Suffolk County Vector Control & Wetlands Management Long Term Plan & Environmental Impact Statement
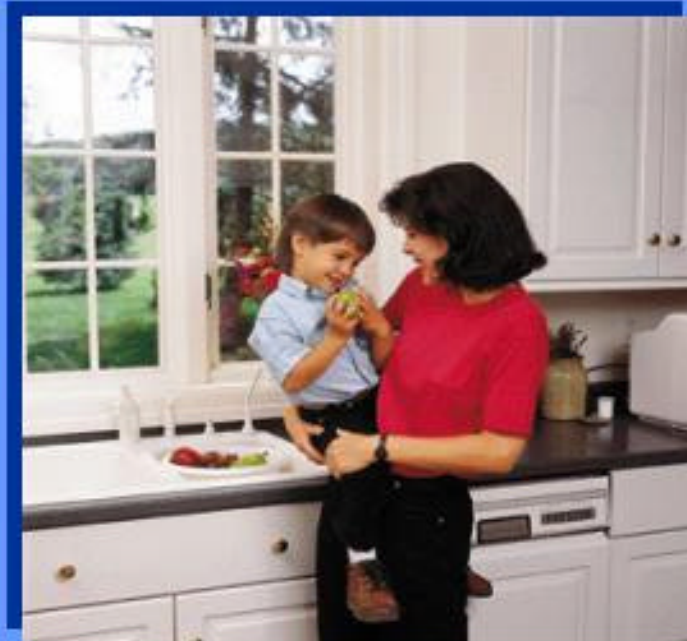
Task 3 Literature Review
Book 6 Part 2: Mosquito Control Pesticides, Breast Cancer & Childhood Diseases

Prepared for:

Suffolk County Department of Public Works
Suffolk County Department of Health Services
Suffolk County, New York

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SUFFOLK COUNTY LONG TERM PLAN

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LIST OF ABBREVIATIONS AND ACRONYMS

ATSDR - Agency for Toxic Substances and Disease Registry
Bt - Bacillus thuriengensis
Bti - Bacillus thuriengensis israelensis
DDE - dichlorodiphenyl dichloroethylene
DDT - dichlorodiphenyl trichloroethane
DNA - Deoxyribonucleic Acid
EPA - Environmental Protection Agency
Extoxnet - Extension Toxicology Network
IARC - International Agency for Research on Cancer
MCF7 - Mammary carcinoma cell line
NHANES - National Health and Nutrition Examination Survey
NPTN - National Pesticide Telecommunications Network
NYSDOH - New York State Department of Health
PIPs - Pesticide Information Profiles
SAR - Structure Activity Relationship
SEER - Surveillance, Epidemiology, and End Results
TIBs - Toxicology Information Briefs
TICs - Toxicological Issues of Concern
USEPA - US Environmental Protection Agency
WWW - World Wide Web

Executive Summary

The potential for chemicals used for mosquito control to cause breast cancer and/or childhood diseases was identified in the Scoping process of the Suffolk County Vector Control and Wetlands Long-Term Plan and Generic Environmental Impact Statement as a subject of particular concern. Therefore, in addition to a report entitled, "Human Health and Domestic Animal Toxicity," this more specific report has been prepared.

Modern mosquito control follows a protocol known as Integrated Mosquito Management. This protocol generally uses non-chemical methods of control as initial means of reducing mosquito populations. However, Integrated Mosquito Management does allow for escalation to chemical means for larval control and to reduce adult mosquito populations. The chemicals widely used for these purposes are a mixture of synthetic and natural formulations.

Breast cancer is the most commonly diagnosed cancer for women in the US. The worldwide distribution of breast cancer suggests there is a significant environmental component to the causation of this disease. For a variety of reasons, many people believe that synthetic chemicals, especially pesticides, may be important factors for breast cancer. Due to higher than average breast cancer rates for Long Island, and the public awareness that pesticide applications are used for mosquito control purposes, it was requested that potential links between the chemicals used for vector control be examined for evidence they may cause breast cancer. Therefore, 15 different chemicals and chemical groups were examined for such links.

According to USEPA, there is some evidence that several of the chemicals that are, or may be, used in Suffolk County for mosquito control may cause cancer, however, there is no direct link between these specific chemicals and breast cancer. As breast cancer is a hormonally related disease, not only were the carcinogenic properties of these chemicals investigated, but evidence of hormonal activity for these chemicals was also sought. Although several studies suggest that certain chemicals may have some weak estrogenicity, the available scientific data did not provide evidence that any of these chemicals have the ability to significantly influence breast cancer development through a hormonal pathway. Therefore, the current state of the scientific literature does not provide any evidence that these chemicals have any effect on breast cancer.

There are also concerns that chemicals in the environment, especially synthetic chemicals such as pesticides, may be impacting children's health. Three specific concerns are that synthetic chemicals cause cancer in children, are associated with neurological problems, and have contributed to the increases in childhood asthma rates. It also has been suggested that children respond differently to these kinds of chemicals, as compared to adults.

The scientific literature was thoroughly reviewed for studies relating the 15 specific chemicals and chemical groups to these childhood illnesses. No studies were found that established a direct relationship. Some studies reported associations between general pesticide exposure and each of the ailments, but the pesticide exposure methods used in these studies did not allow for determinations, by-and-large, as to whether the specific vector control chemicals could be implicated in the relationship.

Therefore, the overall result of the scientific literature search does not provide support for an association between the vector control chemicals and breast cancer, childhood cancer, childhood neurological problems, or childhood respiratory illness. On the other hand, the literature did not provide evidence against an association between the vector control chemicals and breast cancer or childhood diseases. Rather, because of the methodologies used to conduct these studies, it is not possible to draw conclusions with any certainty in either direction. However, the general tendency in American law and regulation is to determine, in the absence of positive proof, that the chemicals do not have the potential impact.

1. Introduction

This report was produced as an adjunct to the broader assessment of chemicals used to control mosquitoes. The toxicology of these primarily synthetic chemicals, created in the past twenty years or so, are discussed more generally in the accompanying report, "Human Health and Domestic Animal Toxicity: Literature Review."

This smaller report is more tightly focused on research that has been conducted regarding potential links between vector control chemicals and breast cancer, and children's illnesses. This is because there is great concern, especially on Long Island, that breast cancer incidence is elevated due to environmental exposure to primarily synthetic chemicals (Toy, 2002). In addition, there are also great concerns that children's illnesses are also being caused by exposure to synthetic chemicals, and that children respond differently to these exposures as compared to adults (Landrigan et al., 2004).

Therefore, due to public concerns that pesticides used for mosquito control may be factors in these situations, this report was specially prepared to review the scientific literature, and focus attention on these two particular issues.

1.1.   *Sources of Information*

Information from a number of public agencies is cited in this document. Following is a description of each of the agencies taken directly from their respective websites.

1.1.1. Agency for Toxic Substances and Disease Registry

> "The mission of the Agency for Toxic Substances and Disease Registry (ATSDR), as an agency of the US Department of Health and Human Services, is to serve the public by using the best science, taking responsive public health actions, and providing trusted health information to prevent harmful exposures and disease related to toxic substances. ATSDR is directed by congressional mandate to perform specific functions concerning the effect on public health of hazardous substances in the environment. These functions include public health assessments of waste sites, health consultations concerning specific hazardous substances, health surveillance and registries, response to emergency releases of hazardous substances, applied research in support of public health assessments,

information development and dissemination, and education and training concerning hazardous substances."

(http://www.atsdr.cdc.gov/about.html)

1.1.2. EXTension TOXicology NETwork

"The EXTension TOXicology NETwork (EXTOXNET) is an effort of University of California, Davis, Oregon State University, Michigan State University, Cornell University, and the University of Idaho. Some of the goals of EXTOXNET are to stimulate dialog on toxicology issues, develop and make available information relevant to extension toxicology, and facilitate the exchange of toxicology-related information in electronic form, accessible to all with access to the Internet. The EXTOXNET InfoBase is accessible via the World Wide Web (WWW). Various types of pesticide toxicology and environmental chemistry information are available from the WWW server at Oregon State University. These include: discussions of toxicological issues of concern (TICs); toxicology newsletters; other resources for toxicology information; toxicology fact sheets; Pesticide Information Profiles (PIPs); and Toxicology Information Briefs (TIBs)."

(http://extoxnet.orst.edu/etn.txt.html)

1.1.3. National Pesticide Telecommunications Network

"The National Pesticide Telecommunications Network (NPTN) is a free information service sponsored by the United States Environmental Protection Agency and Oregon State University. NPTN provides objective, science-based information about a wide variety of pesticide-related subjects."

(http://npic.orst.edu/)

1.1.4. Environmental Protection Agency

"In July of 1970, the White House and Congress worked together to establish the Environmental Protection Agency (EPA) in response to the growing public demand for cleaner water, air and land. Prior to the establishment of the EPA, the federal government was not structured to make a coordinated attack on the pollutants that harm human health and degrade the environment. The EPA was assigned the daunting task of repairing the damage already done to the natural environment and to establish new criteria to guide Americans in making a cleaner environment a reality. The mission of the Environmental Protection Agency is to protect human health and the environment. EPA leads the nation's environmental science, research, education and assessment efforts. EPA works to develop and enforce regulations that implement environmental laws enacted by Congress.

EPA is responsible for researching and setting national standards for a variety of environmental programs, and delegates to states and tribes the responsibility for issuing permits and for monitoring and enforcing compliance. Where national standards are not met, EPA can issue sanctions and take other steps to assist the states and tribes in reaching the desired levels of environmental quality. At laboratories located throughout the nation, the Agency works to assess environmental conditions and to identify, understand, and solve current and future environmental problems; integrate the work of scientific partners such as nations, private sector organizations, academia and other agencies; and provide leadership in addressing emerging environmental issues and in advancing the science and technology of risk assessment and risk management."

(http://www.epa.gov/epahome/aboutepa.htm)

1.1.5. International Agency for Research on Cancer

"The International Agency for Research on Cancer (IARC) is part of the World Health Organization. IARC's mission is to coordinate and conduct research on the causes of human cancer, the mechanisms of carcinogenesis, and to develop scientific strategies for cancer control. The Agency is involved in both epidemiological and laboratory research and disseminates scientific information through publications, meetings, courses, and fellowships. IARC is studying cancer incidence, mortality and survival in numerous countries and is thus playing a leading role in cancer registration worldwide. In laboratory investigations, epidemiological studies and working group meetings, more than 800 agents and exposures have been examined with the aim of unambiguously identifying those which cause cancer in humans. IARC laboratory research concentrates on the interaction of carcinogens with DNA, with the aim of elucidating mechanisms of carcinogenesis. This knowledge not only gives insights into the biology of cancer, but also helps to identify stages where it may be possible to intervene in the process to prevent progression to clinical disease."

(http://www.iarc.fr/)

1.2.   Toxicity of Mosquito Control Pesticides

Information from agencies that categorize pesticide toxicity is presented below from their respective websites.

1.2.1. International Agency for Research on Cancer Evaluation of Carcinogenicity

The following information is from the IARC Evaluation of Carcinogenicity (http://monographs/monoeval/eval.html).

"The body of evidence is considered as a whole, in order to reach an overall evaluation of the carcinogenicity to humans of an agent, mixture or circumstance of exposure. The categorization of an agent, mixture or exposure circumstance is a matter of scientific judgment, reflecting the strength of the evidence derived from studies in humans and in experimental animals and from other relevant data.

Group 1: The agent (mixture) is carcinogenic to humans. The exposure circumstance entails exposures that are carcinogenic to humans. This category is used when there is sufficient evidence of carcinogenicity in humans. Exceptionally, an agent (mixture) may be placed in this category when evidence of carcinogenicity in humans is less than sufficient but there is sufficient evidence of carcinogenicity in experimental animals and strong evidence in exposed humans that the agent (mixture) acts through a relevant mechanism of carcinogenicity.

Group 2: This category includes agents, mixtures and exposure circumstances for which, at one extreme, the degree of evidence of carcinogenicity in humans is almost sufficient, as well as those for which, at the other extreme, there are no human data but for which there is evidence of carcinogenicity in experimental animals. Agents, mixtures and exposure circumstances are assigned to either group 2A (probably carcinogenic to humans) or group 2B (possibly carcinogenic to humans) on the basis of epidemiological and experimental evidence of carcinogenicity and other relevant data.

Group 3: The agent (mixture or exposure circumstance) is not classifiable as to its carcinogenicity to humans. This category is used most commonly for agents, mixtures and exposure circumstances for which the evidence of carcinogenicity is inadequate in humans and inadequate or limited in experimental animals. Exceptionally, agents (mixtures) for which the evidence of carcinogenicity is inadequate in humans but sufficient in experimental animals may be placed in this category when there is strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans. Agents, mixtures and exposure circumstances that do not fall into any other group are also placed in this category.

Group 4: The agent (mixture) is probably not carcinogenic to humans. This category is used for agents or mixtures for which there is evidence suggesting lack of carcinogenicity in humans and in experimental animals. In some instances, agents or mixtures for which there is inadequate evidence of carcinogenicity in humans but evidence suggesting lack of carcinogenicity in experimental animals, consistently and strongly supported by a broad range of other relevant data, may be classified in this group."

1.2.2. US Environmental Protection Agency Evaluation of Carcinogenicity

The following information is from the EPA Evaluation of Carcinogenicity (http://www.epa.gov/ncea/raf/pdfs/cancer_gls.pdf).

"To express conclusions about the weight of evidence for human carcinogenic potential, standard descriptors are utilized as part of the narrative. The descriptors are not meant to replace an explanation of the nuances of the biological evidence, but rather to summarize it. Applying a descriptor is a matter of judgment and cannot be reduced to a formula. Each standard descriptor may be applicable to a wide variety of potential data sets and weights of evidence. There will always be gray areas, gradations, and borderline cases. That is why the descriptors are presented only in the context of a weight of evidence narrative. Using them within a narrative preserves and presents the complexity that is an essential part of the hazard characterization. Risk managers should consider the entire range of information included in the narrative rather than focusing simply on the descriptor. Different conclusions may be reached for a single agent when carcinogenicity is dose or route dependent. For instance, the agent is likely to be carcinogenic by one route of exposure but not by others. In this instance, more than one descriptor is used, one for each route of exposure. Another example would be that an agent is likely carcinogenic above a certain dose range but not likely to be carcinogenic below that range.

Carcinogenic to Humans: This descriptor is appropriate when there is convincing epidemiologic evidence demonstrating causality between human exposure and cancer. This descriptor is also appropriate when there is an absence of conclusive epidemiologic evidence to clearly establish a cause and effect relationship between human exposure and cancer, but there is compelling evidence of carcinogenicity in animals and mechanistic information in animals and humans demonstrating similar mode(s) of carcinogenic action.

Likely to be Carcinogenic to Humans: This descriptor is appropriate when the available tumor effects and other key data are adequate to demonstrate carcinogenic potential to humans. Adequate data are within a spectrum. At one end is evidence for an association between human exposure to the agent and cancer and strong experimental evidence of carcinogenicity in animals; at the other, with no human data, the weight of experimental evidence shows animal carcinogenicity by a mode or modes of action that are relevant or assumed to be relevant to humans.

Suggestive Evidence of Carcinogenicity, but Not Sufficient to Assess Human Carcinogenic Potential: This descriptor is appropriate when the evidence from human or animal data is suggestive of carcinogenicity, which raises a concern for carcinogenic effects but is judged not sufficient for a conclusion as to human carcinogenic potential.

Data Are Inadequate for An Assessment of Human Carcinogenic Potential: This descriptor is used when available data are judged inadequate to perform an assessment. This includes a case when there is a lack of pertinent or useful data or when existing evidence is conflicting, e.g., some evidence is suggestive of carcinogenic effects, but other equally pertinent evidence does not confirm a concern.

Not Likely to be Carcinogenic to Humans: This descriptor is used when the available data are considered robust for deciding that there is no basis for human hazard concern.

1.2.3. US Environmental Protection Agency Evaluation of Neurotoxicity

The following information is from the EPA Evaluation of Neurotoxicity (http://oaspub.epa.gov/eims/eimscomm.getfile?p_download_id=4555)

"The EPA Guidelines for Neurotoxicity Risk Assessment set forth principles and procedures to guide EPA scientists in evaluating environmental contaminants that may pose neurotoxic risks, and inform Agency decision makers and the public about these procedures. The following are the scheme for characterizing the sufficiency of evidence for neurotoxic effects. This scheme defines two broad categories: sufficient and insufficient. Categorization is aimed at providing certain criteria for the Agency to use to define the minimum evidence necessary to define hazards and to conduct dose-response analyses.

Sufficient Evidence: This category includes data that collectively provide enough information to judge whether or not a human neurotoxic hazard could exist. This category may include both human and experimental animal evidence.

Sufficient Human Evidence: This category includes agents for which there is sufficient evidence from epidemiologic studies, e.g., case control and cohort studies, to judge that some neurotoxic effect is associated with exposure. A case series in conjunction with other supporting evidence may also be judged "sufficient evidence." Epidemiologic and clinical case studies should discuss whether the observed effects can be considered biologically plausible in relation to chemical exposure.

Sufficient Experimental Animal Evidence/Limited Human Data: This category includes agents for which there is sufficient evidence from experimental animal studies and/or limited human data to judge whether a potential neurotoxic hazard may exist. Generally, agents that have been tested according to current test guidelines would be included in this category. The minimum evidence necessary to judge that a potential hazard exists would be data demonstrating an adverse neurotoxic effect in a single appropriate, well-executed study in a single experimental animal species. The minimum evidence needed to judge that a

potential hazard does not exist would include data from an appropriate number of endpoints from more than one study and two species showing no adverse neurotoxic effects at doses that were minimally toxic in terms of producing an adverse effect. Information on pharmacokinetics, mechanisms, or known properties of the chemical class may also strengthen the evidence.

Insufficient Evidence: This category includes agents for which there is less than the minimum evidence sufficient for identifying whether or not a neurotoxic hazard exists, such as agents for which there are no data on neurotoxicity or agents with databases from studies in animals or humans that are limited by study design or conduct (e.g., inadequate conduct or report of clinical signs). Many general toxicity studies, for example, are considered insufficient in terms of the conduct of clinical neurobehavioral observations or the number of samples taken for histopathology of the nervous system. Thus, a battery of negative toxicity studies with these shortcomings would be regarded as providing insufficient evidence of the lack of a neurotoxic effect of the test material. Further, most screening studies based on simple observations involving autonomic and motor function provide insufficient evaluation of many sensory or cognitive functions. Data, which by itself would likely fall in this category, would also include information on SAR or data from in vitro tests. Although such information would be insufficient by itself to proceed further in the assessment it could be used to support the need for additional testing."

1.3. Pesticide Exposure Pathways

The following information was synthesized from Kamrin (1997). Chemicals, including pesticides, can enter the body through three routes: inhalation, ingestion and dermal exposure. For example, if a pesticide has been applied in a spray form, the chemical can be inhaled during the spraying, it may penetrate the skin if it gets on unprotected parts of the body and may be ingested while eating if hands are not washed after applying the pesticide. Use of protective clothing and following proper handling and application procedures can greatly reduce the amount of exposure to pesticides. Exposure to pesticides does not have to be restricted to the applicator alone, other people, as well as animals, in the area of the application site can be exposed. Furthermore, pesticides that persist in the environment can continue to expose people long after the actual application occurred.

Whether exposure to pesticides is through the lungs, skin, or stomach, these chemicals will most likely enter the bloodstream. There are several different ways the body handles the chemicals. The chemical properties of the pesticides will determine its distribution and fate. They may be

quickly removed from the bloodstream and excreted through urine or feces. The chemicals may be metabolized into products that may be easier to excrete, or into chemicals that are potentially more toxic. The pesticides may also end up being stored in various tissues of the body, resulting in long-term exposure.

An individual's characteristics, such as age, health, and diet, can influence how the body deals with and may influence the fate of the pesticides to which a person is exposed. Additionally, the health effects of pesticide exposure may be affected by the dose, the number of times the exposure occurs, as well as the length of time over which the exposure occurs.

1.4. Report Constraints

Direct evidence of impacts to human health from synthetic chemicals, such as pesticides, can be difficult to determine. Epidemiology can be used to link disease incidence with causes by finding associations between exposures to potential causes and disease prevalence. Such associations can be difficult to determine for individual chemicals, especially when those chemicals may not often be considered separately. That is the case, generally, for modern mosquito control pesticides. Unlike some other pesticides that have either been in longer usage or have otherwise achieved a degree of notoriety, the pesticides under prime consideration for the risk assessment associated with the Suffolk County Vector Control and Wetlands Management Long-Term Plan generally are not studied as separate substances. This means that most studies of "pesticides" impacts are not clear as to whether or not these specific pesticides were among those chemicals that the people were exposed to.

The pesticides and pesticide-related compounds that will be subjected to the primary risk assessment as part of the development of the Long-Term Plan may include:

- Pyrethrum

- Permethrin

- Sumithrin

- Deltamethrin

- Resmethrin

- Piperonyl butoxide

- Malathion

- Malaoxon

- Garlic Oil

- *Bacillus thuriengensis* (Bt or Bti)

- *Bacillus sphaericus*

- Methoprene

- Temephos

- Monomolecular films (Ethoxylate surfactant, oxcylated fatty acids)

- Petroleum derivative oils (such as GB 1111)

Because these substances are more likely to be part of the full-scale risk assessment, this focused report on the relationship between vector control pesticides and breast cancer and childhood illnesses has focused on them. However, more general reports of pesticide impacts on breast cancer and children's health were also included, as seemed appropriate.

References for Section 1

Kamrin MA. 1997. *Pesticide Profiles: Toxicity, Environmental Impact, and Fate.* Lewis Publishers, New York, NY. 704 pp.

Landrigan, PJ, CA Kimmel, A. Correa, and B. Eskenazi. 2004. Children's health and the environment: public health issues and challenges for risk assessment. *Environmental Health Perspectives* 112(2):257-265.

Toy VS. 2002. What's next. *New York Times, Long Island Weekly Desk.* August 11:1.

2. Mosquito Control Pesticides and Breast Cancer

2.1.   *Carcinogenicity of Mosquito Control Pesticides under Consideration*

2.1.1. Adulticides – Pyrethrum and Pyrethroids

There is a group of related chemicals used for mosquito control purposes. These are pyrethrum (trade name – Pyrocide), pyrethrins, and specific pyrethroids such as permethrin (trade name – Aqua reslin), sumithrin (trade name – Anvil), deltamethrin, and resmethrin (trade name – SBP-1382, Scourge). Pyrethrum is a natural insecticide derived from chrysanthemum flowers. Pyrethrins refer to the specific naturally occurring insecticidal chemicals, whereas pyrethroids are synthetic insecticides based on the chemical structure of pyrethrins. Often, the word pyrethrum is used to refer to both the natural and synthetic types of insecticides (EXTOXNET, 1994).

In a two-year feeding study of rats, moderate to high doses of pyrethrum resulted in benign thyroid tumors in females, while high doses resulted in ovarian tumors and benign liver tumors (National Pesticide Telecommunications Network, 1998). The US Environmental Protection Agency (USEPA) has classified permethrin as a Group C Possible Human Carcinogen. The classification "Group C Possible Human Carcinogen" is assigned to a chemical when limited evidence of carcinogenicity in animals is available, but no human data is available. Pyrethrins have been classified by USEPA as likely to be a human carcinogen by the oral route (US Environmental Protection Agency, 1999). Deltamethrin and permethrin have both been determined to be "not classifiable" for carcinogenicity to humans by The International Agency for Research on Cancer (IARC) (http://monographs.iarc.fr/monoeval/crthall.html).

2.1.2. Adulticides – Piperonyl Butoxide

Piperonyl butoxide, a pyrethrum and pyrethroid synergist, inhibits detoxification of pesticides in insects so that the addition of this chemical to a pesticide reduces required amount of the active ingredient necessary to achieve the desired effect. Liver tumors developed in female mice fed high doses of piperonyl butoxide and in male mice fed middle and high doses (National Pesticide Telecommunications Network, 2000b). However, in other feeding studies conducted in rats

alone or in both rats and mice, investigators found no evidence of carcinogenicity for piperonyl butoxide (Butler et al., 1998; National Pesticide Telecommunications Network, 2000b). USEPA has classified piperonyl butoxide as a Group C Possible Human Carcinogen (US Environmental Protection Agency, 1999).

2.1.3. Adulticides – Malathion

Malathion (tradenames – Fyfanon, Atrapa) is an organophosphate pesticide that inhibits cholinesterase activity. In a two-year feeding study of rats, female rats developed liver tumors at all tested doses ranging from 2.4 to 817 mg/k/g/day. In an 18-month feeding study of mice, an increased incidence of liver tumors was observed in the female mice fed the highest doses of malathion, 1707 and 3448 mg.kg/day (US Environmental Protection Agency, 2000a). The conclusion of USEPA in both studies is that liver tumors only occurred at excessive doses in these animals (National Pesticide Telecommunications Network, 2001). USEPA has classified malathion as having suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential (US Environmental Protection Agency, 2000a). IARC has categorized malathion as unclassifiable as to carcinogenicity in humans (http://monographs.iarc.fr/monoeval/crthall.html). A recent study found that subcutaneous or intraperitoneal injections of malathion resulted in the formation of mammary tumors in rats. The results of this study prompted the authors to propose that alterations at the nervous system level, as caused by exposure to malathion, may alter the molecular pathways that initiate cellular proliferation leading to mammary carcinogenesis (Cabello et al., 2001). More recent studies by these researchers have shown that malathion, when tested in breast cancer cell studies, is capable of altering cell proliferation and transformation (Cabello et al., 2003).

2.1.4. Adulticides – Malaoxon

Malaoxon is a cholinesterase inhibitor that is metabolite of malathion. In a feeding study of this chemical in rats, malaoxon was not found to be carcinogenic. USEPA has determined that there is no evidence of carcinogenicity in male or female rats (US Environmental Protection Agency, 2000a).

2.1.5. Adulticides – Garlic Oil

Garlic oil from the *Allium sativum* plant has been used as a pesticide.   USEPA waived most data requirements for the re-registration of garlic because it is generally recognized as safe in its use as a natural seasoning or flavoring. USEPA believes that the use of garlic as a pesticide is not associated with any significant adverse effects to humans (US Environmental Protection Agency, 1992).

2.1.6. Larvicides - Bacillus thuringiensis

Bacillus thurinngiensis (Bt) (tradenames – Bactimos, Teknar, Vectobac, Aquabac) is a bacterium that produces spores that release a number of chemicals that are toxic to insects when ingested. The subspecies *Bacillus thuringiensis israelensis* (Bti) is specifically toxic to mosquitoes and certain types of flies (National Pesticide Telecommunications Network 2000a). Bti is a naturally occurring soil bacterium registered by USEPA for control of mosquito larvae. Mosquito larvae eat the Bti product that contains a toxin that disrupts the gut by binding to receptor cells present in insects, but not in mammals (http://www.epa.gov/cgi-bin/epaprintonly.cgi). It, therefore, is not believed to be capable of harming people.

2.1.7. Larvicides - Bacillus sphaericus

Bacillus sphaericus is a naturally occurring bacterium, found throughout the world, that is registered by USEPA for use against various kinds of mosquito larvae. Mosquito larvae ingest the bacteria and, as with Bti, the toxin disrupts the gut by binding to receptor cells present in insects, but not in mammals. USEPA considers both microbial pesticides, *Bacillus thuringiensis israelensis* and *Bacillus sphaericus*, essentially nontoxic to humans (http://www.epa.gov/cgi-bin/epaprintonly.cgi).

2.1.8. Larvicides - Methoprene

Methoprene (tradenames – Altosid, Alpicid) is an insect growth regulator that is considered a biochemical pesticide. Methoprene prevents insects from reaching maturity or reproducing by interfering with the insect's life cycle. Based on results of feeding studies in both rats and mice,

which exhibited no increase in tumor incidence, USEPA concluded that Methoprene is not carcinogenic (US Environmental Protection Agency, 2001b).

2.1.9. Larvicides - Temephos

Temephos (tradename – Abate) is an organophosphate pesticide registered by USEPA for the control of mosquito larvae. USEPA does not classify Temephos as a carcinogen, based on the results of a two-year study conducted on rats in which no tumors were induced (US Environmental Protection Agency, 2000b;US Environmental Protection Agency, 2001a). A recent study found Temephos to be mutagenic when tested at levels similar to those applied to household water supplies in Brazil (Aiub et al., 2002). Various concentrations of temephos were used in that study including 2.14 µmol, a concentration slightly higher than the 1.66 µmol usually applied to household water reservoirs in Brazil. The authors concluded that temephos was mutagenic in two of the tests conducted; suggesting that the concentrations applied to household water supplies in Brazil may not be as safe as previously thought.

2.1.10.   Larvicides - Monomolecular Films

Monomolecular films are ethoxylate surfactants and oxcylated fatty acids (under the tradename of Agnique MMF). These films prevent attachment to the water's surface for mosquito larvae and pupae, preventing adults from emerging and causing mosquitoes at various stages of development to drown. They are considered a low toxicity pesticide; according to USEPA, monomolecular films, used according to label directions for larva and pupa control, do not pose a risk to human health. In addition to low toxicity, there is little opportunity for human exposure, since the material is applied directly to ditches, ponds, marshes, or flooded areas that are not drinking water sources (http://www.epa.gov/cgi-bin/epaprintonly.cgi).

2.1.11.   Larvicides – Petroleum-Derivative Oils

Petroleum derivative oils (tradename – Mosquito Larvicide GB 1111) are used to form a coating on top of the water causing larvae, pupae and emerging adult mosquitoes to drown. According to USEPA, these oils are specially derived from petroleum distillates and have been used for many years in the United States to kill aphids on crops and orchard trees, and to control

mosquitoes. When used according to label directions for larva and pupa control, USEPA does not consider these mosquito control measures to pose a risk to human health. As with the use of the monomolecular films, they are considered low toxicity and there is little opportunity for human exposure because they are not applied to drinking water sources (http://www.epa.gov/cgi-bin/epaprintonly.cgi).

Table 2-1 - Summary of carcinogenicity of mosquito control pesticides

Mosquito Control Pesticide	Evaluation of Carcinogenicity
Pyrethrum (trade name – Pyricide); Pyrethrins; Pyrethroids: Permethrin (trade name – Aqua reslin), Sumethrin (trade name – Anvil), Deltamethrin, Resmethrin (trade name – SBP-1382, Scourge)	USEPA: Group C: Possible Human Carcinogen IARC: Not classifiable for carcinogenicity
Piperonyl butoxide (pyrethrum and pyrthroid synergist)	USEPA: Group C: Possible Human Carcinogen
Malathion (tradenames – Fyfanon, Atrapa)	USEPA: Suggestive of carcinogenicity, but not sufficient to assess human carcinogenic potential IARC: unclassifiable as to carcinogenicity in humans Recent evidence of ability to cause breast cancer cell proliferation and transformation
Malaoxon (metabolite of malathion)	USEPA: No evidence of carcinogenicity in rats
Allium Sativum (common name: garlic)	USEPA: Not associated with any significant adverse effects in humans
Bacillus thuringiensis (tradnames – Bactimos, Teknar, Vectobac, Aquabac)	USEPA: Considered essentially non-toxic in humans
Bacillus sphaericus	USEPA: Considered essentially non-toxic in humans
Methoprene (tradenames – Altosid, Alpicid)	USEPA: Not carcinogenic
Temephos (tradename – Abate)	USEPA: Not carcinogenic Recent evidence of mutagenicity
Monomolecular films (Ethoxylate surfactant, oxcylated fatty acids; tradename – Agnique MMF)	USEPA: Does not pose a risk to human health
Petroleum derivative (tradename – Mosquito Larvicide GB 1111)	USEPA: Does not pose a risk to human health

2.2. *Mosquito Control Pesticide Carcinogenicity – Summary*

None of the mosquito control pesticides under consideration are conclusively considered carcinogens by USEPA or IARC. The strongest laboratory evidence for carcinogenicity is for the pyrethroids, specifically permethrin and deltamethrin; both are considered possible carcinogens. Additionally, piperonyl butoxide, a synergist used with pyrethrum and pyrthroids, is also considered a possible carcinogen. There is also some suggestion that malathion may have carcinogenic potential, as evaluated by USEPA, and more recent evidence of an ability to cause cell proliferation and transformation in breast tissue cell lines. Temephos is not considered

carcinogenic by USEPA, however a recent study identified evidence of mutagenicity. USEPA did not identify the other pesticides under consideration as having carcinogenic potential and no other evidence of carcinogenicity was identified in the literature.

2.3.   Hormonal Activity of Mosquito Control Pesticides

Many breast cancer risk factors are hormone related. Epidemiologic and laboratory studies have implicated both exogenous (originating outside the body) and endogenous (produced within the body) sources of estrogen in the etiology of breast cancer. Thus, evidence of hormonal activity associated with any of the pesticides under consideration is included in this review.

The estrogenic potential, ability to act like the hormone estrogen, of certain pyrethroids has been evaluated in several ways.   Using MCF-7 human breast carcinoma cell lines, sumithrin, fenvalerate, d-trans-allerthrin, and permethrin were tested for hormone disruption. All demonstrated an ability to influence several cellular pathways, although not necessarily the same pathway (Go et al., 1999). Testing these same four pyrethroids in two other cell lines resulted in significant estrogenic activity identified for fenvalerate and sumithrin; however, none blocked the action of estrogen (demonstrated estrogen antagonism) or acted as the steroid hormone, progesterone (Garey and Wolff, 1998). Similarly, several pyrethroids, including permethrin and deltamethrin, were found to induce MCF-7 cell proliferation and inhibit binding of estradiol to the estrogen receptor.   Inhibition of estrogen receptor binding of estradiol by a compound indicates that the compound may interfere with normal hormonal activity (Chen et al., 2002). Deltamethrin was found to cause weak, but significant, MCF-7 cell proliferation, however, no estrogen receptor activation was observed (Andersen et al., 2002). A lack of estrogen receptor activation indicates that the compound may not work in the same way as naturally occurring estrogen.   In contrast, the estrogenic or anti-estrogenic activity of several pyrethroids (d-transallethrin, cypermithrin, empenthrin, fenvalerate, imiprothrin, permethrin, d-phenothrin, and prallethrin) could not be demonstrated in a suite of *in vitro* assays based on human estrogen receptor alpha-mediated mechanisms (Saito et al., 2000). Similarly, in an *in vivo* test system used for the evaluation of endocrine disruptor activity, esfenvalerate, fenvalerate, and permethrin were not found to exert estrogenic, anti-androgenic, or adrogenic influences (Kunimatsu et al., 2002).   Animal studies provide some evidence that exposure to pyrethroids may influence

endocrine function; plasma testosterone levels were reduced in a rat feeding study of 39.66 mg/day of cypermethrin (Elbetieha et al., 2001) and decreased ovarian weight was observed in a study of female rats fed a daily dose of 23.98 mg fenpropathrin/kg (ATSDR 2001). Thus, evidence both for and against the hormonal potential for pyrethroids can be found in the literature.

Among the remaining mosquito control pesticides under consideration, malathion was the only pesticide with any studies conducted for hormonal activity. An estrogenic potential evaluation of malathion in both an E-screen, MCF-7 cell proliferation, and estrogen receptor binding test found no estrogenic activity for this insecticide (Chen et al., 2002).

2.4. *Breast Cancer Descriptive Epidemiology*

According to a recent review of worldwide cancer incidence, breast cancer is the second most common cancer in the world when both sexes are combined and the most common cancer among women. The annual incidence rate of breast cancer varies widely with respect to geographic area. Based on the year 2000 world standard population, the Netherlands (91.6/100,000 women per year) and the US (91.4/100,000 women per year) have the highest breast cancer incidence rates in the world; this can be compared to the rate in China (10.0/100,000 women per year), which is among the lowest (Parkin, 2001).

Among US women in 2000, the overall age-adjusted annual incidence rate of invasive breast cancer was 135.1/100,000 women. The incidence rate of breast cancer is strongly associated with age. Among women under 65 years of age, the age-adjusted incidence rate was 90.4 / 100,000 women per year and for women 65 years and older, it was 459.6/100,000 women per year (Ries et al. 2003). It has been estimated that 215,990 women in the United States will be newly diagnosed with breast cancer in 2004, making it the most common cancer among women, more than lung, colorectal and endometrial cancer (Jemal et al., 2004).

There are racial and geographic variations in the annual incidence rates of breast cancer reported across the United States Surveillance, Epidemiology and End Results (SEER) sites. The SEER Program of the National Cancer Institute is an authoritative source of information on cancer incidence and survival in the United States. According to its website,

"SEER began collecting data on cases on January 1, 1973, in the states of Connecticut, Iowa, New Mexico, Utah, and Hawaii and the metropolitan areas of Detroit and San Francisco-Oakland. In 1974-1975, the metropolitan area of Atlanta and the 13-county Seattle-Puget Sound area were added. In 1978, 10 predominantly black rural counties in Georgia were added, followed in 1980 by the addition of American Indians residing in Arizona. Three additional geographic areas participated in the SEER program prior to 1990: New Orleans, Louisiana (1974-1977, rejoined 2001); New Jersey (1979-1989, rejoined 2001); and Puerto Rico (1973-1989). In 1992, the SEER Program was expanded to increase coverage of minority populations, especially Hispanics, by adding Los Angeles County and four counties in the San Jose-Monterey area south of San Francisco. In 2001, the SEER Program expanded coverage to include Kentucky and Greater California; in addition, New Jersey and Louisiana once again became participants. The SEER Program currently collects and publishes cancer incidence and survival data from 14 population-based cancer registries and three supplemental registries covering approximately 26 percent of the US population. Information on more than 3 million *in situ* and invasive cancer cases is included in the SEER database, and approximately 170,000 new cases are added each year within the SEER coverage areas. The SEER Registries routinely collect data on patient demographics, primary tumor site, morphology, stage at diagnosis, first course of treatment, and follow-up for vital status. The SEER Program is the only comprehensive source of population-based information in the United States that includes stage of cancer at the time of diagnosis and survival rates within each stage. The mortality data reported by SEER are provided by the National Center for Health Statistics."

(http://seer.cancer.gov/about/)

In 2000, the annual incidence rate of breast cancer in the US among white women was 140.9/100,000 women while the rate among blacks was 116.3/100,000. The geographic variation is most striking among white women where annual incidence rates ranged from 143.1/100,000 women in the Connecticut registry to 116.8/100,000 women in Utah (Ries et al., 2003). Breast cancer has a high 5-year relative survival rate (87 percent), especially if detected at an early stage (97 percent survival rate) (Jemal et al., 2004).

According to the New York State Cancer Registry - New York State Department of Health (NYSDOH), Nassau and Suffolk counties had among the highest average annual incidence rates of breast cancer in the state, 144.2/100,000 women in Nassau County and 148.4/100,000 women in Suffolk County, for the years 1996-2000. The racial variation in breast cancer incidence observed in the SEER data is found within the two Long Island counties. Among white women,

the average annual incidence rate for the same time period was 148.6 and 150.9/100,000 women in Nassau and Suffolk counties, respectively. In contrast, the annual average breast cancer incidence among black women in these two counties was 108.7 and 113.9/100,000 women (New York Department of Health, 2003).

2.5.   *Epidemiologic Studies of Pesticide Exposure and Breast Cancer*

Epidemiologic studies of breast cancer with measures of exposure to the specific insecticides under consideration, whether through biomarkers, records of pesticide use/application, or self-report, have not been reported in the literature. Although not investigated due to its insecticidal properties, garlic has been investigated as a dietary risk factor for breast cancer. Epidemiologic investigations of dietary sources of garlic and breast cancer risk have reported a moderate protective effect or no association (Fleischauer and Arab, 2001).   The vast majority of epidemiologic studies conducted to date on specific insecticide exposure and breast cancer risk have focused on the organochlorine pesticides such as DDT (dichlorodiphenyl trichloroethane), dieldrin and chlordane or metabolites of these pesticides, such as the DDT metabolite DDE (dichlorodiphenyl dichloroethylene). However, the association between exposure to this family of pesticides and breast cancer risk is not relevant to this review, as the pyrethroids and malathion are not chemically or structurally similar in the least to the traditional organochlorine pesticides.

A large array of literature exists that assesses cancer incidence and pesticide exposure through occupation in industries such as agriculture or pesticide application. The majority of these studies have focused on men, due to the small proportion of women employed in these industries. When possible, many have included women in their study populations, and have assessed breast cancer as an outcome. However, the relevance of these studies is limited, as the specific identification of exposure to the particular mosquito control insecticides of interest is difficult, if not impossible, to infer. Although a job title of farmer or agricultural worker may mean that the study participant is exposed to pesticides on the job and may even provide some indication of the class of pesticides, there is a high likelihood that the person was exposed to many different pesticides, not a single product. Thus, use of this type of exposure determination

prevents the identification of an association between specific pesticides and breast cancer; however, they can indicate whether the potential for such an association exists.

Despite the above limitations, this occupation-based literature is the only epidemiologic literature currently available for use in evaluating whether insecticides used for mosquito control may increase breast cancer risk. Table 2-2 presents the details of epidemiologic investigations of occupational pesticide exposure and breast cancer risk.

In sum, none of the investigations reviewed found any significant increased risk of breast cancer incidence or increased breast cancer mortality associated with: working on a farm or in an agricultural industry; being the spouse of a farmer; being a resident of a farm; or holding a job as a pesticide applicator. Many of these investigations suffer from a lack of control for potential confounding factors as well as potential exposure misclassification. Additionally, given the time periods covered by many of these studies, there is reduced potential for the pesticide exposures experienced by the study participants to be among the mosquito control pesticides that are currently being considered for use. Even with these limitations, it is unlikely that any large or even moderate increases in risk are being obscured.

In summary, the epidemiologic literature does not provide evidence either for or against an association between the currently considered mosquito control pesticides and breast cancer risk.

Table 2-2 - Summary of epidemiologic studies of pesticide exposure and breast cancer risk

Study design and population	Exposure	Measure of association	Variables adjusted for confounding
Wiklund 1983 Retrospective cohort - Sweden, Cancer-Environment registry - 354,228 involved in agriculture, 36,711 females - follow-up 1961-1973 - 444 cases	Female agricultural workers	O/E[b] 99% CI[c] 0.81 (0.71-0.91)	Age and sex
Olsen 1987 Population-based linkage study - Denmark - 18,403 cases in all occupational categories diagnosed 1970-1979 - 152 cases in agriculture; 112 cases in electrical manufacturing	Agriculture, hunting, forestry and fishing	SPIR[e] 95% CI 101 (86-118)	Age and calendar year
Ewertz 1988 Population-based case-control - Denmark - 1694 cases diagnosed 3/1/83-2/29/84, <70 years - 1705 controls, age stratified sample	Women's occupation Home, farming Husband's occupation Farming	OR[f] Farmers used as reference category - all other occupations OR>1.00 Farmers used as reference category - all other husband's occupations OR$\geq$1.00 except shop sales (OR=0.98)	Age, place of residence, parity and both factors in table
Kato 1990 Standardized Proportional Ratio - Aichi, Japan, Cancer Registry, - General population of Aichi prefecture estimated from 1980 and 1985 census data - 103 cases, diagnosed 1979-1987, >30 years	Female agricultural workers	O/E p 0.73 <0.01	Age according to age distribution of cancer patients
Franceschi 1993 Case-control - Northeastern Italy - 132 cases diagnosed 1985-1991, <80 years - 968 controls	Female farmer	RR[g] 95%CI 0.8 (0.5-1.3)	Age, smoking and alcohol

Study design and population	Exposure	Measure of association	Variables adjusted for confounding
Rubin 1993 Nested case-control and Proportionate mortality study - USA - Mortality database maintained at NIOSH (covers 23 states), represents 2.9 million death certificates - 59,196 breast cancer deaths in all occupational groups - 197 cases in farming occupational group, 124 white and 73 black diagnosed 1979-1987 - 59,196 controls randomly selected from all white women who did not die from breast cancer or malignancies of the female reproductive system freq-age matched by 5-yrs	Farming, forestry and fishing occupational group White Black	OR 95% CI 0.84 (0.66-1.07) PMR[h] p 75 <0.01 61 <0.01	None reported
Costantini 1994 Cross-sectional - Italy - 579 cases, 21 in agriculture industry, died 1981-1982, 18 to 64 years - 2,038 deceased and economically active in all occupational groups	Employed in agriculture indusry	MOR[i] p 57 0.02	

Study design and population	Exposure	Measure of association	Variables adjusted for confounding
Wiklund 1994 Prospective cohort - Sweden, 1970 Swedish Population and housing census - 50,682 women worked $\geq$20 hrs/week in agriculture - Expected number of cases calculated on basis of annual cancer incidence among women in 5-yr age groups - Follow-up 1/1/71 to 12/31/87 or death - 1,159 cases	Female agricultural worker	SIR[j] 95% CI 0.83 (0.78-0.88)	

Cantor 1995
Nested case-control
- USA
- Mortality database maintained at NIOSH (covers 24 states)
- 33,509 cases, 29,397 white and 4,112 black, died between 1984-1989
- 117,794 controls (non-cancer deaths), 102,955 white and 14,839 black, frequency matched for age (5-yr), gender and race
	Exposure to insecticides scale (0 to 3)
	
	0
	1
	2
	3
		Whites Blacks
		OR(1) OR(2) OR(1)
		              OR (2)
		
		1.0 1.0 1.0 1.0
		1.19 1.42 0.58[k]
		                0.57[k]
		1.07 1.07 -------
		------- ------- -------
			Age and SES[l]
			(1) all probability levels of exposure
			(2) excluding women with low probability of exposure

Kristensen 1996 Retrospective Cohort - Norway - Farm holders or their spouses (253,624 total; 113,949 women) born after 1924 - Follow-up 1969 to 1991 or death or emigration - 598 cases engaged in agriculture; 148 cases working $\geq$500 hrs/yr on a farm	Women engaged in agriculture Women working $\geq$500hrs/yr on a farm	SIR 95% CI 105 (96-113) 84 (72-99)	None reported

Study design and population	Exposure	Measure of association	Variables adjusted for confounding
Folsom 1996 Population-based prospective cohort - Iowa, USA - 36,295 randomly selected women in 1986 - follow-up through 1992 - 934 cases	Lived on a farm	RR 95% CI Age-adj 0.96 (0.82-1.13) Multi-adj 1.03 (0.87-1.23)	Age, smoking, body mass index, waist-to-hip ratio, education, physical activity, marital status, alcohol use, family history of breast cancer, reproductive characteristics
Pukkala 1997 Retrospective cohort - Finland - 85,151 women farmers on 12/31/78 - follow-up 1/1/79 to 12/31/93 or death or emigration - 1,474 cases	Finnish female farmer	SIR 95% CI 0.77 (0.73-0.80)	None reported
Avnon 1998 Case-control study - Israel - 734 women members of 3 kibbutzim 1989 - 7 cases of breast cancer	Female member of agricultural settlement	Kibbutz O/E p A 3/3.25 >0.05 B 2/1.69 >0.05 S 2/0.93 >0.05	None
Fleming 1999 Retrospective cohort study - Florida - 3,503 female licensed pesticide applicators (1975-1993) - 26 breast cancer cases	Female pesticide applicator	SIR 95% CI 0.61 (0.40, 0.90)	Age and calendar year
Simpson 1999 Proportional incidence study - England and Wales - 381,915 women diagnosed with cancer through UK cancer registry (1971-1990) - 93,951 breast cancer cases	Agricultural occupation	Only reported occupations with significantly increased cancer rates - No pesticide-related occupations and no agricultural occupations were found to have elevated breast cancer rates	Age and social class

Study design and population	Exposure	Measure of association	Variables adjusted for confounding
Settimi 1999 Hopital-based case-control study - 5 areas in Italy - incident cancer cases among residents of catchment area admitted to 8 collaborating hospitals (1990-1992) - reference group drawn from other cancer sites excluding lung cancer, cancers of the female reproductive systems and women with previous oophorectomy - 67 premenopausal and 192 postmenopausal breast cancer cases - 72 premenopausal and 424 postmenopausal controls	Job title of farmer or farm laborer	OR 95% CI Premenopausal Ever employed 1.4 (0.5, 3.4) 1-9 yrs 1.2 (0.3, 4.1) 10-19 yrs 0.4 (0.0, 4.6) 20+ yrs 2.9 (0.5,16.2) Postmenopausal Ever employed 0.4 (0.3, 0.7) 1-9 yrs 0.9 (0.4, 2.3) 10-19 yrs 0.8 (0.3, 2.1) 20+ yrs 0.4 (0.2, 0.8)	Premenopause Use of oral contraceptives alcohol consumption, family history of breast cancer, parity Postmenopause Age at menarche, age at last menstruation, hormone replacement therapy, alcohol consumption, age at first birth, BMI

Duell 2000
Sub-study from a population-based case control study (eligibility was reported farming)
- Eastern and Central North Carolina
- Invasive breast cancer cases diagnosed 1993-1996
- Controls selected from motor vehicle roster (<65) and Health Care & Finance roster (65+)
- Randomized recruitment to achieve 50% African-American and 50% under age 50
  -327 cases and 381 controls who reported farming participated
  -451 cases and 409 controls reported that they never lived or worked on a farm
	Reported having lived or worked on a farm	OR 95%CI
		Ever farmed 1.0 0.8-1.2
		Duration (yrs)
		  1-10 1.2 0.8-1.7
		  11-17 0.8 0.5-1.2
		  18-23 0.7 0.8-1.1
		  >23 0.6 0.4-0.9
			Age, race, age at menarche, parity/age at first birth, lactation, current body size, education, duration of smoking, alcohol consumption, family history of breast cancer, oral contraceptive use, duration of laundry for pesticide user

Study design and population	Exposure	Measure of association	Variables adjusted for confounding
Wang 2002 Retrospective cohort study - New York State - 6,310 female farm residents (1980-1993) - 141 breast cancer cases -622,268 comparison female residents of non-urbanized areas	Female farm resident (farmer or adult relative sharing same last name of farmer who had been a Farm Bureau member)	SIR 95% CI All 0.89 (0.75, 1.05) 30-49 yr 1.17 (0.85, 1.58) 50-69 yr 0.80 (0.64, 0.99) 30-49 yr 0.82 (0.43, 1.47)	None
Fleming 2003 Retrospective cohort study of mortality - United States National Health Interview Survey - 208,855 women (1986-1994) - 7 female pesticide applicators and 1,718 female farmers	Female pesticide exposed worker	RR 95% CI 0.4 (0.1, 1.5)	Age

Footnotes
[b]Observed/expected
[c]Confidence interval
[d]Standardized mortality ratio
[e]Standardized proportionate incidence ratio
[f]Odds ratio

[g]Relative risk
[h]Proportionate mortality ratio
[i]Mortality odds ratio
[j]Standardized incidence ratio
[k]95% CI excludes 1.0
[l]Socioeconomic status

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3. Mosquito Control Pesticides and Childhood Illnesses

3.1. Direct Linkages

There is some limited information available concerning direct linkages between the identified mosquito control chemicals and childhood illnesses.

3.1.1. Adulticides – Pyrethrins and Pyrethroids

Pyrethrins can interfere with normal neurological function. In adults, short-term, high level exposure to these insecticides may cause:

- dizziness

- headache

- nausea

- muscle twitching

- reduced energy

- changes in awareness

- convulsions

- loss of consciousness.

It is likely that the same effects would be experienced by children exposed to high levels of pyrethrum (Agency for Toxic Substances and Disease Registry, 2001a). Overall, pyrethrins and pyrethroids reportedly pose low chronic toxicity to humans, the most common problems resulting from the allergenic properties of pyrethrum (EXTOXNET 1994). In rats, developmental exposure to pyrethroids has been shown to have long-lasting effects causing neurobehavioral and neurochemical deficits in adulthood. Inhalation of pyrethroid-containing mosquito repellants early in a rat's life has been shown to cause damage to the blood brain

barrier, which may indicate that early life exposure to these chemicals could lead to adverse neurological effects (Sinha and Shukla, 2003).

3.1.2. Adulticides – Piperonyl butoxide

Piperonyl butoxide is reported to have low to very low toxicity when ingested, inhaled, or absorbed through the skin by mammals (National Pesticide Telecommunications Network, 2000b).

3.1.3. Adulticides – Malathion

Malathion is an organophosphate pesticide that inhibits cholinesterase activity. Cholinesterase is an enzyme that removes the chemical neurotransmitter acetylcholine from the junctions between nerves cells. Cholinesterase serves as the nervous system's "off switch" and is essential to the normal function of the nervous system. USEPA requires neurotoxicity testing, both acute and subchronic, in animal studies for all pesticides submitted for registration by USEPA. All studies reviewed by USEPA were found to be acceptable and to have met the agency's guidelines (US Environmental Protection Agency, 2000a). The Agency for Toxic Substances and Disease Registry (ATSDR) reported that children who have accidentally swallowed or had skin contact with high amounts of malathion experienced symptoms such as:

- difficulty breathing

- chest tightness

- vomiting

- cramps

- diarrhea

- watery eyes

- salivation

- sweating

- headaches

- dizziness

- loss of consciousness

- death

(Agency for Toxic Substances and Disease Registry, 2001b).

Note that "high amounts of malathion" was not defined in the ATSDR toxicological profile summary of health effects of malathion exposure in children. Very young animals have been identified as more susceptible to the effects of malathion than older animals. Rapid medical treatment of high level exposure to malathion prevents long-term effects, and low level exposure appears to pose few or no health problems (Agency for Toxic Substances and Disease Registry, 2001b).

3.1.4. Adulticides – Malaoxon

Malaoxon (metabolite of Malathion) is a cholinesterase inhibitor that is metabolite of malathion. USEPA did not identify any acute toxicity testing of the malaoxon but calculated that this malathion metabolite appears to have approximately 10 to 30 times greater toxicity (US Environmental Protection Agency, 2000a).

3.1.5. Adulticides – Garlic Oil

USEPA waived most data requirements for the re-registration of garlic oil (from the *Allium sativum* plant) because it is generally recognized as safe in its use as a natural seasoning or flavoring. USEPA believes that the use of garlic as a pesticide is not associated with any significant adverse effects to humans (US Environmental Protection Agency, 1992).

3.1.6. Larvicides - *Bacillus thuringiensis* and *Bacillus sphaericus*

Bacillus thuringiensis and *Bacillus sphaericus* are naturally occurring bacteria. USEPA considers both of these microbial pesticides, essentially nontoxic to humans (http://www.epa.gov/cgi-bin/epaprintonly.cgi).

3.1.7. Larvicides - Methoprene

Methoprene prevents insects from reaching maturity or reproducing by interfering with the insect's life cycle. Evaluation of the toxicity of methoprene by the USEPA indicates that exposure through oral, dermal or inhalation routes is not likely to cause adverse health effects in humans (US Environmental Protection Agency, 2001b).

3.1.8. Larvicides - Temephos

Temephos (tradename – Abate) is an organophosphate pesticide registered by USEPA for the control of mosquito larvae (US Environmental Protection Agency, 2000b; US Environmental Protection Agency, 2001a). Temephos is considered to have low to moderate toxicity compared to other organophosphate insecticides. Symptoms in animals associated with acute exposure to this pesticide include:

- hypoactivity

- labored breathing

- chromodacryorrhea (red tears)

- rough coat

- salivation

- muscle spasm

- tremors.

USEPA did not have sufficient information to evaluate the neurotoxic potential of temephos (US Environmental Protection Agency, 2001a).

3.1.9. Larvicides - Monomolecular Films and Petroleum Oils

Monomolecular films and petroleum derivative oils are considered low toxicity and there is little opportunity for human exposure because they are not applied to drinking water sources (http://www.epa.gov/cgi-bin/epaprintonly.cgi).

3.1.10.   Summary

None of the mosquito control pesticides under consideration are considered to be highly toxic to humans. The organophosphate insecticides or their metabolites (malathion, malaoxon, and temephos) have potential neurological effects in humans due to their mode of action, but are not considered to be neurotoxic in humans. Pyrethroids also act on the nervous system. Evidence of the neurological effects of pyrethroids in animals has been reported, but no assessment of neurotoxicity in humans has been determined. All of the other pesticides under consideration were not considered to pose a risk to human health.

Table 3-1 - Summary of toxicity of mosquito control pesticides under consideration

Mosquito Control Pesticide	Evaluation of Toxicity
Pyrethrum (trade name – Pyricide), Pyrethrins, Pyrethroids: Permethrin (trade name – Aqua reslin), Sumithrin (trade name – Anvil), Deltamethrin, Resmethrin (trade name – SBP-1382, Scourge)	Low chronic toxicity Animal evidence of damage to the blood brain barrier
Piperonyl butoxide (pyrethrum and pyrethroid synergist)	Low to very low toxicity
Malathion (tradenames – Fyfanon, Atrapa)	Meets neurotoxicity requirements (USEPA) Few or no health problem associated with low level exposure
Malaoxon (metabolite of Malathion)	No acute toxicity testing – estimated to be 10-30 times more toxic than malathion
Allium Sativum (common name: Garlic)	Not associated with any significant adverse effects in humans (USEPA)
Bacillus thuringiensis (tradnames – Bactimos, Teknar, Vectobac, Aquabac)	Considered essentially non-toxic in humans (USEPA)
Bacillus sphaericus	Considered essentially non-toxic in humans (USEPA)
Methoprene (tradenames – Altosid, Alpicid)	Not likely to cause adverse health effects in humans (USEPA)
Temephos (tradename – Abate)	Low to moderate toxicity compared to other organophosphates (USEPA) No neurotoxicity data available
Monomolecular films (Ethoxylate surfactant, oxcylated fatty acids; tradename – Agnique MMF)	Does not pose a risk to human health (USEPA)
Petroleum derivative (tradename – Mosquito Larvicide GB 1111)	Does not pose a risk to human health (USEPA)

3.2. *Pesticide Exposure Pathways for Children*

This summary of the pesticide exposure pathways for children is adapted from Environmental Health of Children (Dunn et al., 2003). Children are considered particularly vulnerable to pesticide exposures due to their physiological, behavioral, and biological characteristics. Children eat and drink higher quantities per body size than adults resulting in a greater likelihood of exposure through the consumption of pesticide contaminated foods and beverages. More rapid respiration in children can also result in higher exposure per body volume than in adults. Children's behaviors also increase their pesticide exposure opportunities. These behaviors include living closer to the ground, hand-to-mouth behaviors, and outdoor activity such as playing in parks and playgrounds where pesticides are used. Biologic development in children is rapid and makes them susceptible to chemical insult. Disruption of neurological and organ development can easily occur. Children's blood-barriers are immature. Additionally, children's

ability to detoxify and excrete toxins may be reduced due to their maturing metabolic processes. Beyond immediate effects that can be experienced, early exposure to pesticides in children allows for a longer time period over which chronic or delayed disease can develop.

Further evidence of children's vulnerability to pesticide exposure is found in the data from the National Health and Nutrition Examination Survey (NHANES). An analysis of urinary dialkyl phosphate metabolites of organophosphate pesticides (i.e., malathion) identified statistically significantly higher concentrations of these metabolites in children aged six to 11 year when compared to the concentration levels measured in adults (20 – 59 years of age) (Barr et al., 2004). Similar findings were obtained from a study of farm workers and their children; mean levels of several organophosphate metabolites were slightly higher among children than among adults (Mills and Zahm, 2001). No statistical comparisons between levels in children and adults were made because of small sample sizes.

3.2.1. Childhood Cancer – General Rates

The following review of descriptive epidemiology of childhood cancer is a summary of information presented in Cancer Incidence and Survival Among Children and Adolescents (Ries et al., 1999). Childhood cancer is not a single disease but a wide range of malignancies that vary by histology, organ, race, sex, and age. The major groupings of childhood cancers are:

I.   Leukemia

II.   lymphomas and reticuloendothelial neoplasms

III.   central nervous system and miscellaneous intracranial and intraspinal neoplasms

IV.   sympathetic nervous system

V.   retinoblastoma

VI.   renal tumors

VII.   hepatic tumors

VIII.   malignant bone tumors

IX.   soft-tissue sarcomas

X.   germ-cell, trophoblastic and other gonadal tumors

XI.   carcinomas and other malignant epithelial neoplasms

XII.   other and unspecified malignant neoplasms.

Cancer incidence is documented by the SEER Program of the National Cancer Institute, an authoritative source of information on cancer rates and survival in the United States. Incidence rates for several types of childhood cancer have increased since the 1970s (Figure 3-1). In contrast, mortality has significantly declined over the same time period (Figure 3-1). In general, there appears to be a gender difference in all-sites childhood cancer incidence; when all cancer sites are combined, rates are higher for boys than for girls (Figure 3-1). However, site-specific cancer rates do not always follow this overall trend. Leukemia, lymphoma, and central nervous system neoplasms have the highest incidence rates, while retinoblastoma, hepatic and other neoplasms have the lowest (Figure 3-2).
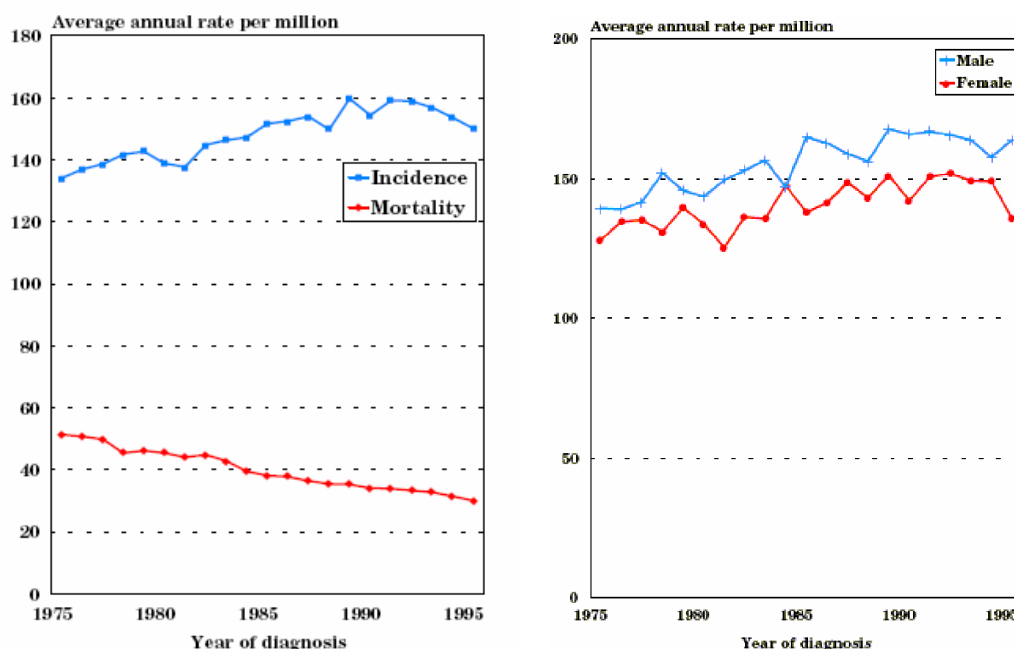
Figure 3-1 - Incidence and mortality rates for childhood cancers (totals and by gender)

(From SEER Figure 1: Age-Adjusted (to the 1970 US standard population) SEER incidence & US mortality rates for all childhood cancers age<20, all races, both sexes, 1975-95)
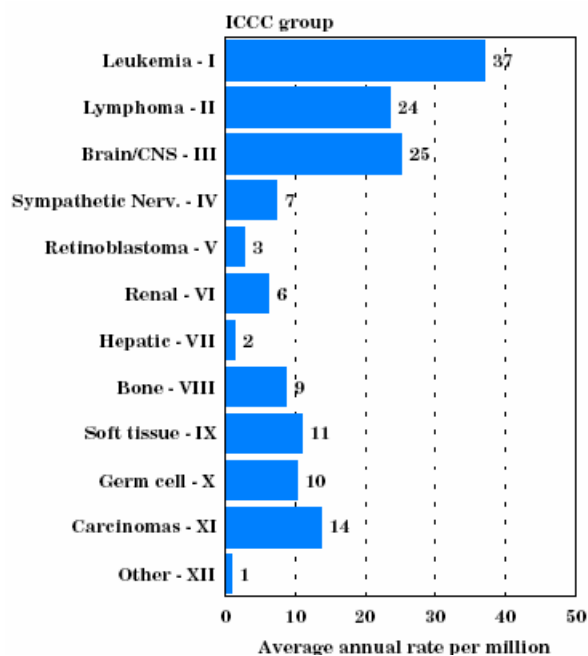
Figure 3-2 – Incidence rates for childhood cancers by cancer type

(Taken from SEER Figure 5: Age-Adjusted (to the 1970 US standard population) incidence rates for childhood cancer by ICCC group, age<20, all races, both sexes, SEER, 1975-95)

The epidemiological literature on the relationship between pesticides and childhood cancer is abundant, and predominately through case control studies (see Table 3-2, below). Overall, the literature suggests moderate associations between pesticide exposure and some cancers in children.

However, in spite of some clear trends, exposure assessments cited in the literature are subject to much confounding. An exposure is considered a "confounder" if it related to the exposure of interest and it is associated with the disease being studied. If a confounder is not accounted for in a statistical analysis then any observed exposure-disease associations may be due to the confounder rather than the exposure being studied.

No actual biomarkers have been measured. Biomarkers are biological indicators of exposure that can be measured in the blood, body fluids, cells, and tissues that can be used as surrogate

measures of chemical dose. Instead, exposure data is based on proximity to areas of pesticide use, and/or more often self-reported interview responses, which are subject to recall bias. Interviews are based on parent's report of their own occupational exposures, household, yard and garden spraying, and their children's direct exposures, since young children are obviously not a dependable source of information. Few studies isolated specific pesticides, and those that did focused on substances not relevant to this review. Despite the numerous specific groupings for childhood cancer, described above, most of the papers are only concerned with leukemias, lymphomas, and brain cancers.

3.2.2. Childhood Cancer - Leukemias

Of the seven studies reviewed that focused on childhood leukemia and pesticides, six found a positive association between disease and exposure (Leiss and Savitz, 1995; Meinert et al., 1996; Kaatsch et al., 1998; Petridou and Dessypris, 2000; Meinert et al., 2000; Ma et al., 2002), although not exclusively significant, and one found no association (Feychting et al., 2001). Pesticide exposure assessment spanned from prenatal development through childhood. All studies supporting an association, focused on exposures inside of or outside of the home, although it is unclear whether this difference causes a variation in risk. The one study that did not find any positive association between leukemia and pesticide use was based on preconception occupational pesticide exposure of the child's father (Feychting et al., 2001). Based on the articles reviewed, it appears that leukemia is linked to non-specific pesticide use; none of these studies provided information on pesticide types beyond general categorization (e.g., insecticides). This finding is consistent with previous reviews (Zahm and Ward, 1998).

3.2.3. Childhood Cancer - Lymphomas

The literature includes several studies on pesticides and lymphomas, which support a positive association between the two. The association is, however, not quite as strong as the association of pesticides with leukemia. One study found significant associations between lymphoma and a child's direct exposure, as well as lymphoma and exposure from a mother's spraying around the house (Buckley et al., 2000).

Three studies found an elevated odds ratio for pesticide use in the home (Leiss and Savitz, 1995; Meinert et al., 2000; Buckley et al., 2000). An odds ratio is a measure of association between an exposure and a disease outcome. An odds ratio of one is interpreted as no association between exposure and disease. An odds ratio greater than one is interpreted as an increased risk of disease associated with the exposure. Two of these were significant on at least one strata of exposure (Leiss and Savitz, 1995; Meinert et al., 2000) and two exhibited a dose response relationship (Meinert et al., 2000; Buckley et al., 2000) although the Buckley findings for indoor use are based on a small sample size. Use of pest strips in the home, which was highly associated with leukemias, was not found to be significantly associated with lymphomas (Leiss and Savitz, 1995). Further, outdoor use of pesticides (yard/garden/farm) yielded no significant relationship with lymphoma in any of the studies reviewed.

3.2.4. Childhood Cancer - Brain and Nervous System

Studies on cancers of the brain and central nervous system also supported an association with pesticide use. Within the seven studies investigating cancers of the brain and central nervous system (including neuroblastomas), odds ratios varied from protective to elevated; however five studies found significant increased risks (Leiss and Savitz, 1995; Olshan et al., 1999; Daniels et al., 2001; van Wijngaarden et al., 2003; Efird et al., 2003). One of these positive associations was significant for general association (ever use) but not when stratified to preconception or child exposure (Daniels et al., 2001). Brain cancer risk associated with outdoor pesticide exposure, either through farm, garden, or yard, was significantly decreased in one study (Schuz et al., 2001a), significantly increased in another (Daniels et al., 2001), and not found with any association in yet another study (Leiss and Savitz, 1995). Two studies reported a positive pesticide association based on parental occupation (van Wijngaarden et al., 2003; Efird et al. 2003). Finally another study found that risks were increased with prenatal exposure in comparison with those exposed during childhood (Zahm and Ward, 1998).

3.2.5. Childhood Cancer - Other Cancers

Other cancers present in the research about pesticides and childhood cancer were often grouped as solid tumors, soft tissue sarcomas, kidney cancers, and/or included general cancer mortality

rates of a geographic area. Results varied by type of cancer. While one study found a high odds ratios relating yard treatment to soft tissue sarcomas (Leiss and Savitz, 1995), no significant findings were identified for total mortalities (Pearce and Parker, 2000; Schreinemachers et al., 1999), solid tumors (Meinert et al., 1996) or kidney cancer (Schuz et al., 2001b). However, other researchers (Zahm and Ward, 1998) suggest the risk of the latter cancer is increased among children whose parents farm for long periods of time. Feychting et al. (2001) found a significant elevation in nervous system tumors related to paternal exposure pre-conception; however this was based on occupational exposure via agricultural, horticultural and forestry management, which may have included exposure to many other possible carcinogens.

3.2.6. Childhood Cancer - Summary

Based on this review, there is epidemiological evidence to support a positive relationship between pesticide exposure and childhood leukemia, lymphomas, and brain cancer. However, due to the lack of focus in research on individual pesticides, and the imperfect measures of exposure assessment, it is difficult to identify which substances are safe for future use. No conclusions can be drawn with respect to the specific mosquito control pesticides that are under consideration.

Table 3-2 - Summary of epidemiologic studies of pesticide exposure and childhood cancer

Study design and Populations	Exposure	Measures of Association				Variables adjusted for confounding
		Leukemia	Lymphomas	Brain/Central Nervous System Tumors	Other	
Leiss, 1995 Population-based case control -Denver, CO, USA, Cancer registry and area hospital records -252 cases; < 15 years; diagnosed between 1976-1983 -222 controls	**Home pest extermination** 0-2 years	OR (95% CI) 0.3 (0.1-0.8)	OR (95% CI) 1.8 (1.1-2.9)	No significant findings at any strata	No significant findings at any strata	Age at diagnosis, father's education, per capita income, residential stability, mother's age, race, sex, maternal smoking, residential wire code (magnetic field exposure), and year of diagnosis (controlled separately)
	Yard Treatment 0-2 years 2 years prior to and through diagnosis	No significant findings at any strata	No significant findings at any strata	No significant findings at any strata	OR (95% CI) (soft tissue sarcomas) 4.1 (1.0-16.0) (soft tissue sarcomas) 3.9 (1.7-9.2)	
	Hanging pest strips (indoors) Last 3 months of pregnancy 0-2years 2 years prior to and through diagnosis	3.0[1] (1.6-5.7) 1.7 (1.2-2.4) 2.6 (1.7-3.9)	No significant findings at any strata	1.8 (1.2-2.9)	Total cancers 1.5 (1.0-2.8)	
Meinert 1996 Population–based case control study -Lower Saxony, Northern Germany, German Children Cancer Registry -173 leukemia cases, and 175 CNS tumors; <15 years; diagnosed 1988 – 1993; -220 local controls, 213 state controls	**Ever use** **In garden** **On farm**	OR (95% CI) (v. local controls) 2.47 (1.13-5.38) 2.52 (1.03-6.14) 1.64 (0.55-0.53)			(solid tumors) No significant findings in any strata	Sex, age, social status, degree of urbanization

---

[1] Unadjusted

Table 2 (continued).		Measures of Association				
Study design and Populations	**Exposure**	**Leukemia**	**Lymphomas**	**Brain/Central Nervous System Tumors**	**Other**	**Variables adjusted for confounding**
Kaatsh 1998 Population based case control study, West Germany, German Childhood Cancer Registry -560 cases; <15 years; diagnosed 1992-1994 -560 controls	**Use in agriculture, household or garden**	OR (95% CI) 2.13 (1.05-4.35)				Socio-economic status
Schreinemachers 1999 Retrospective cohort; -Minnesota, USA, National Center for Health Statistics, 1980-1989 -< 15 years	**Agricultural regions**				SRR (95%) Reference group= Region 4 (urban) No significant results in specific cancers. (Total cancer mortalities) Region Boys Girls 1 0.82 (0.59-1.13) 0.98 (0.67-1.43) 2 1.49 (0.81-2.71) 1.49 (0.71-3.10) 3 1.43 (0.80-2.56) 0.88 (0.35-2.20)	

Olshan 1999
-Population based case control study
- Pediatric Oncology Group and Children's Cancer group; participating hospitals in US and Canada
-538 cases; <19 May 1 1992 and April 30, 1994, -504 controls
	Parental occupation
	
	Paternal
	      Farmers
	   Landscapers
	   Pest Control
	
	Maternal
	      Farmers
					OR (95% CI)
					
					0.9 (0.4, 1.8)
					2.3 (1.0-5.2)
					0.3 (0.0-3.2)
					
					2.2 (0.6-8.8)
						Mother's race, Mother's age, Mother's education, household income in birth year

Table 2 (continued).		Measures of Association				
Study design and Populations	**Exposure**	**Leukemia**	**Lymphomas**	**Brain/Central Nervous System Tumors**	**Other**	**Variables adjusted for confounding**
Petridou 2000 Nationwide case control study -Greece -153 cases of leukemia; <15 years; 1993-1994 -300 controls -136 cases of Acute Lymphoblastic Leukemia (ALL), 266 controls	**Prenatal exposure to pesticides**	RR (95% CI) Leukemia 3.6 (1.2-10.8) ALL 2.9 (0.9-9.9)				Not reported
Meinert 2000 -Population-based case control study, German Childhood Cancer registry -1184 cases with ALL, 234 with non Hodgkin's, 940 solid tumor; diagnosis between Oct 1992-Sept 1994 or living in West Germany, < 15 years AND diagnosis between 1980- 1994, and living near a nuclear installation -2588 controls	Pesticide use In garden On a farm Household insecticides by parent <1/year 2-5/year 6-10/year >10 by pest controller	OR (95% CI) 1.0 (0.8, 1.2) 1.5 (1.0, 2.2) Reference group: < 1/yr 1.0 (0.7, 1.5) 1.0 (0.7, 1.4) 1.3 (0.7, 2.4) 1.8 (1.0, 3.3) 1.3 (0.8, 2.3)	OR (95% CI) 0.8 (0.5, 1.2) 0.5 (0.2, 1.4) Reference group: < 1/yr 1.3 (0.6, 2.8) 1.3 (0.7, 2.9) 1.5 (0.6, 4.1) 2.8 (1.1, 7.2) 2.6 (1.2, 5.7)			

Table 2 (continued).		Measures of Association				
Study design and Populations	**Exposure**	**Leukemia**	**Lymphomas**	**Brain/Central Nervous System Tumors**	**Other**	**Variables adjusted for confounding**
Pearce 2000 Retrospective cohort -Database of live births, kidney cancers and deaths in Cumbria, Northwest England; death certificates; -Born 1950-1993; 1378 cancer mortalities between ages 1-15, plus 7 non fatal kidney cancers	**Parental occupation in agriculture**				MR (exposed/unexposed) All cancer deaths =0.53 Kidney cancer mortalities=0.08	
Buckley 2000 -Population based case control study; participating hospitals -268 cases, February 1986 -June 1990; <20 years -268 controls	**Household insecticides (mother)** <1/week 1-2 / week most days		(non Hodgkin's) OR (95% CI) 0.98 (0.60-1.58) 2.62 (0.96-7.18) 7.33 (0.84-63.85)			Maternal education and race
	Garden sprays (mother) < 1/month => 1/month		1.82 (0.61-5.45) 1.71 (0.67-4.37)			
	Exterminate around home (mother)		2.98 (1.44-6.16)			
	Herbicides/pesticides (child)		2.35 (1.37-4.03)			
	Occupational pesticides (parent)		1.74 (0.82-3.69)			
Schuz 2001 Medical and Pediatric Oncology -Population based Case Control Study, German Childhood Cancer Registry -466 cases, < 15 years; July 1988 - June 1993 in Lower Saxony and October 1992 -September 1993 in West Germany -2458 controls	**Use of pesticides** In garden On farms			OR (95% CI) 0.94 (0.68-1.29) 0.41 (0.18-0.93)		Degree of urbanization and SES, age gender and year of birth
	Use of insecticides 1/year >1 /year			1.38 (0.84-2.25) 1.19 (0.81-1.77)		

Table 2 (continued).		Measures of Association				
Study design and Populations	**Exposure**	**Leukemia**	**Lymphomas**	**Brain/Central Nervous System Tumors**	**Other**	**Variables adjusted for confounding**
Schuz 2001 Eur J Pediart Population based Case Control Study, German Childhood Cancer Registry -177 cases, < 15 years; July 1988 - June 1993 in Lower Saxony and October 1992 - September 1993 in West Germany -2006 controls	**Child exposure** In garden On farms (and gardens)				OR (95% CI) (Wilm's tumor, renal cancer) 0.80 (0.44-1.47) 0.84 (0.32-2.25)	Socioeconomic status, urbanization, age, gender, year of birth
	In house use of insecticides (more than once a year)				1.27 (0.78-2.08)	
	Maternal occupational exposure to pesticides (ever)				2.52(0.50-12.6)	
	Paternal occupational exposure to pesticides after birth				0.97 (0.39-2.37)	
Daniels 2001 -Population based case control study - Pediatric Oncology Group and Children's Cancer group; participating hospitals in US and Canada -538 cases; <19 May 1 1992 and April 30, 1994, -504 controls	As reported by both parents Extermination Home pesticide Garden pesticide			Neuroblastoma OR (95% CI) 　　　　　　　Preconception <u>Ever</u>　　　　<u>/Pregnancy</u> <u>Childhood</u> 1.4 (0.9-2.1)　1.0 (0.5-2.1) 1.5 (0.8-2.6) 1.6 (1.0-2.3)　1.3 (0.8-3.3) 1.4 (0.9-2.2) 1.7 (0.9-2.1)　1.3 (0.8-2.0) 1.8 (1.0-3.1)		Household income and child's age

Table 2 (continued).		Measures of Association				
		Leukemia	Lymphomas	Brain/Central Nervous System Tumors	Other	Variables adjusted for confounding
Feychting 2001 -Prospective cohort study -235,635 children born in 1976, 1977, 1981 and 1982, Swedish Cancer Registry, followed for 15 years -522 cases of childhood cancer: 161 leukemia, 162 nervous system disorders	Paternal occupation agricultural, horticultural, forestry management) before conception	RR (95% CI) 0.90 (0.37-2.19)			RR (95% CI) (Nervous system disorders) 2.36 (1.27-4.39)	Census year, gender, maternal age; SES (only to those born in 1981/1982)
Ma (2002) Population-based case control study - Northern California Childhood Leukemia Study (hospital based) -162 cases from <15, between, 1995-1999; 135 with ALL -162 controls	3 months before pregnancy- 3 years old Professional pest control Insecticides Professional pest control Insecticides	OR (95%) (leukemia) 2.8 (1.4-5.7) 2.6 (1.2-5.4) (ALL) 2.1 (1.1-4.3) 2.2 (1.0-4.6)				Annual household income
Wijngaarden 2002 -Population-based case control study - Children's Cancer Group (US and Canada) - Cases: 154 with astroyctoma and 158 with Primitive Neuroectaldemral tumors (PNET); between 1986 – 1989; diagnosis before 6 years of age -321 controls	Parental occupation to insecticides Father Mother			OR (95%) Astrocytoma PNET 1.5(0.9-2.4) 1.1 (0.7-1.7) 1.9 (1.1-3.3) 1.0 (0.6-1.7)		Maternal age, household income, maternal education
Efrid 2003 -Population based case control Study -San Francisco, Los Angeles, Seattle, USA; Israel, Milan, Italy; Valencia, Spain; Sydney, Australia; Paris, France; Winnipeg, Canada. -1218, <20 years, diagnosis between 1976-1994 -2223 controls	Maternal job related exposure to agricultural chemicals			OR (95%) 2.0 (1.2, 3.2)		Age, center, gender

3.3.   *Respiratory Illness*

3.3.1. Descriptive Epidemiology of Asthma

The following discussion on the epidemiology of asthma is summarized from Summary Health Statistics for US Children (Dey et al., 2004). Asthma is the most common chronic disease among children; nine million U.S. children under the age of 18 have been diagnosed. It is a chronic inflammatory disease of the lungs in which the airways are constricted from inflammation and hyper-responsiveness to triggers such as allergens, infections, exercise, changes in weather, and airway irritants. Asthma episodes can range in severity from mild to life threatening and involve shortness of breath, coughing, wheezing, chest pain or tightness, or a combination of these symptoms. Asthma prevalence has increased across all age groups from 1980 to 1995 and has remained relatively stable through 2000. Young males (age 0-17 years) have a higher likelihood of experiencing an asthma attack than females in the same age group.

3.3.2. Epidemiologic Studies of Pesticides and Respiratory Illnesses

There is a paucity of epidemiologic studies of pesticide exposure and respiratory illnesses, especially studies focusing on children (see Table 3-3). Several cross-sectional studies (those studies that investigate prevalent disease rather than new cases of disease) have investigated home environment conditions and their association with prevalent respiratory problems and one large cohort study of pesticide applicators. Small increases in wheezing were found for malathion use in Ethiopian homes (Yemaneberhan et al., 1997) and among licensed pesticide applicators (Hoppin et al., 2002). Wheezing among children was also found to be associated with ever exposure to pesticides in Lebanon (Salameh et al., 2003) as well as burning mosquito repellants in Taiwan (Yang et al., 1997). Ever exposure is a standard epidemiologic exposure categorization, as in "ever versus never." In the Lebanese study, other respiratory problems including respiratory disease, asthma, and chronic phlegm were all significantly associated with ever exposure to pesticides. Except for the study of pesticide applicators, all of the studies were cross-sectional with the concomitant issue of establishing temporality between exposure and disease. Cross-sectional studies assess both disease status and exposure at the same time; thus, it is usually not possible to determine if the exposure preceded the disease onset. One case report

of long-term occupation exposure to tetramethrin (a pyrethroid insecticide) may have led to asthmatic symptoms (Vandenplas et al., 2000) and an accidental exposure to aerosol pyrethroid insecticide resulted in respiratory problems and an asthma attack (Muller-Mohnssen, 1999).

There is biologic plausibility for an association between organophosphate pesticides, such as malathion, and asthma or other respiratory symptoms. Organophosphate pesticides may contribute to respiratory problems through cholinesterase inhibition. Cholinesterase is an enzyme that removes the chemical neurotransmitter acetylcholine from the junctions between nerve cells. Cholinesterase serves as the nervous system's "off switch" and is essential to the normal function of the nervous system. Decreased cholinesterase can cause impairment of a physiological regulatory mechanism of the autonomic (or involuntary) control of airways (Eskenazi et al., 1999), which may promote constriction of the bronchial air passages (Hoppin et al., 2002). However, pyrethroids act on the sodium ion channels, which are involved in the control the sensory nervous system. Stimulation of these channels causes their prolonged opening resulting in sensory neurons to be stimulated. This action is suspected to be related to the paresthesia symptoms associated with pyrethroid intoxication (Narahashi, 1992). Paresthesia symptoms are those that cause a sensation of pricking, tingling, or creeping on the skin having no objective cause, and usually are associated with injury or irritation of a sensory nerve or nerve root. A biological explanation for the development of respiratory symptoms due to pyrethroid exposure has not been proposed.

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Table 3-3 - Summary of epidemiologic studies of pesticide exposure and respiratory illnesses

Study design and population	Exposure	Measure of association	Variables adjusted for Confounding
Yemaneberhan 1997 Cross-sectional study; Ethiopia; Ages 0-70+ years; Feb. to Mar. 1996 Urban (N=9844) and rural (N=3032) households	Malathion used in home	OR 95% CI Wheeze 1.17 (0.92-1.50)	Age, sex and urban or rural residence
Yang 1997 Cross-sectional study; Taiwan; 4164 children (6 to 12 years) September to November 1994	Mosquito repellant burning	Respiratory problem OR 95% CI Asthma 1.24 (0.88-1.74) Cough 1.26 (1.05-1.50) Wheezing 1.15 (0.86-1.54) Bronchitis 1.13 (0.89-1.43) Allergic rhinitis 0.83 (0.69-1.01)	Age, gender, parent's education, child's allergies, parental COPD, household crowding, age of home
Muller-Mohnssen 1999 Case report Germany 18-year old woman	Accidental exposure to aerosol insecticide of resmethrin and pyrethrins	Chronic bronchitis and alveolitis developed; asthmatic crisis occurred 2 months after exposure	
Vanderplas 2000 Case report, Belgium, 47-year old man	Occupational exposure to tetramethrin	Asthmatic reactions to pure tetramethrin challenge	
Hoppin 2002 Prospective cohort study Agricultural Health Study – pesticide applicators in Iowa and North Carolina, 1994-1997 20,468 participants (16-88 years of age) 3,838 with "wheeze"	Ever use of: Malathion Permethrin (crops) Permethrin (poultry)	OR 95% CI p-trend 1.14 (1.02-1.28) 0.01 1.13 (0.95, 1.35) 0.07 1.26 (1.06, 1.51) <0.01	Age, state, past smoking, current smoking and athma/atopy

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Study design and population	Exposure	Measure of association	Variables adjusted for Confounding
Salameh 2003 Cross-sectional study Lebanon Children age 5-16 years March to June 2000 3,291 children returned completed questionnaires	Any pesticide exposure (including living near agricultural fields, use in home, parent in pesticide-related occupation)	Respiratory problem OR 95% CI Resp. disease 1.71 (1.20-2.43) Asthma 1.73 (1.02-2.97) Chronic cough 1.04 (0.82-1.33) Chronic phlegm 1.90 (1.26-2.87) Ever wheeze 1.99 (1.43-2.78)	Passive smoking, sex, age, weight and BMI, parent's respiratory disease, parent's education, animal raising, and playing with dust

3.4.   Neurological Problems in Children

A review of the epidemiologic literature did not reveal investigations on any particular neurological disease such as epilepsy, cerebral palsy, diseases of the peripheral nerves, headaches, movement disorders, or neurobehavioral disorders. Thus, a summary of the epidemiology of any specific neurological disease is not included in this review.

Several of the mosquito control pesticides under consideration have a mode of action that affects the nervous systems of insects. Thus, it is important to examine the epidemiologic literature for evidence of neurological effects in children. As summarized above, children's nervous systems are particularly vulnerable to toxic insult. However, investigation into pesticide exposure and neurological problems conducted in children or adolescents is sparse and study designs are less than optimal (see Table 3-4). As noted by Eskenazi et al. (1999) in a review of organophosphate pesticides and their potential adverse health effects in children, studies of pesticide exposure on children's health have been limited to birth defects, childhood cancer, and acute pesticide poisonings. It is not possible to draw any conclusions about the potential role any of the pesticides under consideration may play in the incidence of childhood neurological problems. The two studies that examined neurological function in relation to pesticide exposure among children or adolescents found better performance among study subjects that were not considered exposed when compared to those who were considered pesticide exposed (Guillette et al., 1998; Rohlman et al., 2001). Specific pesticides that these children may have been exposed to are not known, but both studies suggested that organophosphate pesticides were likely to have been used. The case-series of Japanese children and adults with long-term exposure to malathion through helicopter spraying linked reported neuro-opthalmological symptoms with this exposure (Ishikawa et al., 1993). However, no rigorous epidemiologic investigation was conducted so that no conclusions about an association between malathion exposure and this neurological problem can be drawn.

Table 3-4 - Summary of epidemiologic studies of pesticide exposure and neurological problems

Study design and population	Exposure	Measure of association	Variables adjusted for Confounding
Ishikawa 1993 Case series Japan 1970 71 cases of Saku disease Children and adults	Helicopter spraying of malathion several times per year for 3-5 years	Reported neuro-opthalmological symptoms: optic neuropathy; retinal degeneration; defective vertical smooth pursuit; myopia; neurologic impairment	
Guillette 1998 Ecologic study Mexico 4 and 5 year old children 28 Valley children 17 Foothill children	Living in the valley – high pesticide use Living in the foothills – low pesticide use	Valley children demonstrated statistically significant decreases in stamina, gross and hand-eye coordination, 30-minute memory and the ability to draw a person	Gender
Rohlman 2001 Comparison study Oregon 1998 Hispanic adolescents aged 13-18 years 102 worked in agriculture 51 not employed in agriculture	(A): Preseason non-agriculture (B): Preseason agriculture (C): Postseason agriculture	Number of tests (out of 17) significantly different from: (B): 6 (C): 3 (A): 6 (C): 8 (A): 3 (B): 8	Bonferroni correction for multiple comparisons

Section 3 Reference List

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