2,4,5-T[49] may have explained any increased risks for

[47] These are referred to as "inerts" in the parlance of the U.S. EPA.

[48] In Canada, under the Toxic Substances Management Policy, contaminants such as dioxin, that may be in pesticides must be addressed by virtual elimination or life-cycle management (PMRA, 1999a). It should be noted that in 1981 Agriculture and Agri-Food Canada set a limit on dioxin levels in 2,4-D products after detecting levels of certain dioxins (PMRA, 1994). The contaminants detected (at levels between 100 and 4000ppb) included dichlorinated, trichlorinated and tetrachlorinated dioxins, but the highly toxic 2,3,7,8-TCDD was not detected in any 2,4-D product (Toronto Public Health, 1988).

[49] Although 2,4,5-T was once registered in Canada for use in forestry and not in lawn and garden products, the PMRA reports that it has not been used in Canada since 1982 and its registration was discontinued in 1985 (PMRA, 2002b).

particular cancers found in chemical workers (Kogevinas, et al. 1997). Pesticide manufacturers commission toxicological testing of the formulated versions of their products as a requirement for registration or re-evaluation (D. Page, personal communication, September 2001). However, epidemiological studies that show associations between pesticide use and effects, typically cannot discern whether these effects are occurring because of exposure to a given active ingredient, a biologically active formulant or contaminants in the product.

Lastly, in the case of some health effects the published studies do not allow for drawing of clear inferences due to the absence of appropriate studies. Conclusions cannot be definitive, not only because of inadequate evidence, but also because the relevant studies have simply not been done. This is particularly true for understanding the influence of chronic low-level pesticide exposure on neurodevelopmental effects (Eskenazi et al., 1999) and pediatric cancers (Olshan & Daniels, 2000).

All of the above methodological and theoretical issues surrounding the human health effects evidence limit our ability to draw firm conclusions and indicate that while some studies provide suggestive evidence and other studies provide contrasting findings, overall, the findings on the association between pesticides and health effects are inconclusive.

6.0 CANCER RESEARCH

6.1 Introduction

Cancer has traditionally been the focus of studies examining health effects from pesticides and other environmental contaminants. There is substantial work that has explored the relationships between pesticide exposure and cancer for commonly used lawn herbicides like the phenoxy acids, as will be discussed below.[50] Data come from experiments using cell cultures and test animals and from epidemiological studies of worker populations. Despite an extensive scientific literature that addresses the possible role of phenoxy herbicides in human cancer etiology, there remains considerable uncertainty and conflicting opinion as to whether or not an association in fact exists. Although animal data are available as per registration requirements, for most other types of lawn pesticides the human carcinogenicity potential is not as well studied and under continuing investigation.

6.2 Studies of Occupational Exposure and Cancer

Although authorities qualify that exposure to lawn and garden pesticides is not a major, possible cause of cancer for the general population (Ritter, 1997), studies of those occupationally exposed to pesticides in general (i.e. not necessarily restricted to lawn and turf pesticides) provide some support for the idea that pesticides may elevate risks of different cancers in these worker populations. A 1993 review concludes that there was no consistent evidence of higher cancer mortality[51] among pesticide manufacturers or applicators (including farmers) compared to the general population (Maroni & Fait, 1993). However individual studies of farmers, pesticide applicators or those working in the manufacture of pesticides have found positive (if inconsistent) associations between certain types of cancers and exposure to pesticides. Most consistently, researchers have found positive associations between potential exposure to pesticides and non-Hodgkin's lymphoma [NHL] (Khuder et al., 1998a; Mao et al., 2000; McDuffie et al., 2001; Zheng et al., 2001), multiple myeloma (Khuder & Mutgi, 1997; Swaen et al., 1992) and prostate cancer (Fleming et al., 1999; Dich & Wiklund, 1998).

The existing studies however, disagree on the question of increased cancer rates among these worker populations, such as farmers. A recent meta-analysis performed by Monsanto researchers (Acquavella et al., 1998c) concludes that, with the exception of lip cancer, they could not show elevated rates for several other types of cancer in farmers. Acquavella and colleagues also underscore that given the pronounced heterogeneity in studies by design type and by nationality of

[50] Substantial research has also addressed the carcinogenicity of insecticides of the organochlorine class. Because these pesticides have not been in use in this country for some decades and are not relevant to a discussion of lawn and garden use pesticides, this literature will not be addressed here.

[51] Mortality studies tabulate and compare death rates from diseases such as cancer and therefore do not fully account for differences in the occurrence of cancer. Mortality studies are less informative of the risks from cancers that are usually non-fatal or have higher survivorship. Differences in cancer occurrence are assessed via incidence studies.

sample population, and because of a bias[52] towards underreporting of null or negative results, this limits the usefulness of meta-analyses in these circumstances. These concerns reflect a longstanding scientific deliberation about the limitations of meta-analyses [see for example, discussions by Shapiro (1994) and Greenland (1994) among others].

Researchers at the Medical College of Ohio performing meta-analyses on studies addressing specific types of cancer in farmers suggest there are slightly to moderately elevated risks for multiple myeloma (Khuder & Mutgi, 1997), NHL (Khuder et al., 1998a) and Hodgkin's disease (Khuder et al., 1999). Although noting inconsistency of findings, based on the preponderance of positive studies and an apparent lack of publication bias, these researchers have also suggested there are weak associations between farming and risks of brain cancer (Khuder et al. 1998b), prostate cancer (Keller-Byrne et al., 1997) and leukemia (Keller-Byrne et al., 1995).

These findings are complicated by the fact discussed earlier that there may be multiple factors influencing cancer risk among those occupationally exposed. Other relevant exposures, such as to fertilizers, solvents, oils, wood dust, diesel exhausts, infectious organisms or sunlight, may influence the risks of cancers among farmers in particular (Ritter, 1997; Infante-Rivard & Sinnett, 1999; Mao et al., 2000). As noted above, direct and verifiable data on actual pesticide exposure are difficult to obtain retrospectively. In addition, it is frequently difficult to assess actual exposure to specific types of pesticides in these workers. As one cohort study discussed below suggests with reference to their proxy measure for exposure, holding a license, allows pesticide applicators access to several dozens of different pesticides including many restricted use products (that would not be available to consumers for lawns and gardens) (Fleming et al, 1999).

A 1999 retrospective, cancer incidence study of a large cohort of licensed pesticide applicators in Florida (n = 33,658) found that standardized incidence rates[53] for all cancer sites were significantly lower compared to the general population for both males and females (Fleming et al. 1999). Most site-specific cancer rates were lower than for the general population. Fleming and colleagues did, however, find statistically significantly higher rates of prostate (353 cases, age-adjusted SIR=1.91; 95% C.I. 1.71-2.13)[54] and testicular cancer (23 cases, age-adjusted SIR = 2.48; 95% C.I. 1.57-3.72) in men. Although the number of female applicators out of the total sample was much smaller (n = 3503) the authors reported significantly higher standardized incidence rate of cervical cancer (11 cases age-adjusted SIR = 3.69; 95% C.I. 1.84-6.61) among women applicators. The study authors acknowledge that a limitation in their analysis was that exposure ascertainment was based on a surrogate measure, the licensure status and number of years a license was held, and that they did not obtain details on pesticide exposure from sample subjects (Fleming et al., 1999).

Studies of NHL have most commonly found some association to pesticide exposure in occupational samples. The previously mentioned meta-analysis of 36 studies of NHL and farming concluded there is a slightly elevated (non-significant) risk of farmers developing NHL compared to the general population (Khuder et al., 1998a). This study showed that case-control studies generally were

[52] Publication bias is generally found to reflect researcher rather than editorial decisions as researchers appear to be more likely to report significant or positive results rather than negative or equivocal results (e.g. see Dickersin & Min, 1993).

[53] SIR is the Standarized Incidence Rate – The rate at which new events occur in a population after removing the possible effects associated with differences in age or other confounding variables (Last, 1988).

[54] The 95% Confidence Interval (C.I.) is a range of values for a variable of interest constructed so that this range has a 95% probability of including the true value of the variable (Last, 1988). The C.I. provides an estimate of the inherent variability in the point estimate.

associated with higher (statistically significant) risk estimates as compared to mortality/incidence or cohort studies. For example, the above-mentioned Florida cohort study found NHL risks were lower among pesticide applicators than compared to the general population (Fleming et al., 1999). Khuder and colleagues (1998a) meta-analysis also found that studies in American farmers generally were associated with higher risk estimates than was the case for non-American studies. These differences are reflective of the heterogeneity of studies analysed.

A national case-control study conducted by researchers at academic and medical institutions has studied the exposure characteristics of 517 cases of NHL in Canada (McDuffie et al., 2001). The authors found statistically significant increases in risk of NHL for several potential pesticide exposures including some phenoxy herbicides, OPs, carbamates and amide fungicides as well as, certain organochlorine pesticides. Relative to other phenoxy herbicides and other pesticides, their reported odds ratios[55] for 2,4-D and NHL were modest, although statistically significant (O.R. 1.32; 95% C.I. 1.01-1.73).[56] For example, odds ratios for two other phenoxy herbicides, dicamba and mecoprop were higher at 1.68 (95% C.I. 1.00-2.81) and 2.33 (95% C.I. 1.58-3.44) respectively. The highest odds ratio was for aldrin, a banned organochlorine pesticide (O.R. = 3.42; 95% C.I. 1.18-9.95).[57]

Other studies have found positive associations between NHL and specific pesticides or categories of pesticides other than herbicides. Among these are included, fungicides (Hardell & Eriksson, 1999; McDuffie et al., 2001) and insecticides such as the carbamate, carbaryl (Nanni et al., 1996; Zheng et al., 2001), OPs, such as diazinon (Waddell et al., 2001) and lindane (Blair et al., 1998).

[55] The ratio of two odds. Odds is defined as the ratio of the probability of occurrence of an event to that of nonoccurrence (Last, 1988).

[56] For C.I.'s of odds ratios, generally if the C.I. includes the value "one", (one indicating that the odds are equivalent for both exposed versus unexposed) the data are suggestive of lack of effect.

[57] Other significant predictors of NHL in this sample were a family and previous personal history of cancer.

6.3 Studies of Cancer and the Phenoxy Herbicides

Much of the debate on the carcinogenicity of pesticides has centred on the risks from the common lawn care herbicides, the phenoxy acids. Animal studies suggest that the phenoxy acids, such as 2,4-D, generally have very low to no risk of producing birth defects, genetic mutations or cancer (WHO, 1996). This evidence implies that there is limited biological plausibility for hypotheses that these phenoxy herbicides act as genotoxic carcinogens.

Studies of workers from chemical plants where phenoxy herbicides and chlorophenols are made have shown inconsistent results. There is some degree of increased odds for NHL and other cancers in samples from Germany (Becher et al., 1996) and the Netherlands (Hooiveld et al., 1998). However, a study of NHL and soft tissue sarcoma (STS) in chemical workers worldwide suggested increased risks for STS but ambiguous results for NHL (Kogevinas et al., 1997). Most cohort studies have not shown an association between 2,4-D and NHL or other cancers (e.g. see Asp et al., 1994; Lynge, 1998; Burns et al., 2001). Exposure to different phenoxy herbicides and to dioxin contaminants[58] in some phenoxy herbicides (2,4,5-T in particular) may explain the moderate increase in risks of some cancers in these workers (Kogevinas et al., 1997).

A small cohort study of Swedish lumberjacks showed that cancer incidence was only significantly elevated in a small subgroup of foremen (n=15 out of 514) who were highly exposed to phenoxy herbicides (a mixture of 2,4-D and 2,4,5-T) (Thorn et al., 2000).

Other studies however, have not supported the conclusion that these herbicides increase the risks of these specific cancers because their findings have been weak or negative. A recent Dow Chemical study of workers involved in making 2,4-D did not show increased risks of death[59] from any cancers, including NHL and STS (Burns et al., 2001).

Because 2,4-D has been in use for over five decades and is the most widely used herbicide, there has been a considerable volume of scientific research devoted to studying its effects. Several major scientific panels have evaluated that body of research over the years and have described the evidence for cancer effects in humans as “limited”, “inconclusive”, “inconsistent” and “weak”.[60]

In 1992, Munro and colleagues[61] conducted a comprehensive review of studies examining the toxicology and epidemiology of 2,4-D (Munro et al., 1992). Munro and colleagues applied the Hill (1965) criteria for assessing causation from scientific data. They concluded that the data on 2,4-D did not support that it was a cause of any health effects in humans. In their review of over one hundred epidemiological studies, they determined that few have sufficient rigour in their exposure assessment to provide meaningful information.

Other review panels have concluded that studies of 2,4-D require ongoing examination. 2,4-D is the most commonly used of herbicides and therefore many more people are exposed to it than to other

[58] See footnotes 48 and 49 above for further discussion on dioxin contamination of phenoxy herbicides.

[59] See footnote 51 for the limitations of cancer mortality studies.

[60] These groups include, the Harvard School of Public Health, Joint Science Advisory Board/Science Advisory Panel of the U.S. EPA, 1994, Health Canada, among others, as summarized in the 1996 WHO report.

[61] Dr. Munro and colleagues were involved as independent researchers from Cantox, a toxicology research consulting company.

pesticides. As such, even if 2,4-D exposure were associated with only modest increases in cancer risk it would be of concern given the potential for population exposure (California EPA, 1998). U.S. EPA (1997a) places 2,4-D in the Group D category for human carcinogenicity potential. The Group D categorization means that the evidence is inadequate and cannot be interpreted as indicative of either the presence or absence of cancer effects. The most recent review of the studies on 2,4-D by University of Michigan researchers also suggests that the information available isn't adequate to conclude that 2,4-D causes cancer (Garabrant & Philbert, in press).

Recently the Health and Consumer Protection Directorate-General for the Commission of the European Communities concluded that use of 2,4-D-containing products does not breach acceptable safety requirements. They also concluded that available evidence from epidemiological studies does not allow for establishing a clear association between cancer development and exposure to phenoxy herbicides (European Commission, 2001). 2,4-D is currently under priority evaluation by both the PMRA (under the Action Plan for Urban Use Pesticides) and the U.S. EPA, although the carcinogenicity classification has already been addressed as indicated above (U.S EPA, 1997a). The PMRA's 2,4-D re-evaluation in relation to lawn and turf use is slated for completion by spring 2002.

6.4 Studies of Childhood Cancer

The role of pesticides in childhood cancers has been a focus of study over the last decade. Although the epidemiological evidence is limited[62] and far from conclusive, it suggests that exposure to pesticides in general (i.e. not restricted to lawn and garden pesticides) may contribute to moderately increased risks of certain cancers in children (Olshan & Daniels, 2000; Zahm & Ward, 1998). Some childhood leukemia may be related to parental exposure to pesticides. As recent reviews here above have pointed out, there is need for further studies with stronger exposure measures before we have better understanding of how pesticides may or may not influence the etiology of childhood cancer (Olshan & Daniels, 2000; Zahm & Ward, 1998).

Epidemiological study of pesticides as a risk factor in childhood cancer presents many challenges and limitations. The first challenge is that our understanding of the factors causing childhood cancer is far less well defined compared to that for adults (Olshan et al., 2000). Although the mechanisms of action of carcinogens may be generally similar between adults and children, it is also recognized that there may be major differences in susceptibility to carcinogens of the developing individual compared to the adult (U.S. EPA, 2000c). Relevant exposure windows and the precise biological mechanisms by which cancer comes about in children are not entirely clear (Kristensen et al., 1996). Direct exposure of developing tissues of the fetus or young infant is one potential route. Inheritance of damaged germ cell DNA from either mother or father is another mechanism that may explain the appearance of cancer in childhood. There is both experimental and epidemiological evidence suggesting that exposures to environmental toxicants (in general) *in utero* and during early childhood, increase the likelihood of cancer occurrence in both children and adults (Olshan et al., 2000).

It should be noted that childhood cancer is also difficult to study because it is a rare health outcome in the epidemiological sense. Statistics published by the National Cancer Institute of Canada (2001) for 1992-96, indicate that the age-standardized incidence rate (ASIR) for all childhood cancers was

[62] Data is derived from case reports and case-control epidemiological studies mainly although there has been one cohort study examining cancer risks in the children of Norwegian farmers (Kristensen et al, 1996). There have been only 40 odd published epidemiological studies examining pediatric cancers and limited experimental data (Olshan & Daniels, 2000).

about 16 per 100,000 children (ages 0 to 19) or, an average of 1,266 Canadian children diagnosed annually with cancer during that time. Data from Health Canada suggest that the childhood cancer incidence rate has hovered around this figure from 1984 to 1998, the years for which these data are currently available (Health Canada, 2002).[63]

As with studies of adult-onset cancer, exposure ascertainment is problematic in epidemiological studies of pediatric cancers (Olshan & Daniels, 2000).

With these cautions in mind, researchers suggest nonetheless that certain childhood cancers may be related to pesticide exposures either directly or via parental exposure. Meta-analysis of several dozen studies indicates there is reason to suspect that pre-conceptional, prenatal and early childhood exposures to pesticides are associated with moderate increases in childhood brain tumours and leukemias (Daniels et al., 1997). Home use of pesticides appeared to account for the greatest risk of these cancers but research has not clearly implicated yard and garden pesticides alone (Infante-Rivard et al, 1999; Daniels et al., 1997; Leiss and Savitz, 1995). Some specific pesticide exposures that have been positively associated with elevated risks of certain pediatric cancers are flea and tick treatments, no-pest strips and lindane-based lice treatments (Pogoda & Preston-Martin, 1997; Daniels et al., 1997; Leiss and Savitz, 1995).

Two groups studying paediatric non-Hodgkin's lymphoma report increased risks with frequent use of some pesticides in the home although results are not always statistically significant (Buckley et al., 2000; Meinert et al., 2000). The Children's Cancer Group in the U.S. determined that there were significantly increased odds of NHL among children of mothers reporting frequent use of household insecticides around the time of pregnancy (O.R. for use 1 to 2 times per week = 2.67; 95% C.I. 0.96-7.18) (Buckley et al., 2000). Significantly increased risks of NHL were also associated with prenatal exposure to insecticides from professional exterminator applications around the home (O.R. 2.98; 95% C.I. 1.44-6.16) and for a child's direct exposure to pesticides (O.R. 2.35; 95% C.I. 1.37-4.03) (Buckley et al., 2000). There were positive but non-significant associations between childhood NHL and prenatal exposure to garden sprays or parental occupational exposure (Buckley et al., 2000).

A large case-control study of childhood leukemia and NHL by researchers from the Johannes Gutenberg-University of Mainz, Germany found that there were positive associations between lymphomas and residential use of insecticides, with less pronounced risks for leukemia and no associations for other types of childhood cancer and home insecticide applications. Meinert and colleagues (2000) were unable to confirm a previous finding from a smaller study of positive association between pesticide use in gardens and childhood leukemia (Meinert et al., 1996).

Researchers from McGill University and Université de Montréal have conducted the largest Canadian case-control study of the risk of childhood acute lymphoblastic leukemia (ALL) with exposure to pesticides used in and around the home (Infante-Rivard et al., 1999). Mothers of cases and controls were questioned extensively regarding their use of pesticides in and around the home for categories of pest control scenarios. Infante-Rivard and colleagues (1999) found that risks of childhood ALL were higher with increased use of herbicides, plant insecticides and products for

[63] While we cannot adequately discuss data on childhood cancer trends in Canada in the present report, it is worthwhile noting that there has been a debate concerning historical childhood cancer trends in the U.S.. Some researchers have contended that rates of childhood cancer there have increased 1% per year for the last 25 years (Gurney et al, 1996), however a recent report by the U.S. National Cancer Institute clarifies that, with the exception of transient increases in the mid 1980s that were explained by improved detection methods (the use of MRI versus CT scans) and classification of tumours, childhood cancer rates in the U.S. have not changed substantially since the mid 1980s (Linet et al., 1999).

trees either during pregnancy or from birth to date of diagnosis. Risks were higher the more frequent was the use of pesticides in and around the home. Although there was considerable overlap in pesticide uses in and around the home, many mothers indicating exposure to multiple agents, the authors showed independently increased risks for childhood ALL when mothers reported using herbicides during pregnancy (O.R. = 1.56; 95% C.I. 0.96-2.55). An increased risk with prenatal exposure to some pesticides agrees with recent clinical research suggesting that ALL may be initiated *in utero* (Infante-Rivard et al., 1999).

Several studies have examined the risk associated with cancer in the children of parents exposed to pesticides at work with varying results. Increased risk of brain tumour, NHL and Wilms tumour (a type of kidney cancer) have been found in various Scandinavian studies of children whose parents worked on farms (Kristensen et al., 1996; Hardell & Eriksson, 1999; Feychting et al., 2001). A study by Fear and colleagues (1998) used data from death certificates of children 0 to 14 years for three time periods in England and Wales. They conclude that children of fathers who had possible exposure to pesticides through their work (i.e. farmers, agricultural workers, agricultural machinery drivers, gardeners and foresters) had overall reduced risk of all cancers combined but statistically significant increase in the risk of death from kidney cancer (Fear et al., 1998). Others have determined increased risks of cancer in the children of fathers occupationally exposed to pesticides. Feychting and co-workers (2001) found higher relative risk[64] of nervous system tumours but not childhood leukemia with paternal exposure to pesticides. Nanni and colleagues (1996) found that life on a farm or in an animal breeding context before age 13 was an independent factor increasing the risk for chronic lymphocytic leukemias and non-Hodgkin's lymphoma in adults who were farmers or animal breeders.

[64] Relative Risk – the ratio of the risk of disease or death among the exposed to the risk among the unexposed; this usage is synonymous with risk ratio.

7.0 NEUROTOXICITY RESEARCH

7.1 Introduction

Specific lawn and garden pesticides (mainly insecticides) have been associated with negative effects on the central or peripheral nervous systems of animals and humans. The neurological symptoms following acute exposure to the neurotoxic organophosphate and carbamate groups of insecticides are best described.

The epidemiological data describing the long-term effects from chronic, low-level exposure to neurotoxic pesticides is still limited (Baldi et al., 2001). Most studies have assessed occupationally exposed subjects on tests of neuropsychological performance with suggestive (although varying) findings of subclinical deficits.

Another thrust of recent research has been to examine the association of pesticide exposure with the development of neurodegenerative disorders such as Parkinson's Disease (PD). Evidence suggests that exposure to some pesticides, interacting with genetic and other factors, may increase the susceptibility to PD.

The evidence of the potential for toxicity to the developing nervous system from exposure to specific pesticides is restricted to experimental studies of laboratory animals and cell cultures. Limited data are available only for certain insecticides; however, they are suggestive of the possibility of differential susceptibility of the immature brain and nervous system to adverse, persistent effects (Eskenazi et al., 1999). The potential for differential susceptibility is currently being addressed in the re-evaluation of organophophate insecticides (PMRA, 2002b).

7.2 Acute Neurotoxic Effects

Some pesticides are associated with effects on the central or peripheral nervous systems of animals and humans. Organophosphates (OPs) and carbamates are designed to be neurotoxic to living organisms. The mechanism of action in both classes of pesticide is to inhibit proper functioning of the enzyme cholinesterase, which is responsible for metabolizing the neurotransmitter acetylcholine. Acute exposure to anticholinesterase pesticides above certain dose levels produces both immediate and delayed neurological and cognitive symptoms. These are reversible in the case of carbamate exposures and irreversible for OPs (Steenland, 1996; Steenland et al., 1994). Studies of exposed workers have shown effects including sensory and motor problems, cognitive and psychological changes from acute exposure to OPs and carbamates. Other outdoor use pesticides that can be neurotoxic with acute, high-level exposure include pyrethroids (Vijverberg & van den Bercken, 1990), and the chlorphenoxy herbicide, 2,4-D (Costa, 1997; Mattson et al., 1997). Previous studies concluded however, that unless there is "substantial overexposure", 2,4-D is an unlikely cause of

neurological dysfunction (such as polyneuropathy) based on human[65] and toxicological data (Mattsson & Eisenbrandt, 1990).

The effect of acute exposure may also manifest as long-term, delayed effects as in the clinical syndrome "organophosphate induced delayed (poly)neuropathy" (OPIDN), which involves malfunction of the nerves that transmit impulses to the limbs (Keifer & Mahurin, 1997). Termiticide applicators reporting prior chlorpyrifos poisoning demonstrated lower performance on a number of tests of neurologic function (Steenland et al., 2000).

7.3 Chronic Neurotoxic Effects

There are limited data and opinions diverge as to the neurological effects of long-term low-level exposures to pesticides. Evidence is suggestive that chronic exposure to pesticides may also manifest as subtle (subclinical) changes in brain function. Several studies have identified increased risks of neuropsychological deficits appearing in those occupationally exposed to pesticides (see for example, Stephens et al., 1995; Beach et al., 1996; Cole et al., 1997; Bosma et al., 2000). Others however, have not clearly shown such long-term neurocognitive deficits (see for example, Steenland et al., 2000; Daniell et al., 1992).

A cohort study of pesticide applicators exposed to chlorpyrifos for termite treatment found only limited evidence of neurobehavioural deficits on a variety of tests (Steenland et al., 2000). Although it was not detected on quantitative tests, the exposed subjects did report symptoms such as fatigue, reduced muscle strength, memory problems and mood disturbances significantly more often (Steenland et al., 2000).

A large prospective cohort study of aging in the Netherlands showed that the risk of mild cognitive dysfunction (MCD)[66] was increased in those with past exposure (generally occupational) to pesticides but not other occupational chemicals, such as metals and organic solvents (Bosma et al., 2000).

A large cross-sectional study of nearly a thousand French vineyard workers who are chronically exposed to pesticides (mainly fungicides) demonstrated impaired performance on neuropsychological tests that was indicative of slower information processing ability (Baldi et al., 2001). Compared to controls (non-exposed workers), workers exposed (both directly and indirectly) scored poorer on tests of memory, attention, verbal fluency and abstract thinking (Baldi et al., 2001). While these mild neuropsychological deficits are subclinical in nature, the authors suggest that they may have implications for quality of life or they might be indicative of further long-term progressive degenerative changes (Baldi et al., 2001).

[65] In the late 1950s and early 1960s 2,4-D was used experimentally as a treatment for cancer and disseminated coccidioiomycosis and there has been extensive study of the Vietnam war veterans exposed to Agent Orange of which 2,4-D was one component (Mattsson & Eisenbrandt, 1990).

[66] MCD was defined as scores in the lowest 10th percentile for at least two out of five tests of mental function, or cognitive impairment without dementia (Bosma et al., 2000).

7.4 Studies of Neurodegenerative Effects

Epidemiological and experimental research on the etiology of the neurodegenerative condition Parkinson's Disease (PD) has focused recently on the role of exposure to pesticides. [67] An ecological study suggested an environmental link to PD finding a correlation between regional prevalence of PD and the volume of pesticides sold in nine rural areas of Quebec (Barbeau et al., 1987). A number of case-control studies have found that exposure to pesticides is associated with significantly increased odds of developing the disease. The link between pesticide use and PD has most often been seen among those occupationally exposed, particularly farmers.[68] Some authors conclude that there is "reasonable" (if somewhat conflicting) evidence for an association between exposure to pesticides and risk of PD (Le Couteur et al., 1999).

Researchers from the Medical College of Ohio have conducted a meta-analysis of results from 19 studies published between 1989 and 1999 (Priyadarshi et al., 2000). Seventeen of 19 studies examined reported increased odds of PD with exposure to pesticide (primarily herbicide), although only eight of these reached statistical significance. The combined odds ratio estimated from the meta-analysis was 1.94 (95% C.I.: 1.49 to 2.53), suggesting a moderate but significant elevation in the risk of PD with exposure to pesticides (Priyadarshi et al., 2000).

Where studies provided an estimate of duration of exposure, longer exposure was associated with increased risk of developing PD although not in a dose-dependent fashion. Typical for case-control epidemiological studies, exposure assessment is inexact and only generally determined. The precise pesticides that are associated with such increased risk remain to be determined. However, some studies have implicated organophosphates, the fungicide maneb and the botanical insecticide rotenone (Le Couteur et al., 1999).

The mechanisms by which pesticides might increase the risk of PD are under investigation but could involve genetic or non-genetic influences on the ability to metabolize xenobiotics and pesticides acting as either direct or indirect neurotoxicants.

Uversky and colleagues (2001) of the University of California propose that complex interaction between hydrophobic pesticides and a brain protein alpha-synuclein of unknown function, which is found in dense deposits known as Lewy bodies in the brains of PD patients. Their *in vitro* tests indicate that rotenone, dieldrin and paraquat all induced changes in alpha-synuclein. Although none of these is a currently used lawn and garden pesticide (except for rotenone), these results suggest a possible molecular basis for this disease of unclear etiology.

Several researchers suggest that the increased risk for PD from pesticide exposure occurs among a subset of individuals with specific genetic susceptibility (Hubble et al., 1998; Le Couteur et al., 1999). For example, PD risk was substantially greater in patients who had <u>both</u> past pesticide exposure and the *CYP 2D6 29B+* mutation[69] of a gene that normally codes for activity of a series of detoxifying liver enzymes (part of the cytochrome 450 group of enzymes) (Hubble et al., 1998). The

[67] Pesticides have been examined due to the observation that a neurotoxic contaminant of illicit drugs, 1-methyl-4phenyl-1,2,3,6-tetrahydropyridine (MPTP), was found to lead to rapid development of parkinsonism (a condition of frequently reversible symptoms that are similar to PD) in some drug addicts and that a metabolite of MPTP bears structural similarity to the agricultural herbicide paraquat (Langston et al 1983).

[68] Preliminary research by Nelson of Stanford University has suggested there may be a link between use of home garden pesticides and PD (as reported by Stephenson, 2000).

[69] This mutation can be found in about 10% of populations of European-derived origin (Kurth et al, 1998).

altered form results in no activity in this enzyme system and impairs the ability to metabolize chemicals such as pesticides. Other candidate genetic polymorphisms (alternative forms) that appear to be associated with increased risk of PD are found in the pesticide metabolizing enzymes paraoxonase and the glutathione transferases (Le Couteur, et al. 1999). Not all individuals with PD have the above genetic mutations.

While firm conclusions about the role (if any) of lawn and garden pesticides in the etiology of PD cannot be made, the research discussed above warrants further investigation because of some evidence suggesting possible biological mechanisms of effect (Sherer et al., 2001).

Amyotrophic lateral sclerosis (ALS, also known as "Lou Gehrig's disease") is another multifactorial, neurodegenerative condition that has been studied for the effects of occupational exposure, including pesticides. One case-control study by University of Washington researchers found significantly increased odds in men of developing ALS with exposure to agricultural chemicals, higher exposures having higher odds (McGuire et al., 1997). A recent cohort mortality study of workers exposed to 2,4-D also showed significantly increased relative risk of death attributed to ALS with two cases in this sample (Burns et al., 2001). This study draws attention to other animal or human studies that do not support this finding.

7.5 Neurological Vulnerability of the Young

During vulnerable periods of development, the brain and nervous system of the fetus, infant or child is especially sensitive to the effects of neurotoxic substances (Rice and Barone Jr, 2000). Evidence from mainly from animal studies shows that if exposure to neurotoxic pesticides (such as chlorpyrifos) occurs some time during the long process of neurological development (from *in utero* to adolescence) it can result in developmental neurotoxicity (Rice & Barone Jr, 2000). Developmental neurotoxicity can manifest as changes in nervous system functioning, including changes in cognition and behaviour. The PMRA reports that in their standard risk assessment protocol they account for greater susceptibility in the young by imposing additional safety factors where warranted (PMRA, march 2002, personal communication).

While there are data for only a few classes of insecticides, several published studies show early periods of vulnerability to the neurotoxic effects of OPs and some carbamates in young animals (Eskenazi et al., 1999; Won et al., 2001). The insecticide chlorpyrifos has been best studied for developmental neurotoxicity in experimental investigations (Rice & Barone Jr 2000). Chlorpyrifos appears to reduce the number of brain cells in the young when pregnant animals are exposed (Chanda & Pope, 1996; Whitney et al., 1995). A recent experimental *in vitro* study suggests that OP pesticides might act by inhibiting DNA synthesis resulting in direct effects on cell replication in specific neural cells (Qiao et al., 2001). On the other hand, Dow Chemical researchers have not found differentially higher susceptibility of the young to chlorpyrifos with exposure of pregnant and nursing rats (Maurissen et al., 2000). Similarly, Sheets (2000) of the Bayer Corporation concurs that, based on the magnitude of the cholinesterase inhibition response, young animals are not more sensitive than adults to low doses of either OP or pyrethroid insecticides.

Researchers at the Duke University Medical Center have demonstrated in another study however, that neonatal rats exposed to chlorpyrifos[70] demonstrated negative changes in neurocognitive behaviour (more pronounced in males) that were evident in adolescence and adulthood (Levin et al.,

[70] As discussed earlier, chlorpyrifos is no longer available in Canada for home use.

2001). Researchers at Johns Hopkins School of Public Health have also demonstrated impaired cognitive ability in weanling rats administered relatively low levels of chlorpyrifos (Jett et al., 2001). This cognitive dysfunction appeared without significant alteration of brain cholinesterase activity, suggesting that the effects are not mediated through cholinesterase inhibition (Jett et al., 2001). This finding contrasts with the conclusion that neurobehavioural effects in adult humans are unlikely in the absence of clear cholinesterase inhibition (Clegg & van Gemert, 1999). The research team at Duke University Medical Center has demonstrated possible alternative biological mechanisms to explain the observed effects in exposed neonatal animals (see for example, Slotkin et al., 2001; Qiao et al., 2001; Crumpton et al., 2000).

To date, there has been only one epidemiological study examining the neurobehavioural impacts in children from presumed exposures to pesticides. This ecological study assessed cognitive, behavioural and motor functions in a small sample of preschool children from an agricultural community in Mexico. The Yaqui Valley Indian community of northern Mexico adopted chemical-based agriculture several decades ago and therefore, children are routinely exposed to pesticides from agricultural as well as household use. Guillette and colleagues report that high levels of organochlorine pesticides (such as DDT and its metabolites[71]) have been measured in newborn cord blood and breast milk in this community suggestive of *in utero* and postnatal exposure. Although Guillette and colleagues did not collect exposure data (direct or indirect), they propose that these children are exposed to several pesticides in common use in North America and to additional pesticides that are not registered for use in Canada (such as DDT) (Guillette et al., 1998). Compared to children from the Foothills community, who are relatively less exposed[72] but otherwise similar for genetic, economic and social features, the Yaqui Valley children exhibited substantially impaired stamina, gross and fine motor coordination, memory and drawing ability as well as other differences in play behaviour (Guillette et al., 1998). Follow-up investigation indicates that the behavioural and cognitive deficits of valley children remain in place two years later (Guillette, 2002).

While the findings of this study clearly have limited applicability to children in Toronto, they are mentioned here to highlight the lack of epidemiological information in this area. The Mexican children likely have higher exposure than the average Canadian child and are also exposed to pesticides that are not in use in Canada. This study is also limited in what it can say about the precise role of pesticides in causing these cognitive and behavioural differences because it lacks direct biological data on actual exposure for individual children. Guillette and co-worker's study has nonetheless been held up as suggestive of a need for better understanding of the potential neuro-developmental effects from "real-world", complex exposures to pesticides. These have not to date been adequately studied in children elsewhere. As previously noted, currently developmental neurotoxicological testing may be requested when assessment of the standard toxicity data requirements indicates evidence suggestive of developmental effects on neurological development (PMRA, 2002b).

[71] The persistent organochlorine pesticide DDT was banned for use in Canada in the 1970s but continued to be used in Mexico up until 1999.

[72] The Foothills community eschews chemical pest control and their only pesticide exposure is to aerial spraying against malaria-carrying mosquitoes.

8.0 REPRODUCTIVE AND DEVELOPMENTAL EFFECTS RESEARCH

8.1 Introduction

Substances with reproductive toxicity produce adverse effects on the "differentiation, development or adult functioning of the reproductive system" (Lemasters et al., 2000: 505). Some pesticides have been positively associated with certain reproductive and developmental effects such as fertility problems, reduced sperm count, increased time to pregnancy, early pregnancy loss, spontaneous abortion, fetal death, certain birth defects and altered growth (Sever et al., 1997; Garcia, 1998). Evidence comes largely from animal studies and from those exposed occupationally (mainly through agricultural work). While researchers are cautious in drawing definitive conclusions, the epidemiological evidence suggests that there may be moderately elevated risks of reproductive and developmental effects when exposures (largely occupational or agricultural) to some pesticides (not restricted to lawn and garden pesticides) occur during preconceptional (that is, both maternal or paternal), prenatal or postnatal time frames (Nurminen, 1995; Sever et al., 1997; Garcia, 1998).

The precise nature of the effects from exposure to pesticides will depend on the dose received, the chemical properties and the timing of the exposure with respect to critical events and processes that occur during reproductive development (Pryor et al., 2000). Reproductive toxicity incorporates the effects on either male or female reproductive systems. In general, reproductive toxicity can manifest in the exposed individual as adverse effects on reproductive function or, if exposure occurs *in utero*, structural abnormalities or altered pregnancy outcome may be observed.

As is the case for research on other chronic health effects in relation to exposure to pesticides, available epidemiological data are limited and there is a need for further high quality research which assesses exposure to specific pesticides (Garcia, 1998). Because the majority of the available studies focus on those exposed occupationally or on rural populations exposed to agricultural pesticides, they do not allow for firm inferences as to the potential for reproductive effects from the use of lawn and garden pesticides, although it is likely that the risk is much lower given the lower levels of exposure.

8.2 Maternal Exposures

This section will consider the potential for effects on reproductive function from studies of women exposed (largely occupationally) to pesticides. Maternal exposures to pesticides during pregnancy are a possible route to developmental outcomes in the embryo and fetus, manifest as spontaneous abortion or fetal death[73], congenital malformations or intrauterine growth retardation (Sever et al., 1997). Data suggest that maternal as opposed to paternal exposure to pesticides is associated with relatively higher risks for reproductive effects (Arbuckle & Sever, 1998).

[73] Spontaneous abortion refers to pregnancy loss occurring prior to completion of the 20th week of gestation whereas fetal death refers to pregnancy termination at week 20 and beyond.

Some studies suggest that female agricultural workers have an increased time to pregnancy (Nurminen, 1995). Female greenhouse workers in Denmark were found to have reduced fecundability when they reported spraying pesticides and not using gloves (Abell et al., 2000). The Ontario Farm Family Health Study, a relatively large, retrospective cohort study being conducted by Health Canada researchers, indicates that when women participated in pesticide activities they were more likely to have reduced fecundability (Curtis et al., 1999). However, potential environmental exposure of women (where pesticides were used on the farm but women did not directly participate) was not clearly associated with decreased fecundability (Curtis et al., 1999).

Several studies have found that women who had exposure to pesticides during pregnancy, either through work in agriculture or environmental exposures, have higher risk of spontaneous abortion or stillborn babies although there is inconsistency in these studies (Curtis et al., 1999; Nurminen, 1995). The Ontario Farm Family Health Study collected information from over 2,100 women representing almost four thousand pregnancies and nearly 400 spontaneous abortions (Arbuckle et al., 2001). Although they describe this as an exploratory study, Arbuckle and co-workers' recent report is one of very few studies to try to examine the risks of reproductive toxicity from exposure to specific pesticides.[74] Modestly increased risks (20 to 40% relative increase) of early spontaneous abortion were associated with preconception exposure to certain active ingredients including glyphosate, carbaryl and 2,4-D in this cohort of Ontario farm women (Arbuckle et al., 2001).[75] Postconception exposure was largely unassociated with increased risks of miscarriage. Although older maternal age is a known independent risk factor for spontaneous abortion, Arbuckle and colleagues (2001) observed an interaction between maternal age and pesticide exposure. Women thirty-five and older with preconception exposure to carbaryl had almost four times the risk of spontaneous abortion compared to unexposed women of the same age. Preconception exposure to phenoxy acetic acid herbicides in older women carried greater than double the risk. Exposure to more than one type of pesticide among older women increased the risk substantially as well, such that these women exposed to carbaryl and 2,4-D had 27 times the risk of spontaneous abortion compared to similar women exposed only to carbaryl (Arbuckle et al., 2001). The recent weight of evidence review of 2,4-D studies concludes that there is little evidence of reproductive toxicity from 2,4-D, although it should be noted that the above study by Arbuckle and colleagues is not among those reviewed (Garabrant & Philbert, in press).

Epidemiological studies of congenital effects from exposure to specific pesticides are limited. Studies of women exposed occupationally suggest that first trimester exposure to pesticides in general (i.e., not restricted to lawn and garden pesticides) may be associated with an elevated risk of certain birth defects such as cleft lip and palate (Nurminen et al., 1995; Garcia et al., 1999), spina bifida (Kristensen et al., 1997) and limb reductions (Garry et al., 1996). A Danish study found that boys born to mothers who were farmers or professional gardeners have higher incidence of cryptorchidism (undescended testes) (Weidner et al., 1998). An ecological study in Spain suggests that rates of cryptorchidism may be higher in agricultural regions of high pesticide use (Garcia-

[74] The authors of the study noted that the relatively small number of spontaneous abortions did not allow for the estimation of risks with certainty.

[75] Other research from this same study reports that when exposure was assessed directly from levels of pesticides or metabolites measured in urine, exposures were very low for those occupationally exposed and not appreciable for those participants not directly involved in mixing or handling pesticides (Ritter, 2002).

Rodriguez et al., 1996). Infants born to mothers who worked in orchards or greenhouses had higher risks of spina bifida and hydrocephaly (Kristensen et al., 1997).[76]

A large, exploratory case-control study of selected birth defects occurring in California elicited information on mother's potential for periconception exposure to pesticides from occupation, residential use, pet flea treatment, gardening and proximity to agricultural regions (Shaw et al., 1999). The patterns observed were not as would be predicted, but may reflect weak ascertainment of exposure. Specifically, counter to what would be expected given that occupational exposures are generally higher, mother's occupational exposure to pesticides did not appear to increase the risks for any of the studied anomalies (oro-facial clefts, neural-tube defects, specific heart defects and limb anomalies). Maternal exposure to pet flea treatments also did not increase the risks of these birth defects. However, maternal exposure to pesticides used in gardening, whether the mother herself or a professional applied them, was associated with increased risks for most of the anomalies studied. Maternal exposure to agricultural pesticides appeared to increase the risks for neural tube defects (NTD).

As with most retrospective studies, the information on specific pesticide active ingredients was inadequate for all types of exposures in the study by Shaw and colleagues (1999). Sparseness of data for certain categories of exposure did not allow for adequate comparisons at finer levels. For example, one specific product associated with increased risks for NTD was rose dust for treatment of aphids, used by 10 out of 15 case mothers, yielding an odds ratio of 3.3 (95% C.I. 1.2 to 8.5) specific to this exposure. The likely active ingredient for such a product at the time (the 1980s) was the botanical insecticide, rotenone. No more specific analysis of the relationship between pesticide exposure and risk of these birth defects was possible.

A small case-control study by the National Cancer Institute reports a moderately elevated risk of foetal death from congenital anomalies with maternal exposure to specific restricted-use pesticides (i.e. not available for lawn and garden use) during organogensis (weeks 3 to 8 of gestation) (Bell et al., 2001). Odds ratios were higher when timing and location of exposure were defined more precisely. Specifically, odds ratios were higher for potential exposures during weeks 3 to 8 than for exposure during the first 20 weeks, and odds ratios were higher for potential exposures within a one square mile radius as opposed to a 9 square mile radius from mother's residence. Risks were greatest for potential exposure (during weeks 3 to 8 of gestation) to insecticides such as the pyrethroids (O.R. 2.0, 95% C.I. = 0.8-4.9) and the (organo)phosphates groups (O.R. 3.0, 95% C.I. = 1.4 to 6.5). Risks were also moderately increased for exposure to carbamates.

This study had more objective exposure assessment because it was independent of birth outcome and not based on maternal recall. Information on potential exposure was extracted from the California State Pesticide Use Report, which compiles detailed data on the date, location and amount of restricted-use agricultural pesticides applied in the state. These data were mapped to mother's address and provided a proxy measure for exposure.[77] Unfortunately, due to the time lapse from pesticide application to the time of the study, it was not feasible to verify whether these women were actually exposed during the relevant periods either by biological data or time activity questionnaire data. Researchers for Monsanto and Dow Chemical (Acquavella & Burns, 2001) have criticized this

[76] The reader is reminded that the pesticides used and the patterns of their use in different countries may not be directly comparable to the situation in Canada.

[77] Broad exposure was defined as that where the application occurred within a 9 square-mile radius of mother's residence, whereas narrow exposure was defined as occurring when application was within a 1 square mile radius of mother's residence (Bell et al, 2001).

study on the grounds that exposure was unlikely (or at best, not appreciable) given spray drift models and the results of the aforementioned experimental bystander exposure study (Harris et al., 1992) and a biomonitoring study of Ontario farm families (Ritter et al., 1998).

In general, the findings of Bell and colleagues (2001) support those of other studies identifying an increased risk for birth defects when there is potentially high exposure (not restricted to lawn and garden pesticides) that occurs early, during sensitive times *in utero* (Nurminen, 2001).

8.3 Paternal Exposures

Although less well studied directly, reproductive effects may also be observed from pesticide exposures in men. Some studies in animals have described toxicological effects on semen quality after exposure to specific pesticides (Yousef et al., 1995). Limited research suggests that male fecundity may be affected by both occupational and environmental exposures to pesticides although data have not been consistent (Mattison, 1990). A 1984 study of a large sample of chemical and agricultural workers reported mean and median sperm counts that were normal, but 8.7% of the sample had sperm counts fewer than 20 million per millilitre (Whorton & Meyer, 1984).[78] Declining sperm count and increased abnormal sperm were found to be associated with exposure to 2,4-D in a small study of Italian farm sprayers (Lerda & Rizzi, 1991). Carbaryl-exposed production workers showed only a small, non-significant excess of sperm samples with low counts (Whorton et al., 1979).

The Ontario Farm Family Health Study did not find that father's participation in pesticide activities was associated with increased time to pregnancy (Curtis et al., 1999). Studies of rural workers in France and farmers and greenhouse workers in Denmark found no relation between time to pregnancy and male exposure to pesticides (Thonneau et al., 1999). The Danish study has also found no evidence for higher male fecundability in organic versus traditional farmers (Larsen et al., 1998).

Gametes are only susceptible to mutagenic effects from environmental exposures during the period of their formation. In contrast to oogenesis, which occurs entirely during fetal development of the female, spermatogenesis is a lifelong process once puberty is reached. As a result, the ongoing susceptibility of male gametes to environmental exposures before conception imparts a broader risk of genetic damage that can affect pregnancy outcome (Nurminen, 2001). The study of Ontario farmers indicates that increased risks for miscarriage and premature delivery occurred when fathers reported mixing and handling specific pesticides [including OPs, carbaryl and the phenoxy herbicide 4-(2,4-dichlorophenoxy)butyric acid (2,4-DB)] in the three months before conception (Health Canada, 1998b; Savitz et al., 1997). Risks were greatest for early spontaneous abortion (less than 12 weeks gestation) when fathers reported not wearing proper protective gear during pesticide activities (Arbuckle et al., 1999a). Although their recent work reported exposures from women subjects, Arbuckle and colleagues (2001) speculate that the relationship between pre-conception exposure and increased risk of early spontaneous abortions is suggestive of a paternally-mediated mechanism.

2,4-D was detected in the semen of half of a small sample of farmers who had recently used this herbicide (Arbuckle et al., 1999b). This is the only study to examine pesticide levels in semen. The evidence for spermatoxicity from 2,4-D exposure in humans is limited to one small study (Lerda & Rizzi, 1991). The presence of 2,4-D in seminal fluid suggested to Arbuckle and colleagues that "at least some pesticides may be delivered to the target site where damage to spermatozoa could occur"

[78] Low sperm count is defined as sperm concentration less than 20 million per ml.

(Arbuckle et al., 2001: 856). Damage to spermatozoal DNA from preconception exposures may affect embryonic viability (Arbuckle et al., 2001) although animal studies suggest that 2,4-D is not teratogenic or linked to developmental effects. These findings warrant further research on whether excretion of pesticides in semen provides a mechanism for male-mediated reproductive effects nonetheless (Arbuckle et al., 1999b).

Very few studies have examined the risks for congenital anomalies specifically from paternal exposure to pesticides. Although Garcia and colleagues (1998) did observe positive associations between paternal exposures to some agricultural pesticides and select congenital malformations, most associations were not statistically significant. They did not find an increased risk of congenital malformations from paternal exposure to organophosphate or carbamate insecticides (Garcia et al., 1998).

A major ecological study by Garry and colleagues (University of Minnesota and U.S EPA) (1996) has examined the patterns of birth defect rates for the state of Minnesota, matching these with data on licensed pesticide appliers (primarily men) as well as quantitative pesticide use data for the state. Their analysis suggested that rates of birth defects were significantly elevated among the children born to licensed private appliers (farmers). They also demonstrated significantly greater risk of birth defects in children born to members of the general population living in areas where volume of phenoxy acid herbicides (mainly 2,4-D, but MCPA as well) and fungicides was highest. Finally, rates of birth defects were also highest among infants conceived during the spring, the season of highest use of pesticides.

These samples of farmers (or those living in agricultural areas) would be expected to have higher exposure to pesticides that are not restricted to lawn and garden pesticides (and also to other risk factors not accounted for here).

8.4 Hormonal Alterations

Endocrine disruption is a relatively newly emerging and highly complex area of research. The ability of environmental chemicals, including some pesticides, to be hormonally active[79] (that is, to act as endocrine mimics or inhibitors or to interfere with normal functioning of endocrine chemicals) is also an important area of concern among regulatory agencies and toxicologists (National Toxicology Program, 2001; National Research Council, 1999; Foster, 1998).

Research and understanding of the mechanisms of endocrine disruption have burgeoned, but it remains an area of enormous scientific uncertainty and gaps in data (National Research Council, 1999). This is also an area of scientific controversy as some researchers conclude that the human health risks from low-level exposures to substances of comparatively low hormonal potency are minimal and not biologically plausible (Safe, 2000). Others researchers however, state that, such conclusions "may be too conservative and misleading" (Foster, 1998: S38).

Structural and functional development of the reproductive system is precisely orchestrated by a broad variety of chemical messengers known collectively as the endocrine system. The endocrine system produces traditional hormones and other chemical factors (including growth factors, interleukins and cellular receptors) that regulate developmental processes via interactions at cellular receptors sites and by turning on or off specific genes at programmed times. Development is highly

[79] The recent National Research Council (1999) review of this issue uses the term "hormonally active agents" as more broadly representative of the effects of these substances.

sensitive to subtle fluctuations in the circulating levels of these normal chemical messengers which typically are measured in the parts per trillion.

There are both natural and man-made chemicals that are known to alter the production, transport, metabolism and activity at receptor sites of normal chemical messengers. The endocrine disruptor hypothesis proposes that chronic exposure to low-levels of these hormonally active agents may produce adverse developmental effects by disrupting normal hormonal signaling (Colborn & Clement, 1992). Most is known concerning the disruption of reproductive hormones, in particular, the effects of androgen antagonists (anti-androgens) and estrogen mimics. Interfering with hormonal function is one possible route to reproductive effects. Researchers now appreciate however, that a number of other hormonal systems may be altered by such contaminants, including thyroid hormones, progesterone, glucocorticoids and retinoids with potentially far-reaching implications for development and functioning in other body systems.

The strongest evidence for endocrine effects from environmental toxicants comes from animal studies which suggest that low-dose exposure can alter development and functioning of reproductive, neurological and immunological systems (Gray & Ostby, 1998; Colborn, 1996; Voccia et al., 1999; Porter et al., 1999). A recent meeting of an expert panel convened by the U.S. National Toxicology Program and National Institutes of Environmental Health discussed and evaluated the evidence for low-dose effects from exposures to certain compounds (National Toxicology Program, 2001). The panel concluded cautiously that there was credible evidence for low dose effects in test animals from exposure to certain hormonally active compounds.

The implications of hormonal alterations for human health are less well understood but are an important concern. The potential for irreversible adverse effects from exposure to the fetus or the young child are particularly important (Foster, 1998). There is concern that structural anomalies of the reproductive system, such as cryptorchidism and hypospadias, reproductive cancers, such as testicular[80] and prostate, and functional effects such as reduced sperm quality may be linked to developmental exposures to endocrine disruptors although the evidence in humans is not firmly established.

For example, there are reports of increasing incidence in anomalies of the male reproductive organs such as cryptorchidism, for reasons that are unclear (Chilvers et al., 1984). One proposed explanation, based on a number of lines of evidence, is that prenatal exposure to estrogen mimicking or anti-androgenic substances may disrupt normal testicular descent (Foster, 1998). As mentioned above, an ecological study in Spain suggests that rates of cryptorchidism are higher in areas where there is potentially greater exposure to pesticides (Garcia-Rodriguez, et al., 1996). A small study comparing maternal serum hormone concentrations during early gestation in mothers who gave birth to sons with cryptorchidism suggests a possible association between low maternal testosterone and altered testicular descent (Key et al., 1996). Animal experiments indicate that cryptorchidism can be induced by prenatal exposure to either estrogenic or androgen antagonistic properties (Imajima et al., 1997; McMahon et al., 1995).

[80] It should be noted that Canadian statistics demonstrate that there was nearly a 60% increase in testicular cancer incidence in Ontario between 1964 and 1996, with the greatest increase occurring among adolescent and young men aged 15 to 29 years (Weir et al., 1999). These trends agree with reports of increased incidence in testicular cancer worldwide (Sharpe & Skakkebaek, 1993). It is hypothesized that this trend may reflect greater *prenatal* exposure to hormonally active agents although there is a need for studies to confirm or refute this possible relationship (National Research Council, 1999; Klotz, 1999).

Among pesticides, most is known about methoxychlor and vinclozolin. The insecticide methoxychlor[81] has been found to display estrogenic activity and be linked to immune system effects in experimental animals following exposures in the parts per million range (below the NOAELs) (National Toxicology Program, 2001). Vinclozolin (an agricultural use fungicide) has been found to act as an androgen antagonist although there have been no studies examining effects below the NOAELs (National Toxicology Program, 2001).

Several dozen different pesticides have been associated with endocrine disrupting ability (Sonnenschein & Soto, 1998; European Commission, 2000). Most of these are of the organochlorine type and therefore not registered in Canada any longer. However, according to one source, lawn and garden pesticides that have been categorized as having potential endocrine-disrupting activity include 2,4-D[82], aldicarb, benomyl, carbaryl, chlorpyrifos, endosulfan, malathion, maneb, some pyrethroids and pyrethrins (European Commission, 2000).

Some pyrethroid insecticides are suspected androgen antagonists as they have been found to displace testosterone from its carrier protein, sex hormone binding globulin (SHBG)[83] and inhibit testosterone binding at the androgen receptor in cultures of human skin cells (Eil & Nisula, 1990). These androgen disturbances may increase normal testosterone availability to cells and may disrupt normal testosterone initiated function. Pyrethroids may also elicit effects indirectly by interfering with the rate of synthesis or metabolic breakdown of hormones (Garey & Wolff, 1998; Go et al., 1999).

There has been some human evidence of hormonal activity of 2,4-D from work by researchers at University of Minnesota. Garry and co-workers (2001) showed raised luteinizing hormone and subsequently increased testosterone levels in the serum of male forest pesticide applicators after 2,4-D spraying. The reproductive consequences of these hormone changes to the individual men are not clear. Although it has not yet been studied, the authors suggest that such changes in women could be of great concern to reproductive biology.

Although our knowledge of the exact implications of hormonally active agents for human health is unquestionably limited, testing for endocrine-disrupting potential is part of the data requirements for PMRA's expanded risk assessment of pesticides that are new or under re-evaluation (PMRA, 2002a). PMRA states that there is recognition among regulators of the need for further methodological refinements to allow detection of all mechanisms of endocrine disruption and that as these assessment tools are developed and validated they will be incorporated in their requirements. They further state that it is current practice to apply an additional safety factor where toxicity tests indicate notable endocrine effects (PMRA, March 2002, personal communication).

The endocrine disrupting issue (and the screening tests, which have led to multiple lists of endocrine disrupting chemicals, none of which is in agreement), is presently an area of intense research activity, debate, and controversy. Hence it is difficult at this stage to form defensible evidence-based decisions (Foster, 2002).

[81] Methoxychlor is listed in the PMRA labels database as an insecticide for home use on gardens and outdoor areas.

[82] The 2,4-D Industry Task Force II on Research Data states in its materials that the U.S. EPA has classified 2,4-D as not having endocrine effects.

[83] Naturally occurring sex hormones are typically found bound to SHBG which confines the hormone to the circulation and limits the availability of free circulating hormone to the cells.

9.0 OTHER CHRONIC HEALTH EFFECTS RESEARCH

9.1 Respiratory Effects Research

Medical case reports, epidemiological and experimental studies suggest there may be a relationship between pesticide exposure and respiratory effects. Respiratory effects have been observed as the outcome of both acute and chronic exposures to pesticides. Acute exposure to cholinesterase inhibiting pesticides such as OPs and carbamates is known to disrupt both autonomic and parasympathetic control of airways. These effects of acute toxic exposures can produce respiratory symptoms such as bronchoconstriction, increased airway secretions and breathing difficulties.

Case reports and epidemiological studies have shown an association between increased occurrence of occupational asthma and exposure to some pyrethroid, OP and carbamate insecticides in farmers (Box & Lee, 1996; Senthilselvan et al., 1992; Garry et al., 1994; Thrasher et al., 1993).

Some researchers suggest that there is a biologically plausible association between exposure to OP (and carbamate) pesticides and respiratory disease in children because of the aforementioned link between cholinesterase inhibition and dysfunction in nervous system control of air passages (Eskenazi et al., 1999). These researchers suggest that the anti-cholinesterase activity of OPs may influence the occurrence and severity of asthma in the young. This is an area that requires further study to more fully characterize the possible role, if any, of pesticide exposure in childhood asthma.

9.2 Immune System Research

While the exact immunological effects from pesticides are not well characterized, "there is evidence that some pesticides affect (the) human immune system" even under relatively low-dose exposure (Colosio et al., 1999: 291). Some organophosphate and carbamate lawn care insecticides have been found to cause immunotoxicity from tests in animals and cell cultures and therefore these effects would be accounted for in the risk assessment. The related health effects in some studies of experimental animals include diminished host resistance to infections, as well as promotion of tumour growth (Repetto & Baliga, 1997).

Human data on immunotoxic effects from pesticides are limited at best. This is in part because very few studies have specifically examined changes to human immune parameters with exposure to pesticides. The immune system is also highly complex and all the relevant cellular and molecular mechanisms by which immunotoxicity can occur are not well known (Bannerjee, 1999). The toxicity to the immune response may be influenced by characteristics of the individual including their age, disease or nutritional status (Bannerjee, 1999). For example, the effects of exposure to DDT in rats was influenced by dietary protein content as rats fed on a 3% protein diet displayed suppressed immune responses that were not the case for rats fed diets of 12 or 20% protein content (Bannerjee, 1999). The intrinsic inter-individual variability of immune parameters makes it difficult to study and interpret effects observed.

Epidemiological studies of pesticide immunotoxicity have focussed primarily on those exposed occupationally either through manufacture or application of pesticides. Several studies have observed that certain pesticides can alter human immune system function, including changes in cell

numbers and cell ratios as well as impairment of cell activity levels among other observations (Colosio et al., 1999).

A sample of workers exposed to chlorpyrifos demonstrated both decreases and increases in different types of lymphocytes as well as the presence of auto-antibodies (Thrasher et al., 1993). In some of these individuals the exposure was associated with non-specific respiratory symptoms and a flu-like illness but these were not clearly linked to the observed cell alterations.

Exposure to commercial formulations of the phenoxy herbicides 2,4-D and 4-chloro-2-methylphenoxyacetic acid (MCPA) in a small sample of farmers (n = 10) was associated with significant reductions in various immune cell populations[84] and significantly diminished proliferation of lymphocytes upon mitogen stimulation (Faustini et al., 1996). The cell numbers returned to normal within two to three months. However the lymphoproliferative responses remained below baseline levels. Faustini and colleagues (1996) suggest that exposure to such formulations of these herbicides produced temporary immunosuppressive effects and that there should be further study of the potential for such a mechanism to contribute to cancer etiology with repeated exposures.

Follow-up study of the Yaqui children has shown that the Valley children (whom researchers deduced had greater exposure to pesticides) have greater rates of common illnesses such as respiratory problems, allergies and rashes compared to the lesser-exposed Foothills children (Guillette, 2002). Guillette suggests this may indicate some relationship to immune system dysfunction, which may or may not be related to pesticide exposure, although there was no corroborating direct evidence of actual exposure in study subjects.

In most studies, the clinical significance of the any observed immune alterations has not been clear. It also remains to be determined whether the immune changes observed in these studies represent temporary or adaptive responses or early changes that might lead to further immune dysregulation and ultimately disease expression (Colosio et al., 1999).

Despite limited human evidence and conflicting opinions among researchers as to the role of pesticides in immune system dysfunction in humans, there is agreement that the issue warrants improved and routine screening of pesticides for immunological toxicity and further careful epidemiological studies that investigate the precise immune system effects in humans (Repetto & Baliga, 1998; Acquavella et al., 1998a). As outlined in section 3.1 above, it is current practice that if standard toxicity tests indicate the potential for immune effects, further immunotoxicity test data will be required (PMRA, 2001d).

[84] Namely, CD4, CD8, NK and CD8 cells.

10.0 CONCLUSIONS

There remain considerable gaps in our knowledge and questions regarding the effects from pesticide exposures at low levels. The major questions concern the likely long-term effects at current levels of exposure to multiple sources of pesticides, although the question at hand involves the role of lawn and garden pesticides alone.

It is exceedingly difficult to track the long-term effects in people of repeated exposures to low levels of pesticides. Therefore, it is not surprising to see a wide range of conclusions in the epidemiological literature regarding the possible adverse effects of common lawn and garden pesticides. Some studies suggest possible significant and serious health concerns, whereas other studies do not. Determining actual exposure levels and the precise pesticides to which people are exposed is a challenge in the majority of population-based studies. Recent biomonitoring studies in the United States, particularly those assessing exposure in children, suggest that there may be widespread, low-level exposure to some commonly used home and garden pesticides and their degradation products.

Without further careful, prospective health studies, we cannot determine if these low-level chronic exposures can result in either short or long term health effects. There is, nonetheless, a growing sense among researchers, medical practitioners and regulators that despite the scientific uncertainty we should, at the very least, be concerned about the potential for long-term effects of pesticides on children's health. Health advocates also work to disseminate messages to prevent exposure to toxicants, reduce unnecessary uses of these agents and seek less toxic forms of common products.

In striving to better protect child health from exposure to common pesticides, regulators have incorporated newer scientific assessment methods and additional safety factors where data are uncertain to minimize the risks of exposure. The PMRA has expedited re-evaluations of key lawn and garden pesticides and has already entered into voluntary agreements to phase-out residential use products containing two common lawn insecticides. In managing the risks from pesticides PMRA also mandates precautions that are to be included on label instructions and must be followed to avoid undue risk of harm. Although there are mechanisms in place that aim to ensure professionals who apply pesticides follow regulatory standards[85], there is little monitoring to ensure that the public is adequately compliant with these directions and precautions to avoid risks of undue exposures.[86]

[85] It should be noted that Toronto Public Health's survey indicated that while most of the respondents (n = 109) who had hired professional lawn care companies knew whether or not chemical pesticides had been applied to their lawns, 11% of those who had used these services did not know. The survey results indicate also that about 40% of those hiring a lawn-care company responded that they had not been given information on appropriate precautions after their lawn had been treated with a chemical pesticide (Toronto Public Health, 2002).

[86] Population surveys suggest that when asked, most Canadian homeowners who apply chemical pesticides to their lawns themselves, state that they are careful to read the label instructions and that they understand the risks and appropriate precautions (see for example, Toronto Public Health, 2002; Canadian Consumer Specialty Products Association, 2002). However, it is clear that responses to surveys will not always adequately reflect user practice. An interesting example of actual user practice comes from the results of the aforementioned University of Guelph exposure studies using volunteer homeowner applicators. Despite being provided with verbal instructions regarding all key aspects of the application, including the mandatory use of the protective apparel, at least two out of 11 homeowners failed to follow instructions regarding the use of

The health effects and potential risks from exposure to pesticides may never be completely understood. Different interpretations have emerged from a consideration of the totality of the evidence alongside its attendant limitations. Many researchers agree that further refinements in the studies conducted are required before epidemiology can provide definitive answers (Watterson, 1994; Landrigan & Goldman, 1998; Olshan & Daniels, 2000). Ultimately, interpretation of the evidence must call on the judgement of scientific experts from a number of disciplines such as, toxicology, epidemiology, genetics and public health. It is the judgement of Toronto Public Health that a precautionary approach concerning residential-use pesticides is prudent and advisable.

gloves at all times during the application (Harris et al., 1992). Similarly EPA researchers conducting the NOPES study discussed in Section 4.1 noted that although respondents generally used appropriate pesticides and generally followed label directions, few took appropriate precautions (such as wearing gloves, washing hands, changing clothing) to reduce exposures (Immerman & Schaum, 1990b: 60).

11.0 IMPLICATIONS AND CONCLUDING OBSERVATIONS

- Overall, this broad evaluation of studies examining exposure and health effects data, although unable to make definitive statements about risks from specific residential-use pesticides, supports that from a public health standpoint, avoiding unnecessary uses of pesticides is prudent.

- Encouraging reduced or minimal reliance on pesticides for lawns and gardens can be one important strategy, particularly because lawn pesticide use has generated considerable public concern and because this aligns with the stated objectives of government initiatives such as PMRA's Healthy Lawns Strategy.

- Minimizing pesticide use is important where there is likely to be exposure of infants, young children, pregnant women, the elderly and those with pre-existing illnesses, the members of society most immediately identifiable as being potentially more vulnerable to chemical exposures. It would be particularly sound to encourage people to avoid pesticide use in areas where young children are likely to be exposed.

- Prudent practices among Toronto's citizens should be encouraged regarding the use of pesticides indoors as well as outdoors.

- Toronto Public Health should work with appropriate government agencies and representatives of other stakeholder groups to ensure that at a minimum, messages about the proper use of pesticides and legally mandated precautions are effectively communicated to the public. It would also be important for the City of Toronto to provide a supportive environment that encourages people to use least toxic products or appropriate non-toxic alternatives in pest management approaches.

- Toronto Public Health also supports ongoing research, informed by multiple perspectives (including epidemiology, genetics, toxicology and public health), on exposures to pesticides and the potential for health effects among vulnerable subpopulations, including the unborn, young, old, malnourished and sick.

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APPENDIX 1 – Table 1: Pesticides Commonly Used or Available for Lawn and Garden Applications

Pesticide	Class	Target	Mode of Action	Some Trade or Common Names	Acute Toxicity[87]	Regulatory Status
HERBICIDES						
2,4-dichlorophenoxyacetic acid (2,4-D)	Phenoxy acid	Various broadleaf weeds	Systemic herbicide Affects plant growth	Killex, Tricep, Premium 3-way, Par III and Trillion[88]	Moderate to slight	General Use Pesticide Under re-evaluation since 1992; APUUP[89]
Mecoprop (MCPP)	Phenoxy acid	Various broadleaf weeds	Systemic herbicide Affects plant growth	Killex, Tricep, Premium 3-way, Par III and Trillion	Slight	General Use Pesticide APUUP
Dicamba	Phenoxy acid	Various broadleaf weeds	Systemic herbicide Affects plant growth	Killex, Tricep, Premium 3-way, Par III and Trillion	Slight	General Use Pesticide APUUP
4-chloro-2-methyl-phenoxyacetic acid (MCPA)	Phenoxy acid	Various broadleaf weeds	Systemic herbicide Affects plant growth	Herbatox (?)	Slight	General Use Pesticide APUUP
Glyphosate	Organophophate	Broadleaf weeds, grasses	Broad spectrum, non-selective, systemic	Roundup Gallup, Landmaster, Pondmaster, Ranger, Rodeo, Touchdown	Slight	General Use Pesticide
INSECTICIDES						
Carbaryl	Carbamate	Various insects (earwigs, ants, grasshoppers)	Cholinesterase inhibitor (reversible)	Sevin	Slight	General Use Pesticide APUUP

[87] High acute toxicity means the substance is extremely dangerous if not properly handled and can be fatal in relatively small amounts (0.1 to 3.0 mls).
Moderate acute toxicity means the substance is of moderate danger if not properly handled. They can be fatal in larger amounts than high acute toxicity substances (3 to 30ml).
Low acute toxicity means the substance should be handled with caution, but is only fatal if there is deliberate ingestion of amounts greater than 30ml. (Source: OMAFRA, 1999)

[88] Mixtures of 2,4-D, dicamba and mecoprop.

[3] APUUP = Action Plan on Urban Use Pesticides, the re-evaluation of seven common lawn and garden pesticides (PMRA, 2000a)

Pesticide	Class	Target	Mode of Action	Some Trade or Common Names	Acute Toxicity[87]	Regulatory Status
Chlorpyrifos	Organophosphate	Various insects Grubs	Cholinesterase inhibitor	Dursban, Lorsban, Pyrifos	Moderate to slight	Re-evaluation of organophosphates (PMRA, 1999) Phase-out of residential use products by 2002 (PMRA, 2000c)
Diazinon	Organophosphate	Various insects	Cholinesterase inhibitor	Basudin	Moderate	Re-evaluation of organophosphates (PMRA, 1999) and APUUP Phase-out of residential use products by 2003 (PMRA, 2001d)
Malathion	Organophosphate	Various insects (aphids, spider mites, tent caterpillars, etc.)	Cholinesterase inhibitor		Moderate	General Use Pesticide Re-evaluation of organophosphates (PMRA, 1999) and APUUP
D trans allethrin (bioallethrin or allethrin)	Pyrethroid	Various insects Spiders		various	Moderate	General Use Pesticide
Permethrin	Pyrethroid	Various insects ear wigs, spiders, sowbugs		various		General Use Pesticide
Resmethrin	Pyrethroid	Various insects Hornets, wasps		various		General Use Pesticide
Imidacloprid	Chloro-nicotinyl	Various insects	Blocks nicotinergic pathways	Merit	Slight	Restricted use, only by licensed applicators
FUNGICIDES						
Benomyl	Benzimidazole	Disease, mold on fruits & vegetables		(Benlate)	Slight	General Use Pesticide (Voluntary withdrawal of product announced in U.S. Oct 2001)
Captan	Phthalimide	Plant disease, blight, mold			Slight	General Use Pesticide

Sources: EXTOXNET Pesticide Information Profiles http://ace.orst.edu/info/extoxnet/pips/ghindex.html; OMAFRA (1999); PMRA label search http://64.26.129.82/search/queryhit.htm

APPENDIX 2 – Environmental Fate and Effects of Lawn Care Pesticides

There are, generally speaking, only incomplete data available regarding the environmental impacts of chemical pesticide products used on lawns in Toronto. Described below are some water quality studies undertaken by Environment Canada, and toxicological information about the active ingredients most commonly found in lawn care pest control products. But, significant gaps in our knowledge remain.

Lawn Care Pesticide Movement and Environmental "Fate"

Lawn-care pesticides can move from the point of application into air, water and soil. Some lawn and garden pesticides may persist in the environment, such as Benomyl, described below. Each pesticide or family of pesticides exhibits different behaviour, depending on its physical-chemical properties. Understanding how pesticides move in the environment is a first step in determining how their use may result in unintended exposures to other species.

The physical-chemical properties that determine how lawn-care pesticides will behave in the environment are: their solubility in water; their ability to leach through soil; their volatility; their persistence and their tendency to partition between different phases (for example water and air or water and fatty animal tissue). Lawn-care pesticides exhibit a range of values for each of these physical-chemical properties.

Lawn-care pesticides are known to move from their point of application into the air, water and soil. In one study, water samples collected in 1998 from Toronto's Humber River and Don River were found to contain a number of lawn-care pesticides including MCPP (mecoprop), 2,4-D and diazinon (Struger et al., 1999). Lawn-care pesticides have been detected in the urban surface waters of Hamilton and Guelph as well (Struger et al., 1994). Preliminary analysis of 1999 and 2000 samples of Toronto rivers also shows consistent patterns of pesticide pollution, including higher pesticide concentrations after precipitation and runoff events (Struger, 2002).

In Ontario's urban ponds and streams, maximum detected diazinon concentrations have, in tests undertaken in 1998-99, exceeded the Ontario Water Quality Objective for the Protection of Aquatic Life (Struger et al., 1999). Maximum 2,4-D concentrations have, in studies undertaken in 1994, exceeded the Canadian Water Quality Guidelines for the Protection of Freshwater Aquatic Life by more than three times (Struger et al., 1994). More recent studies show a decline in some of these concentrations (Struger, 2002).

Concentrations of lawn-care pesticides in excess of criteria for the protection of aquatic life are not uncommon. A study in the United States found that diazinon, carbaryl and malathion were among the four insecticides most frequently detected in urban streams. In spring and summer, carbaryl and diazinon were found to exceed US criteria for the protection of aquatic life in many of the urban streams tested (Hoffman et al., 2000). Carbaryl and diazinon in shallow groundwater have also been found by the U.S. Geological Survey to exceed aquatic-life criteria. Kolpin and colleagues concluded that "such exceedences may be significant to the health of aquatic ecosystems" and that urban and suburban pesticide uses "significantly contribute" to the presence of pesticides in shallow groundwater (1998:565, 558).

These studies in Ontario and in the US show that lawn care pesticides do migrate off the properties to which they are applied and that they exist in amounts sufficient to harm aquatic life.

Ecotoxicity of Lawn-care Pesticides

Aquatic life, bees, birds and beneficial soil organisms can be harmed by pesticides used on lawns and gardens. As described below, some of the lawn-care pesticides that are currently used in North America are known to be toxic to a variety of non-target organisms.

Insecticides and Fungicides

Carbaryl is a wide-spectrum carbamate insecticide, which controls over 100 species of insects on agricultural crops and garden plants as well as pets. Products for sale in Canada may contain solutions of 5% to 10% carbaryl and are used, among other things, to control pests on roses and to control fleas on dogs and cats. Carbaryl is lethal to many non-target insects, including bees and beneficial insects, and is moderately toxic to aquatic organisms. Carbaryl is practically non-toxic to wild bird species. Carbaryl can bioaccumulate in some aquatic animals (e.g., snails and catfish) and plants on which other animals feed (e.g., duckweed and algae). The bioaccumulation risk posed by carbaryl is dependent upon the water's acidity, and ranges from little risk in alkaline waters to potentially significant risk in acidic waters (Kidd & James, 1991).

Diazinon is an organophosphate insecticide used to control cockroaches, silverfish, ants, and fleas in residential, non-food buildings. Diazinon is highly toxic to bees and other beneficial insects, birds, fish, mammals and aquatic invertebrates (U.S. EPA, 2000e; Kidd and James, 1991). According to the U.S. EPA (2000e), diazinon use in open spaces poses "a widespread and continuous hazard" to birds. If they are present at or shortly after the time diazinon is applied, ducks and Canada geese may be exposed to the LC50 (the concentration that will kill 50% of the individuals) (U.S. NLM, n.d.). According to the U.S. EPA (2000e), one granule of a diazinon pesticide is enough to kill a small bird.

Products containing diazinon are in both the "restricted" and "non-restricted" use categories in Ontario, which means products for use in the home are readily available to purchase in retail outlets. However, as part of the ongoing re-evaluation of the organophosphate class of insecticides, the PMRA has already instituted a phase-out of all residential use products containing diazinon that will be complete by December 2003 (PMRA, 2001b).

Malathion is a kind of organophosphate insecticide and kills insects by interfering with the action of important enzymes in the nervous system. Malathion is an active ingredient in products commonly used indoors to kill bedbugs, carpet beetles, centipedes, millipedes, clothes moths, clover mites, cockroaches, crickets, earwigs, fleas, houseflies, silverfish, sowbugs and wasps. Outside uses of products containing malathion include control of aphids, boxelder twig borers, leafhoppers, leafminers, sowflies, scale insects, spiny elm caterpillars, spruce budworm, spruce gall aphids, spruce spider mite and tent caterpillars.

The U.S. EPA has expressed concern over both spray drift from very low-volume applications and the environmental fate of one of malathion's degradates, malaoxon (U.S. EPA, 2000d). Malathion is very toxic to bees and can kill fish (Kidd & James, 1991). Malathion's toxicity to fish ranges widely from very highly toxic in walleye to highly toxic in brown trout, moderately toxic in fathead minnows and slightly toxic in goldfish (U.S. NLM, n.d.; Kidd & James, 1991; Johnson & Finley, 1980). Aquatic invertebrates

and aquatic-stage amphibians are also extremely sensitive to this pesticide (Howard, 1991). Both acute and chronic risks exist for fish and aquatic invertebrates (U.S. EPA, 2000d).

Malathion is not considered to be bioacumulative, but samples of brown shrimp have shown malathion concentrations approximately three orders of magnitude greater than the surrounding water concentrations (Howard, 1991).

Unlike the other pesticides mentioned here, Imidacloprid is a restricted use insecticide that can only be applied by licensed professionals.[90] It is considered to be a less toxic alternative to the currently registered products (chlorpyrifos, diazinon and carbaryl) for soil-inhabiting lawn pests like Japanese beetle (PMRA, 2001a). Due to its persistence in soil, the label instructions state that a food crop must not be planted within one year of an Imidacloprid treatment. The label warns that Imidacloprid may contaminate groundwater in some situations and that the pesticide must be "kept out of lakes, streams, ponds or other aquatic systems" (PMRA, 2001a). It also warns that the pesticide can be highly toxic to aquatic invertebrates.

Imidacloprid is highly toxic to bees (Kidd & James, 1991). Consequently, the product label advises, "do not apply, or allow it to drift to blooming crops or trees if bees are visiting the treatment area" (PMRA, 2001a).

Benomyl is a fungicide, sold in Ontario under the trade name Benlate. People might use Benlate on fruit trees on their property to treat some kinds of fungus and blight diseases. Benomyl is very toxic to highly toxic to different fish species, and the primary degradation product, carbendazim, carries the same order of toxicity (U.S. NLM, n.d.). Benomyl is moderately toxic to redwing blackbirds (Cummings et al, 1992). Benomyl is toxic to earthworms (Potter et al., 1990; U.S. Department of Agriculture, 1984). The manufacturers of Benomyl recently submitted notice to the U.S. EPA Office of Pesticide Programs requesting cancellation of the registration for all benomyl-containing products (2001b).

Herbicides

2,4-D, a chlorinated phenoxy compound, functions as a systemic herbicide and is used to control many types of broadleaf weeds. It is used in cultivated agriculture, in pasture and rangeland applications, forest management, home, garden, and to control aquatic vegetation.

2,4-D is the most widely used lawn care herbicide in Canada (Industry Task Force II on 2,4-D Research Data, no date).

2,4-D is moderately toxic to some bird species and slightly toxic to waterfowl (U.S NLM, n.d.; Weed Science Society of America, 1994; Kidd & James, 1991). The toxicity of 2,4-D varies between fish species, and toxicity to an individual species is thought to vary from highly toxic to modestly toxic, depending on the pesticide formulation (U.S. EPA, 1988; Stevens & Sumner, 1991).

MCPA is a systemic postemergence phenoxy herbicide used to control annual and perennial weeds (including thistle and dock) in cereals, flax, rice, vines, peas, potatoes, grasslands, forestry applications,

[90] All other lawn care pesticides mentioned in this section are sold in Ontario as Schedule 3 category pesticides, meaning they are available for household yard use without a permit or licence.

and on rights-of-way. This herbicide may be used in formulation with many other products, including bentazone, bromoxynil, 2,4-D, dicamba, fenoxaprop, MCPB, mecoprop, thifensulfuron, and tribenuron.

MCPA is modestly toxic to freshwater fish and moderately toxic to wildfowl (Weed Science Society of America, 1994; Kidd & James, 1991).

Mecoprop is a selective, hormone-type phenoxy herbicide. It is applied postemergence and is used on ornamentals and sports turf, for forest site preparation, and on drainage ditch banks for selective control of surface creeping broadleaf weeds such as clovers, chickweed, lambsquarters, ivy, plantain and others. It is also used on wheat, barley, and oats. Mecoprop is absorbed by plant leaves and translocated to the roots. It affects enzyme activity and plant growth. It acts relatively slowly requiring three to four weeks for control. Mecoprop is virtually non-toxic to birds, bees or aquatic life.

Lawn care products for sale in Ontario, and applied to lawns by lawn care companies often contain a mixture of three phenoxy herbicides, namely 2,4-D, mecoprop and dicamba.

It should be noted that all of the toxicological evaluations described above have been developed by singly assessing individual active ingredients. However, the way that most 'non-target' species are exposed to pesticides in the environment is in complex mixtures of unknown concentrations. Ecotoxicologists are increasingly investigating the impacts of complex environmental mixtures on organisms. However, the large number of chemicals released to the environment, and the dynamics of natural systems, make this a complicated process. Until advances are made and more research is completed, it will be impossible to identify and evaluate the risk posed to non-target species by these mixtures of environmental chemicals.