Sublethal Effects of Exposure to Cholinesterase-inhibiting Pesticides: Humans and Vertebrate Wildlife

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By

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Introduction

Synthetic and toxic chemicals (of anthropogenic origin) are ubiquitous in the environment at generally low but measurable levels. Pesticide use throughout the US has resulted in the presence of pesticides in surface and ground water supplies (Kolpin et al. 1998; Hopkins et al. 2000), and agrochemicals have been identified as a primary cause of water quality loss nationally (USGS 1999).

Current pesticide regulations in the environmental and human health fields are designed to protect human and wildlife communities from large-dose exposures to pesticides and prevent acute disease symptoms and mortality. However, little protection is currently afforded to humans and wildlife to prevent low-level exposures and sublethal effects (RESOLVE 1994). With improved field monitoring techniques, scientists are producing a growing body of literature documenting in wildlife subtle, adverse effects of low-level chemical exposure on some of the most sensitive physiological processes (e.g. reproduction, development, cognition, and behavior) (reviewed in Grue et al. 1997).

Sentinel animals have alerted humans to chemical hazards in the environment for centuries (van der Schalie et al. 1999). Important breakthroughs in public and environmental health have been made in the last several decades as a result of physiological studies of birds and eggshell formation during the DDT era (Albers et al. 2000) and, since then, of developmental abnormalities due to endocrine disruption from exposure to a wide variety of chemicals (Myers et al. 2003). An integrated examination of the parallels between human and wildlife health with respect to exposure to organochlorine chemicals yielded greater insights, greater awareness, and modified public policies, plus increased activity to mitigate adverse effects.

This proven strategy for advancing environmental protection through integrating wildlife and human toxicity studies has not been extended to one of the most important classes of chemicals actively applied to the environment—the ChE-inhibiting organophosphate and carbamate pesticides. Of all pesticides used, 10% or 122 million pounds of active ingredient are insecticides (US EPA 2004). Approximately 95% of the insecticides applied in the US are these "second generation" compounds (Aspelin and Grube 1999) which replaced organochlorine pesticides (such as DDT) which were found to have intolerable adverse effects due to persistence and biomagnification. Although organophosphates and carbamates are relatively less persistent, they are more acutely toxic, so environmental protection efforts have focused on preventing acute effects.

Several comprehensive reviews of the effects literature are available. A review of lawn and garden pesticide effects by Vanderlinden et al. (2002) provides a good overview of effects from herbicides, insecticides, and fungicides primarily used in Canada. Sanborn et al. (2004) provide a rigorous systematic assessment of chronic human health effects from pesticides. Rolland and Patrick (2000) provide a summary of human and wildlife health threats from environmental chemicals however, as mentioned above, a characterization of human and wildlife effects specific to cholinesterase-inhibiting pesticides is lacking.

We evaluated relevant studies from the wildlife and human health literature and characterized current knowledge of adverse effects from non-acute exposures specifically to organophosphate and carbamate pesticides. This product provides a current synthesis and interpretation of the relevant scientific information concerning sublethal effects in humans and vertebrate wildlife from exposure to cholinesterase-inhibiting pesticides. Detailed reviews of the scientific literature are contained in Appendices 1 (humans) and 2 (wildlife). What follows are methods and an abstracted summary of key findings from each review.

Methods

The objective of this literature review was to characterize the effects to humans and wildlife resulting from low-level exposure to cholinesterase-inhibiting compounds (Table 1). Review papers pertaining to the neurological, genotoxic, immunotoxic,

carcinogenic, reproductive, metabolic, respiratory, dermatological, ecological, and miscellaneous effects on human and wildlife were obtained and reprints of published peer-reviewed review papers and primary literature were examined. Literature searches were conducted through ISI Web of Science®, the National Library of Medicine's PubMed and TOXLINE, and through Web-based search engines. Gray literature resources from Toronto Public Health were utilized for further insights to the primary literature (Vanderlinden et al. 2002; Sanborn et al. 2004). Studies were limited from 1980s to present, although for some outcomes older studies are reviewed for completeness. An attempt was made to include all studies conducted in the United States and Canada. Most studies from other countries are included although the review may not be complete.

Effects targeted included: neurological, neurobehavioral, genetic, cytological, immunological, carcinogenic, reproductive, developmental, metabolic, respiratory, dermatological, and ecological for both wildlife and humans. Laboratory studies to support human health effects were included only to provide context and are not comprehensively reviewed.

The epidemiological study types found in the reviewed human literature were case-control and cohort (Newman et al. 2001). Case reports were not included in this review. In case-control studies, subjects with a specific adverse effect or disease are compared against similar subjects who are effect-free. Subjects' histories are reviewed in order to identify risk factors that may be linked to the effect or disease. Recall bias may influence the results. People may have fallible memories or may exaggerate exposures in order to explain their own illness. Surrogate responders for subjects who are dead may not have complete knowledge of the exposure (Waddell et al. 2001). Cohort studies observe large populations, often following forward in time to determine if people with certain characteristics or risk factors are more likely to develop a disease or show an effect compared to people who do not have the characteristic or risk factor. Bias may occur from the "healthy worker effect" whereby workers exhibit lower rates of mortality from the general population due an increased likelihood that healthy individuals are more likely to be employed or to remain employed than less healthy workers. Confounding factors such as age, gender, lifestyle factors (smoking, diet), and

exposure to other types of contaminants can mask associations and require measurement to control bias. Inadequate sample size may also limit the power of some studies.

Lack of detailed exposure characterization is inherent in all epidemiological studies (Alavanja et al. 2004). In the absence of direct quantification, indirect measurements such as occupation type, length of time on the job, number of acres farmed, general “ever” or “never” used the pesticide information, or the number of years since first started using a particular pesticide may be used as input into exposure measure. The specific exposure measure can vary between studies making comparisons difficult. Additionally, pesticides may be categorized into general groups such as “insecticides” or “herbicides” rather than specific compounds. Confounding exposure may also be due to inert ingredients in pesticide formulations, pesticide mixtures (single exposures to one pesticide are rare), and contaminants that result from the manufacturing process.

Epidemiological studies alone are insufficient to prove a “cause” and “effect” but rather associate or link a risk factor with a disease outcome thus providing supporting evidence for establishing causality. These associations are reported statistically as relative risk or odds ratios which are generally a measure of the risk of developing the outcome or being a case when the risk factor is present (Sabo 1999).

Wildlife studies regarding contaminants are mainly toxicological or ecological. Exposure can be manipulated through a variety of oral or dermal means and through various media such as direct dosing, dietary routes, or through the air or water. Confounding variables can be limited by confining the experiment to a cage with precise experimental conditions or the range can be expanded to include ecosystem interactions. Ecological studies evaluate risk factors by coupling residue analyses, environmental contaminant monitoring, and biomarkers of exposure with measures of effects or other ecologically relevant endpoints on either the individual or the population.

Although authors in both the human and wildlife health fields have employed various statistical tools to interpret primary data, readers are challenged to understand the significance of “no effects” results. Very rarely do authors provide information (such as post-hoc power analyses) to clarify the meaning of null results and many authors err

in presenting null results as evidence of “no effects.” In general, parametric analysis requires authors to interpret null effects as “no differences detected”; primary emphasis is thus placed on significant results and the importance of null results is unknown without analyses to determine if sample sizes were adequate to detect differences given inherent variability. Null findings could also result from chance alone along with systematic and unmeasured bias or uncertainties arising from incorrect qualitative factors such as a limited exposure assessment or not choosing the most sensitive effects outcome or species.

Ecotoxicological Terminology

A complex nomenclature has developed to describe chemical exposure and effects in humans and wildlife. Although exposure and effects have their own distinct attributes (such as object, timing, and magnitude), they are often defined in the literature in relation to each other (e.g. sublethal exposure; see examples in Brown and Brix 1998). Furthermore, identical descriptors are frequently used to characterize both exposure and effects (e.g. acute exposure; acute effects). Because imprecise use of non-standardized terms can result in a lack of clarity in communicating research findings, we attempted to use consistently specific terms for interpreting and describing the ecotoxicological findings reviewed in this paper. Terms were selected that offer the most precise meaning for describing exposure and effects. In addition, redundant terms were eliminated and terms used to describe both exposure and effects (e.g. acute) were limited to one context.

Mode of Action. Target and non-target exposure is used in the wildlife literature to identify wildlife targeted for pesticide action (i.e. the pests) as opposed to biota exposed collaterally. Occupational/therapeutic/bystander exposure in the human health literature similarly describes the context in which humans are exposed to chemicals. Dermal/oral/inhalation are precise terms that describe the route of exposure in humans and animals. Direct and indirect effects are used throughout the wildlife literature to describe toxic assaults directly on the organism of interest as opposed to toxic impacts to the habitat (including prey base) the organism of interest utilizes. This distinction, and the use of primary versus secondary poisoning to describe the food chain dynamics

of toxic exposure, are less helpful than identifying “direct” effects as toxicological and “indirect” effects as ecological.

Timing of Exposure and Effects. Several identical terms are used to describe the timing elements (onset, frequency and duration) of exposure and effects. Exposure and effects may have immediate or delayed onsets, short or long term duration, and frequencies of single or multiple events (within a given duration; e.g acute or chronic exposure or effects). The most problematic of these is “acute” which is simultaneously used to describe the timing and magnitude of effects. Although “acute” is used to describe an exposure that generally results in an immediate and severe effect, providing a quantitative description of the latency and magnitude of effect would be more instructive. Similarly, “subchronic” is another term of limited value because it is non-intuitive and introduced in the literature as a result of regulatory jargon.

Magnitude of Exposure and Effects. More clarity is available from the terms typically used to describe the magnitude of exposure and effects. However use of the term “sublethal” is confusing. Sublethal is used to describe both exposure and effects (ie a sublethal exposure is one which results in sublethal effects). A further complication is that “sublethal” implies the magnitude of *immediate* effects since these low level exposures have been shown to result in mortality of exposed animals, although not necessarily within a short time of exposure. More helpful would be the adoption of quantified terms to describe small/large doses, low/high level exposure, and mild/severe effects. The focus of the current paper is on morbidity or “sublethal” effects although, as noted, effects to animals that don’t result immediately in death often have profound consequences to animal vigor, including death which may occur at varying times after exposure.

Abbreviations

3,5,6-trichloro-2-pyridinol (TCP); acetylcholinesterase (AChE); anticholinesterases (anti-ChEs); butyrylcholinesterase (BChE); cholinesterase (ChE); confidence interval (CI); meta-analysis relative risk (MMR); multiple myeloma (MM); non-Hodgkin’s lymphoma (NHL); odds ratio (OR); organophosphates (OPs); red-blood cell or erythrocyte acetylcholinesterase (RBC AChE); relative risk (RR).

Summary

1 Neurological effects

Humans. Neurological and neurobehaviorial effects have been described in studies investigating chronic exposure to anti-ChEs in sheep farmers, agricultural, greenhouse, and orchard workers, and pesticide applicators. The neurological effects noted in the literature include increased prevalence of self-reported symptoms such as sleep problems, fatigue, dizziness, gastrointestinal upset, and loss of strength in the extremities; decreased sensory nerve function; decreased motor function; symptoms of parkinsonism; and changes in brain and muscle electrical activities. Effects tend to be more pronounced in workers with the highest exposure. However, most of the results are inconsistent and exposure measurements either do not exist or the method of measurement varies and therefore comparisons between studies are difficult.

Neurobehavioral effects resulting from an acute episode or long-term exposure to anti-ChEs include increased depressive disorders and anxiety. Deficits in cognitive function were observed in workers with varying levels of exposure and in some studies, long-term deficits were detected. Reported symptoms include memory disturbances, poor concentration, anger, fatigue, tension, and confusion.

Vertebrate Wildlife. Vertebrate wildlife exhibit a broad spectrum of neurological signs when exposed to low and high doses of anti-cholinesterase pesticides. Signs include clinical signs of intoxication such as vocalization, salivation, rapid heart beat, rapid breathing, tremors, and incoordination in mammals; decreased singing, hypothermia and gastrointestinal distress in birds; tremors and convulsions in reptiles; paralysis in amphibians; and muscle paralysis, loss of equilibrium, tetany and convulsions in fish. Behavioral dysfunction has been documented in most vertebrates including impacts to learning in mammals, birds, and fish; hyperactivity in mammals and birds sometimes followed by behavioral “slumps” and lethargy in mammals, birds, amphibians and fish; and impacts on memory in mammals and birds. Studies show that all vertebrate classes experience disruption of feeding when exposed to cholinesterase-inhibiting chemicals either through pesticide-induced anorexia, prey-avoidance, altered aggressive behaviors and feeding hierarchies, and/or impacts to vision, learning and

memory. Increased risk of predation as a result of pesticide exposure has also been documented in most vertebrate classes (mammals, birds, fish) either because of disrupted predator-avoidance behaviors or other behavioral dysfunctions. Studies of mammals and reptiles indicate that males, with higher baseline cholinesterase levels, may be less sensitive to pesticides than females.

2 Genotoxic effects

Humans. Effects of exposure to anti-ChE compounds include increased aneuploidy in sperm genetic material and increased chromosomal aberrations and fragile sites in lymphocytes. One study reported no change in micronuclei frequency with low exposure to malathion however, numerous studies indicate an increased frequency of micronuclei with pesticide mixtures that include anti-ChEs. While effects tend to be increased in workers with higher exposure, cytogenetic effects have been observed in workers with low exposure to organophosphates and pesticide mixtures containing anticholinesterases .

Vertebrate Wildlife. Very little information is available on the genotoxic effects of cholinesterase-inhibiting chemicals in wildlife. Studies on mammals, amphibians and fish show that carbofuran, carbaryl and malathion cause DNA strand breakage in some vertebrates.

3 Immunotoxic effects

Humans. Epidemiological data revealed immune function impairment associated with long-term exposure to anti-ChEs in pesticide applicators, agricultural workers, persons ingesting contaminated groundwater or living adjacent to agricultural lands, and organophosphate production workers. Decreases in immune system markers, changes in T-cell ratios, and neutrophil dysfunction indicate humoral and cellular dysfunction. Evidence of elevated autoantibodies suggests possible autoimmune effects. Elevated biomarkers for oxidative stress are also reported.

Vertebrate Wildlife. Laboratory mice have been shown to undergo disruptions in immunoglobulin concentrations as a result of *in utero* or lactational exposure to anti-cholinesterases. No information is available on the immunotoxic effects of pesticide exposure in wild vertebrates.

4 Carcinogenic effects

Humans. In studies that have discerned pesticide types, odds ratios ranging from 1.5 to 7.1 for risk of non-Hodgkins lymphoma have been associated with exposure to OPs such as diazinon, malathion, chlorpyrifos and to the carbamate, carbaryl, in lawn pesticide applicators and agricultural workers. Increased risk for leukemia has been reported in both adults and children after exposure to OPs and carbamates. Increases in breast tissue lesions that may act as biomarkers for breast cancer were found in women greenhouse workers exposed primarily to anti-ChE compounds and to a lesser extent, triazines and other herbicides. Risk for breast cancer was also increased in farm women who did not directly handle the compounds. Increased risk for prostate cancer with anti-ChEs and increased risk for small lymphatic lymphoma or lung cancer in farmers handling OPs has also been observed. While little evidence exists for risk of brain cancer in adults, several studies have associated exposure to pet flea collars, maternal pesticide use, and home pesticide application of anti-ChEs with childhood brain cancer. Studies also suggest that risk increases when exposure occurs during critical developmental periods in early childhood.

Vertebrate Wildlife. No information is available on the potential carcinogenic effects of cholinesterase-inhibiting pesticides on wildlife.

5 Reproductive effects

Humans. Occupational studies have shown significant associations for maternal as well as paternal exposure to pesticides and adverse reproductive outcomes. Specifically, anti-ChE compounds have been implicated in the following adverse outcomes: changes in hormone levels such as adrenocorticotropic and follicle-stimulating hormones; impaired semen quality and concentration; increased risk of

spontaneous abortion and congenital defects resulting in fetal death; and altered birth parameters such as low birth weight and birth length with home and agricultural exposure to OPs.

Vertebrate Wildlife. Reproduction integrates a number of physiological systems in vertebrates and impacts to reproductive performance as a result of pesticide exposure may result from biochemical, histological, physiological and/or behavioral alterations. Reproductive hormones, including luteinizing hormone, follicle-stimulating hormone, and testosterone in mammals and luteinizing hormone in birds, are adversely affected by exposure to pesticides. Other effects include alterations to testes and sperm, altered sperm capacitation, infertility, maternal weight loss, decreased birth weight, increased stillbirths and decreased litter size documented in mammals; reduced egg-laying, decreased nest attentiveness, decreased hatching success, decreased fledge weight, and increased time to fledging in birds; and decreased egg production, inhibited ovarian development, decreased egg hatchability, and reduced fry production in fish. Exposure to an organophosphate (malathion) has been shown to adversely affect morphogenesis and cause skeletal deformities in amphibians. An organophosphate (parathion) has been found to bioconcentrate in the eggs of lizards.

6 Metabolic effects

Humans. Contrary to wildlife, hyperthermia is a common in humans exposed to poisoning doses of anticholinesterases. With lower dose exposures, the interaction of anticholinesterases with thermoregulatory system functions may affect the ability to dissipate heat while working or exercising.

Vertebrate Wildlife. Impact to thermoregulation has been identified as one of the most important outcomes of pesticide exposure in homoiothermic mammals and birds. A hypothermic response is typical in mammals other than humans, and in birds. Hypothermia may reduce metabolic rate and therefore reduce the activation of toxic compounds and metabolites, however hypothermic birds and amphibians show greater vulnerability to cold stress.

7 Respiratory effects

Humans. Decreased pulmonary function and increased incidence of asthma was reported in three studies on OP manufacturers and farmers exposed to OPs and carbamates.

Vertebrate Wildlife. Very little information is available on respiratory effects of pesticide exposure in wildlife. Clinical signs in fish include gill muscle paralysis, increased amplitude of respiration, and asphyxiation.

8 Dermatological effects

Humans. Cases of allergic dermatitis or erythema are common in workers with high and frequent exposure to organophosphates however, the incidence of these effects was found to be rare in adult populations exposed to low doses of mosquito control pesticides. Increased incidence of dermatological effects in children suggests that more research regarding subpopulations sensitive to OP exposure is needed.

Vertebrate Wildlife. No information from studies on mammals, birds, or fish, however both reptiles and amphibians have shown dermatological sensitivity to cholinesterase-inhibiting chemicals. Phosphamidon has been shown to cause shedding of body scales and color change in agamas, and a number of organophosphate and carbamate pesticides produce damage to melanophores, blisters, negative effects on palate and gill epithelium, and pigmentation effects in amphibians.

9 Miscellaneous Effects

Humans. Paraoxonase polymorphisms resulting in decreased paraoxonase activity were associated with increased symptom reporting, decreased sperm quality, and decreased fetal growth parameters. Increased chronic fatigue symptoms were found with farmers at the highest level of exposure associated with sheep-dipping tasks. Changes in bone formation and decreased bone density were also found in farmers exposed to sheep dips.

Vertebrate Wildlife. Documented effects in mammals include muscle necrosis. Studies show amphibians may exhibit a reduction in red blood cell numbers, edema and liver cell abnormalities as a result of exposure to cholinesterase-inhibiting pesticides.

10 Ecological effects

Humans. (no information)

Vertebrate Wildlife. Impacts to wild mammal communities include inhibited reproduction, population size reduction, and increased population turnover rates. Causal mechanisms include not only physiological effects to mammals, but also impacts to populations of plants and animals comprising prey and other habitat components. In addition, dominance relationships can be impacted by differential effects of pesticides on mammalian members of communities. Documented impacts to birds include reduced population size as a result of reproductive effects.

Conclusions

A compilation and interpretation of the scientific literature investigating sublethal effects of exposure to cholinesterase-inhibiting pesticides in humans and wildlife revealed a body of knowledge relatively advanced in some areas, and undeveloped in others. An extensive literature has developed on the neurotoxicity, carcinogenicity and reproductive effects of pesticides on human health. Other physiological endpoints have been much less studied. Neurophysiological, behavioral and metabolic pathways, especially as they impact foraging, reproduction, and survival, have received the greatest attention from wildlife scientists. The wildlife literature is dominated by studies of birds, but increasing attention is being focused on amphibians and reptiles. Information on wild mammals is surprisingly sparse. The areas of greatest overlap in the human health and wildlife effects literature are neurotoxicity and effects to reproduction.

Several reported neurotoxicological symptoms are similar between humans and wildlife such as fatigue and lethargy, gastrointestinal distress, dizziness and loss of equilibrium, and possibly anxiety and hyperactivity. Behavioral effects on mood and

memory tend to be present in both humans and wildlife exposed to anti-cholinesterase compounds, while potential similarities in effects on learning are not as evident.

Exposure to cholinesterase-inhibiting pesticides is associated with adverse effects to reproductive performance in both humans and wildlife. Alterations to reproductive hormones, sperm quality, reproductive organs, and reduced production of offspring and offspring viability have been widely reported in the human and wildlife literature. In addition, genotoxicological studies show evidence of chromosomal aberrations in both humans and wildlife.

Finally, our synthesis and analysis reveals two significant areas of impact that are somewhat distinctive in the human and wildlife literature. A research focus on the carcinogenicity of pesticides in long-lived humans has provided evidence that exposure to cholinesterase-inhibiting compounds may be linked to certain lymphatic and blood cancers. Studies of wild mammal and bird populations have shown significant effects to the highest levels of biological organization (i.e. population, community, ecosystem) as a result of the toxicological effects of pesticides on animals and their habitat components.

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Table 1: Anticholinesterase chemicals and their chemical class. Chemicals are sorted alphabetically within chemical class. Adapted from S. Orme and S. Kegley, *PAN Pesticides Database,* Pesticide Action Network, North America (San Francisco, CA. 2004), http:www.pesticideinfo.org. © 2000-2005 Pesticide Action Network North America

Chemical Name	CAS Number	Use Type	Chemical Class
Diammonium ethylenebis(dithiocarbamate)	3566-10-7	Microbiocide	Dithiocarbamate
Metam-potassium	137-41-7	Fumigant, Herbicide, Fungicide, Microbiocide, Algaecide	Dithiocarbamate
Metam-sodium*	6734-80-1, 137-42-8 (dihydrate)	Fumigant, Herbicide, Fungicide, Microbiocide, Algaecide	Dithiocarbamate
Potassium dimethyl dithio carbamate	128-03-0	Microbiocide	Dithiocarbamate
Sodium dimethyl dithio carbamate	128-04-1	Fungicide	Dithiocarbamate
Ziram*	137-30-4	Fungicide, Microbiocide, Dog and Cat Repellent	Dithiocarbamate, Inorganic-Zinc
Mercuric dimethyl dithiocarbamate	15415-64-2	Microbiocide	Inorganic-Mercury, Heavy metal, Dithiocarbamate
2-(4,5-Dimethyl-1,3-dioxolan-2-yl)phenyl-N-methylcarbamate	7122-04-5	Insecticide	N-Methyl Carbamate
2,3(and 3,4)-Dichlorobenzyl methylcarbamates	62046-37-1	Insecticide	N-Methyl Carbamate
2,4-Dimethyl-1,3-dithiolane-2-carboxaldehyde O-(methylcarbamoyl)oxime	26419-73-8	Insecticide	N-Methyl Carbamate
2-cyclopentylphenyl methylcarbamate	3282-00-6	Insecticide	N-Methyl Carbamate
2-Hydroxyphenyl methylcarbamate	10309-97-4	Insecticide	N-Methyl Carbamate
3,4-Dichlorobenzyl methylcarbamate	2328-31-6	Insecticide	N-Methyl Carbamate
3,5-Diisopropylphenyl methylcarbamate	330-64-3	Insecticide	N-Methyl Carbamate
3-hydroxycarbofuran	16655-82-6	Breakdown product	N-Methyl Carbamate
4-(((Dimethylamino)methylene)amino)-m-tolyl methylcarbamate	17702-57-7	Insecticide	N-Methyl Carbamate
4-(Methylamino)-3,5-xylyl methylcarbamate	10389-50-1	Insecticide	N-Methyl Carbamate
4-(Methylformamido)-3,5-xylyl methylcarbamate	10233-94-0	Insecticide	N-Methyl Carbamate
4-(Methylthio)-m-tolyl methylcarbamate	3566-00-5	Insecticide	N-Methyl Carbamate
4-Amino-3,5-xylyl methylcarbamate	831-76-5	Insecticide	N-Methyl Carbamate
5,6,7,8-Tetrahydro-1-naphthyl methylcarbamate	1136-84-1	Insecticide	N-Methyl Carbamate

Chemical Name	CAS Number	Use Type	Chemical Class
6-(and 2)-chloro-3,4-xylyl methylcarbamate	8063-85-2	Insecticide	N-Methyl Carbamate
Aldicarb	116-06-3	Insecticide, Nematicide	N-Methyl Carbamate
Aldicarb sulfoxide	1646-87-3	Breakdown product	N-Methyl Carbamate
Allyxycarb	6392-46-7	Insecticide	N-Methyl Carbamate
Aminocarb	2032-59-9	Insecticide	N-Methyl Carbamate
Bendiocarb	22781-23-3	Insecticide	N-Methyl Carbamate
Bufencarb mixture	8065-36-9	Insecticide	N-Methyl Carbamate
Bufencarb-1	2282-34-0	Insecticide	N-Methyl Carbamate
Bufencarb-2	672-04-8	Insecticide	N-Methyl Carbamate
Butacarb	2655-19-8	Insecticide	N-Methyl Carbamate
Butocarboxim	34681-10-2	Insecticide	N-Methyl Carbamate
Butoxycarboxim	34681-23-7	Insecticide	N-Methyl Carbamate
Carbanolate	671-04-5	Insecticide	N-Methyl Carbamate
Carbaryl	63-25-2	Insecticide, Plant Growth Regulator, Nematicide	N-Methyl Carbamate
Carbofuran	1563-66-2	Insecticide, Nematicide	N-Methyl Carbamate
Carbosulfan	55285-14-8	Insecticide	N-Methyl Carbamate
Cloethocarb	51487-69-5	Insecticide, Molluscicide	N-Methyl Carbamate
Dichlormate	1966-58-1	Herbicide	N-Methyl Carbamate
Dimetan	122-15-6	Insecticide	N-Methyl Carbamate
Dioxacarb	6988-21-2	Insecticide	N-Methyl Carbamate
Ethiofencarb	29973-13-5	Insecticide	N-Methyl Carbamate
Fenethacarb	30087-47-9	Insecticide	N-Methyl Carbamate
Fenobucarb	3766-81-2	Insecticide	N-Methyl Carbamate
Formetanate	22259-30-9	Insecticide	N-Methyl Carbamate
Formetanate hydrochloride	23422-53-9	Insecticide	N-Methyl Carbamate
Isolan	119-38-0	Insecticide	N-Methyl Carbamate
Isoprocarb	2631-40-5	Insecticide	N-Methyl Carbamate
m-Cumenyl methylcarbamate	64-00-6	Insecticide	N-Methyl Carbamate
Methiocarb	2032-65-7	Insecticide, Molluscicide	N-Methyl Carbamate

Chemical Name	CAS Number	Use Type	Chemical Class
Methiocarb sulfone	2179-25-1	Breakdown product	N-Methyl Carbamate
Methiocarb sulfoxide	2635-10-1	Breakdown product	N-Methyl Carbamate
Methomyl	16752-77-5	Insecticide, Breakdown product	N-Methyl Carbamate
Mexacarbate	315-18-4	Insecticide	N-Methyl Carbamate
Mobam	1079-33-0	Insecticide	N-Methyl Carbamate
o-(2-Propynyloxy)phenyl methylcarbamate	3279-46-7	Insecticide	N-Methyl Carbamate
Oxamyl	23135-22-0	Insecticide, Nematicide	N-Methyl Carbamate
Pirimicarb	23103-98-2	Insecticide	N-Methyl Carbamate
Promacyl	34264-24-9	Insecticide	N-Methyl Carbamate
Promecarb	2631-37-0	Insecticide	N-Methyl Carbamate
Propoxur	114-26-1	Insecticide	N-Methyl Carbamate
Terbutol	1918-11-2	Herbicide	N-Methyl Carbamate
Thiodicarb	59669-26-0	Molluscicide, Insecticide	N-Methyl Carbamate
Thiofanox	39196-18-4	Insecticide	N-Methyl Carbamate
Trimethacarb	12407-86-2	Insecticide, Molluscicide, Dog and Cat Repellent	N-Methyl Carbamate
Trimethacarb, (2,3,5)- component of	2655-15-4	Insecticide, Molluscicide	N-Methyl Carbamate
Trimethacarb, (3,4,5)- component of	2686-99-9	Insecticide, Molluscicide	N-Methyl Carbamate
XMC	2655-14-3	Insecticide	N-Methyl Carbamate
Xylylcarb	2425-10-7	Insecticide	N-Methyl Carbamate
(E)-Mevinphos	298-01-1	Insecticide	Organophosphorus
(Z)-Mevinphos	338-45-4	Insecticide	Organophosphorus
2,5-dichloro-alpha-(chloromethylene)benzyl diethyl phosphate	2701-86-2	Insecticide	Organophosphorus
2,5-dichloro-alpha-(dichloromethylene)benzyl diethyl phosphate	5723-62-6	Insecticide	Organophosphorus
Acephate	30560-19-1	Insecticide	Organophosphorus
Acethion	919-54-0	Insecticide	Organophosphorus
Acetoxon	2425-25-4	Insecticide, Breakdown product	Organophosphorus
Akton	1757-18-2	Insecticide	Organophosphorus

Chemical Name	CAS Number	Use Type	Chemical Class
Amidithion	919-76-6	Insecticide	Organophosphorus
Amiton	78-53-5	Insecticide	Organophosphorus
Amiton oxalate	3734-97-2	Insecticide	Organophosphorus
Anilofos	64249-01-0	Insecticide	Organophosphorus
Athidathion	19691-80-6	Insecticide	Organophosphorus
Azamethiphos	35575-96-3	Insecticide	Organophosphorus
Azethion	72348-92-6	Insecticide	Organophosphorus
Azinphos-ethyl	2642-71-9	Insecticide	Organophosphorus
Azinphos-methyl	86-50-0	Insecticide	Organophosphorus
Azinphos-methyl oxygen analog		Breakdown product	Organophosphorus
Azothoate	5834-96-8	Insecticide	Organophosphorus
Bensulide	741-58-2	Herbicide	Organophosphorus
Bromophos	2104-96-3	Insecticide	Organophosphorus
Bromophos-ethyl	4824-78-6	Insecticide	Organophosphorus
Butathiofos	90338-20-8	Insecticide	Organophosphorus
Cadusafos	95465-99-9	Insecticide	Organophosphorus
Carbophenothion	786-19-6	Insecticide	Organophosphorus
Chlorethoxyphos	54593-83-8	Insecticide	Organophosphorus
Chlorfenvinphos	470-90-6	Insecticide	Organophosphorus
Chlormephos	24934-91-6	Insecticide	Organophosphorus
Chlorphoxim	14816-20-7	Insecticide	Organophosphorus
Chlorprazophos	36145-08-1	Insecticide	Organophosphorus
Chlorpyrifos	2921-88-2	Insecticide, Nematicide	Organophosphorus
Chlorpyrifos oxygen analog	5598-15-2	Insecticide, Breakdown product	Organophosphorus
Chlorpyrifos-methyl	5598-13-0	Insecticide	Organophosphorus
Chlorthion	500-28-7	Insecticide	Organophosphorus
Chlorthiophos (mixture of isomers)	60238-56-4	Insecticide	Organophosphorus
Chlorthiophos I	21923-23-9	Insecticide	Organophosphorus
Chlorthiophos II	77503-29-8	Insecticide	Organophosphorus
Chlorthiophos III	77503-28-7	Insecticide	Organophosphorus

Chemical Name	CAS Number	Use Type	Chemical Class
cis-Azodrin	919-44-8	Insecticide	Organophosphorus
cis-Methocrotophos	69632-93-5	Insecticide	Organophosphorus
Coumaphos	56-72-4	Insecticide	Organophosphorus
Coumaphos oxon (metabolite of coumaphos)	321-54-0	Breakdown product	Organophosphorus
Coumithioate	572-48-5	Insecticide	Organophosphorus
Crotoxyphos	7700-17-6	Insecticide	Organophosphorus
Cyanofenphos	13067-93-1	Insecticide	Organophosphorus
Cyanophos	2636-26-2	Insecticide, Avicide	Organophosphorus
Cyanthoate	3734-95-0	Insecticide	Organophosphorus
Cythioate	115-93-5	Insecticide	Organophosphorus
DDVP (dichlorvos)	62-73-7	Insecticide, Breakdown product	Organophosphorus
Demephion-O	682-80-4	Insecticide, Breakdown product	Organophosphorus
Demephion-S	2587-90-8	Insecticide	Organophosphorus
Demeton	8065-48-3	Insecticide, Nematicide	Organophosphorus
Demeton-O	298-03-3	Insecticide	Organophosphorus
Demeton-O-methyl	867-27-6	Insecticide	Organophosphorus
Demeton-S	126-75-0	Insecticide	Organophosphorus
Demeton-S-methyl (mixture)	8022-00-2, 919-86-8	Insecticide	Organophosphorus
Demeton-S-methyl sulfone	17040-19-6	Breakdown product, Insecticide	Organophosphorus
Dialifor	10311-84-9	Insecticide	Organophosphorus
Diamidafos	1754-58-1	Insecticide, Nematicide	Organophosphorus
Diazinon	333-41-5	Insecticide	Organophosphorus
Diazoxon	962-58-3	Breakdown product	Organophosphorus
Dichlofenthion	97-17-6	Insecticide, Nematicide	Organophosphorus
Dicrotophos	141-66-2	Insecticide	Organophosphorus
Dimethoate	60-51-5	Insecticide	Organophosphorus
Dimethoate-ethyl	116-01-8	Insecticide	Organophosphorus
Dioxabenzofos	3811-49-2	Insecticide	Organophosphorus
Dioxathion	78-34-2	Insecticide	Organophosphorus

Chemical Name	CAS Number	Use Type	Chemical Class
Diphenprofos	59010-86-5	Insecticide	Organophosphorus
Disulfoton	298-04-4	Insecticide, Nematicide	Organophosphorus
Disulfoton sulfone	2497-06-5	Insecticide	Organophosphorus
Disulfoton sulfoxide	2497-07-6	Breakdown product	Organophosphorus
Ditalimfos	5131-24-8	Fungicide	Organophosphorus
DMCP	3309-87-3	Insecticide	Organophosphorus
Edifenphos	17109-49-8	Insecticide	Organophosphorus
Endothion	2778-04-3	Insecticide	Organophosphorus
EPBP	3792-59-4	Insecticide	Organophosphorus
EPN	2104-64-5	Insecticide	Organophosphorus
Ethephon	16672-87-0	Plant Growth Regulator	Organophosphorus
Ethion	563-12-2	Insecticide	Organophosphorus
Ethion, O-analog	17356-42-2	Breakdown product	Organophosphorus
Ethoprop	13194-48-4	Insecticide, Nematicide	Organophosphorus
Ethyl (2-mercaptoethyl)carbamate, S-ester of O,O-dimethyl phosphorodithioate	5840-95-9	Insecticide	Organophosphorus
Etrimfos	38260-54-7	Insecticide	Organophosphorus
Famphur	52-85-7	Insecticide	Organophosphorus
Famphur, O-analog	960-25-8	Breakdown product	Organophosphorus
Fenamiphos	22224-92-6	Insecticide, Nematicide	Organophosphorus
Fenamiphos sulfone	31972-44-8	Breakdown product	Organophosphorus
Fenamiphos sulfoxide	31972-43-7	Breakdown product	Organophosphorus
Fenitrothion	122-14-5	Insecticide	Organophosphorus
Fensulfothion	115-90-2	Insecticide, Nematicide	Organophosphorus
Fenthion	55-38-9	Insecticide, Avicide	Organophosphorus
Fenthion oxon	3254-63-5	Breakdown product	Organophosphorus
Fonofos	944-22-9	Insecticide	Organophosphorus
Formothion	2540-82-1	Insecticide	Organophosphorus
Fosmethilan	83733-82-8	Insecticide	Organophosphorus
Fospirate	5598-52-7	Insecticide	Organophosphorus

Chemical Name	CAS Number	Use Type	Chemical Class
Fosthiazate	98886-44-3		Organophosphorus
Fosthietan	21548-32-3	Fumigant, Nematicide	Organophosphorus
Gardona (trans-isomer)	22350-76-1		Organophosphorus
Heptenophos	23560-59-0	Insecticide	Organophosphorus
Hexylthiofos	41495-67-4	Insecticide	Organophosphorus
Iodofenfos	18181-70-9	Insecticide	Organophosphorus
Iprobenfos	26087-47-8	Fungicide	Organophosphorus
IPSP	5827-05-4	Insecticide	Organophosphorus
Isazophos-methyl	42509-83-1	Insecticide	Organophosphorus
Isochlorthion	2463-84-5	Insecticide	Organophosphorus
Isofenphos	25311-71-1	Insecticide	Organophosphorus
Isomalathion (metabolite of malathion)	527751	Breakdown product	Organophosphorus
Isothioate	36614-38-7	Insecticide	Organophosphorus
Isoxathion	18854-01-8	Insecticide	Organophosphorus
Leptophos	21609-90-5	Insecticide	Organophosphorus
Lythidathion	2669-32-1	Insecticide	Organophosphorus
Malaoxon	1634-78-2	Breakdown product	Organophosphorus
Malathion	121-75-5	Insecticide	Organophosphorus
Malathion dicarboxylic acid	1190-28-9	Breakdown product	Organophosphorus
Mecarbam	2595-54-2	Insecticide	Organophosphorus
Mecarphon	29173-31-7	Insecticide	Organophosphorus
Menazon	78-57-9		Organophosphorus
Mephosfolan	950-10-7	Insecticide	Organophosphorus
Merphos	150-50-5	Defoliant, Plant Growth Regulator	Organophosphorus
Merpofos	3568-56-7	Insecticide	Organophosphorus
Methacrifos	62610-77-9	Insecticide	Organophosphorus
Methamidophos	10265-92-6	Insecticide, Breakdown product	Organophosphorus
Methidathion	950-37-8	Insecticide	Organophosphorus
Methidathion oxygen analog		Insecticide	Organophosphorus

Chemical Name	CAS Number	Use Type	Chemical Class
Methyl paraoxon	950-35-6	Breakdown product	Organophosphorus
Methyl parathion	298-00-0	Insecticide, Nematicide	Organophosphorus
Methyl phenkapton	3735-23-7		Organophosphorus
Methyl trithion	953-17-3	Insecticide	Organophosphorus
Methyl-carbofenthion		Insecticide	Organophosphorus
Mevinphos	7786-34-7, 26718-65-0	Insecticide	Organophosphorus
Miral	42509-80-8	Insecticide	Organophosphorus
Monocrotophos	6923-22-4	Insecticide	Organophosphorus
Monocrotophos (isomer unspecified)		Insecticide	Organophosphorus
Morphothion	144-41-2	Insecticide	Organophosphorus
Naled	300-76-5	Insecticide	Organophosphorus
Naphthalophos	1491-41-4	Insecticide	Organophosphorus
O-(2-chloro-4-nitrophenyl) O-isopropyl ethylphosphonothioate	328-04-1		Organophosphorus
O-(4-Nitrophenyl) O-phenyl methylphosphonothioate	2665-30-7		Organophosphorus
O,O,S-Trimethyl phosphorodithiate (as impurity)	2953-29-9	Impurity	Organophosphorus
O,O-diethyl O-naphthaloximido phosphorothioate	2668-92-0	Insecticide	Organophosphorus
O,O-diethyl phosphoro chloridothionate	2524-04-1	Insecticide	Organophosphorus
O,O-Diethyl S-(4,6-dimethyl-2-pyrimidinyl) phosphorodithioate	333-40-4	Insecticide	Organophosphorus
O,O-diethyl-O-phenyl phosphorothioate	32345-29-2	Insecticide	Organophosphorus
O,O-dimethyl S-(2-(ethylsulfinyl)-1-methylethyl) phosphorothioate	2674-91-1	Insecticide	Organophosphorus
O-ethyl O-(4-(methylthio)phenyl) methylphosphonothioate	2703-13-1		Organophosphorus
O-ethyl O-methyl S-propylphosphorothioate (metabolite of ethoprop)	76960-87-7	Breakdown product	Organophosphorus
O-Ethyl S-(4-methylphenyl) ethylphosphonodithioate	333-43-7		Organophosphorus
O-Ethyl S-propyl phosphorothioic acid (Metabolite of ethoprop)	31110-62-0	Breakdown product	Organophosphorus
Omethoate	1113-02-6	Insecticide, Breakdown product	Organophosphorus

Chemical Name	CAS Number	Use Type	Chemical Class
Oxydemeton-methyl	301-12-2	Insecticide	Organophosphorus
Paraoxon	311-45-5	Breakdown product	Organophosphorus
Parathion	56-38-2	Insecticide	Organophosphorus
Phenkapton	2275-14-1	Insecticide	Organophosphorus
Phenthoate	2597-03-7	Insecticide	Organophosphorus
Phenthoate acid	13376-78-8	Impurity	Organophosphorus
Phorate	298-02-2	Insecticide, Nematicide	Organophosphorus
Phorate sulfone	2588-04-7	Breakdown product	Organophosphorus
Phorate sulfoxide	2588-03-6	Breakdown product	Organophosphorus
Phoratoxon	2600-69-3	Breakdown product	Organophosphorus
Phoratoxon sulfone		Breakdown product	Organophosphorus
Phoratoxon sulfoxide	2588-05-8	Breakdown product	Organophosphorus
Phosalone	2310-17-0	Insecticide	Organophosphorus
Phosalone oxygen analog		Insecticide, Breakdown product	Organophosphorus
Phosfolan	947-02-4		Organophosphorus
Phosmet	732-11-6	Insecticide	Organophosphorus
Phosmetoxon	3735-33-9	Breakdown product	Organophosphorus
Phosnichlor	5826-76-6	Insecticide	Organophosphorus
Phosphamidon	13171-21-6	Insecticide	Organophosphorus
Phostebupirim	96182-53-5	Insecticide	Organophosphorus
Phoxim	14816-18-3	Insecticide	Organophosphorus
Phoxim-methyl	14816-16-1	Insecticide	Organophosphorus
Pirimiphos ethyl	23505-41-1	Insecticide	Organophosphorus
Pirimiphos ethyl, oxygen analog	36378-61-7	Breakdown product	Organophosphorus
Pirimiphos-methyl	29232-93-7	Insecticide	Organophosphorus
Primidophos	39247-96-6	Insecticide	Organophosphorus
Profenofos	41198-08-7	Insecticide	Organophosphorus
Propaphos	7292-16-2	Insecticide	Organophosphorus
Propetamphos	31218-83-4	Insecticide	Organophosphorus
Propoxon	5823-13-2	Insecticide	Organophosphorus

Chemical Name	CAS Number	Use Type	Chemical Class
Prothidathion	20276-83-9	Insecticide	Organophosphorus
Prothiofos	34643-46-4	Insecticide	Organophosphorus
Prothion	5969-94-8	Insecticide	Organophosphorus
Prothoate	2275-18-5	Insecticide	Organophosphorus
Pyrazophos	13457-18-6	Fungicide	Organophosphorus
Pyridiphenthion	119-12-0	Insecticide	Organophosphorus
Quinalphos	13593-03-8	Insecticide	Organophosphorus
Quinalphos-methyl	13593-08-3	Insecticide	Organophosphorus
Quinitofos	1776-83-6	Insecticide	Organophosphorus
Quinothion	22439-40-3	Insecticide	Organophosphorus
Ronnel	299-84-3	Insecticide	Organophosphorus
S-(1,1-Dimethylethyl) O-ethyl ethylphosphonothioate	83318-76-7	Insecticide	Organophosphorus
S-(4-(1,1-dimethylethyl)phenyl) O-ethyl ethylphosphonodithioate	329-21-5	Insecticide	Organophosphorus
S,S,S-tributyl phosphorotrithioate	78-48-8	Defoliant, Plant Growth Regulator	Organophosphorus
Sophamide	37032-15-8	Insecticide	Organophosphorus
Sulfotep	3689-24-5	Insecticide	Organophosphorus
Sulprofos	35400-43-2	Insecticide	Organophosphorus
Sulprofos oxon	38527-90-1	Breakdown product	Organophosphorus
Temephos	3383-96-8	Insecticide	Organophosphorus
Temephos sulfoxide	17210-55-8	Breakdown product	Organophosphorus
TEPP	107-49-3	Insecticide	Organophosphorus
Terbufos	13071-79-9	Insecticide, Nematicide	Organophosphorus
Terbufos sulfone	56070-16-7	Breakdown product	Organophosphorus
Terbufos sulfoxide	10548-10-4	Breakdown product	Organophosphorus
Tetrachlorvinphos	22248-79-9, 961-11-5	Insecticide	Organophosphorus
Thiometon	640-15-3	Insecticide	Organophosphorus
Thionazin	297-97-2	Insecticide	Organophosphorus

Chemical Name	CAS Number	Use Type	Chemical Class
Thionazin, oxygen analog	7359-55-9	Insecticide, Breakdown product	Organophosphorus
Tolclofos-methyl	57018-04-9	Fungicide	Organophosphorus
Triazophos	24017-47-8	Insecticide	Organophosphorus
Trichlorfon	52-68-6	Insecticide	Organophosphorus
Trichloronat	327-98-0	Insecticide	Organophosphorus
Vamidothion	2275-23-2	Insecticide	Organophosphorus
3-iodo-2-propynyl butyl carbamate	55406-53-6	Fungicide, Wood Preservative	Other Carbamate
6-Methyl-2-propyl-4-pyrimidinyl dimethylcarbamate	2532-49-2		Other Carbamate
Alanycarb	83130-01-2	Insecticide	Other Carbamate
Benfuracarb	82560-54-1	Insecticide	Other Carbamate
Dimetilan	644-64-4	Insecticide	Other Carbamate
Mecarbinizid	27386-64-7		Other Carbamate
Pyrolan	87-47-8	Insecticide	Other Carbamate
Butylate	2008-41-5	Herbicide	Thiocarbamate
cis-Diallate	17708-57-5	Herbicide	Thiocarbamate
Cycloate	1134-23-2	Herbicide	Thiocarbamate
Diallate	2303-16-4	Herbicide	Thiocarbamate
EPTC	759-94-4	Herbicide	Thiocarbamate
Furathiocarb	65907-30-4	Insecticide	Thiocarbamate
Isopolinate	3134-70-1	Herbicide	Thiocarbamate
Methiobencarb	18357-78-3	Herbicide	Thiocarbamate
Molinate	2212-67-1	Herbicide	Thiocarbamate
Molinate sulfoxide		Breakdown product	Thiocarbamate
Pebulate	1114-71-2	Herbicide	Thiocarbamate
Pyributicarb	88678-67-5	Herbicide	Thiocarbamate
Thiobencarb	28249-77-6	Herbicide	Thiocarbamate
Thiobencarb sulfoxide		Breakdown product	Thiocarbamate
trans-Diallate	17708-58-6	Herbicide	Thiocarbamate

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APPENDIX 1

Sublethal Effects of Exposure to Cholinesterase-inhibiting Pesticides: Humans

1 Neurological effects

1.1 Adult

Exposure to organophosphates (OPs) is associated with numerous neurological effects. Profiles of effects are categorized into several syndromes including acute cholinergic episode, OP-induced delayed neuropathy (OPIDN), an intermediate myasthenia syndrome (IMS), and chronic OP-induced neuropsychiatric disorder (COPIND) (Lotti 1992; Sultatos 1994; Eyer 1995; Weiss 1997; Brown and Brix 1998; Eskenazi et al. 1999; He 2000; Jamal et al. 2002; Salvi et al. 2003).

Briefly:

1. Acute episode – usually a poisoning or poisonings associated with a short term (within 24 hour) exposure that results in peripheral and central nervous system actions and irreversible inhibition of cholinesterase enzymes;

2. OPIDN – results from exposure to certain OPs and is characterized by the irreversible inhibition of neuropathy target esterase and axonal degeneration in the upper and lower extremities. OPIDN is not associated with acetylcholinesterase (AChE) inhibition although the mechanism of effect is not known;

3. IMS – a delayed respiratory and neck muscle weakness occurring after an acute episode with severe poisoning and its mechanism is not understood. The reader is referred to reviews by Brown and Brix (1998) and Jamal (1997) for information OPIDN and IMS.

4. COPIND – this term is largely used as a means of differentiating a diverse and inconsistent set of long-term neurophysiological and neurobehaviorial effects from other OP syndromes. COPIND is difficult to profile due to varying degrees and durations of symptoms ranging from chronic fatigue, peripheral neuropathy, and autonomic nervous system disturbances to cognitive dysfunction and mood disorders. Effects may result from exposure to one or more high-doses or to lower, long-term doses of OP, either with or without cholinergic involvement.

An acute episode is distinguished from the continuum of exposure and effect scenarios by a degree of noticeable nervous system symptoms and cholinergic involvement and generally results from a high-dose exposure to anticholinesterase compounds. Evidence exists of subtle long-term neurotoxicity from one or more acute poisoning episodes (Ray 1998; He 2000; Jamal et al. 2002; Kamel and Hoppin 2004; Alavanja et al. 2004b). The effects described include “increased symptom prevalence, deficits in cognitive and psychomotor function, decreased vibration sensitivity, and impaired nerve conduction” and differ from those noted with OPIDN (Alavanja et al. 2004b).

Evidence of chronic neurological effects from long-term low-level exposure is more contradictory, inconsistent, and inconclusive (D'Mello 1993; Ray 1998; Lotti 2002; Kamel and Hoppin 2004; Alavanja et al. 2004b). Some reviewers argue that most studies, including some high quality studies, support evidence of effects (Jamal et al. 2002) while other studies note only subtle or no effects (Brown and Brix 1998; Ray 1998; He 2000; Lotti 2002). Similar to reported long-term effects from acute exposure, studies that report effects from chronic exposure describe an increase in the prevalence of symptoms such as chronic fatigue, memory loss, depression, as well as deficits in central and peripheral nervous system function (Jamal 1997; Jamal et al. 2002; Kamel and Hoppin 2004).

Neurobehavioral studies indicate cognitive and psychomotor dysfunction with acute and chronic exposure to OPs (Jamal 1997; Ray 1998; He 2000; Alavanja et al. 2004b). Neurobehavioral and cognitive effects described include changes in intellectual functioning, thinking ability, and memory impairments. Additionally, psychological deficits reported include depressive disorders, anxiety, and confusion. However, these results are inconsistent and the clinical significance of long-term subtle effects remains unknown (Eyer 1995; He 2000; Kamel and Hoppin 2004).

Exposure scenarios are often difficult to define thus linking acute or chronic exposure with effects may not be possible. Occupationally exposed people who generally have low level exposure may not know if they have ever had a mild acute episode “since occupationally exposed individuals may experience a non-specific flu-like syndrome related to organophosphate exposure, as well as mild episodes of acute

toxicity for which they do not seek medical attention" (Daniell et al. 1992; Ray and Richards 2001; Kamel and Hoppin 2004).

Timing between exposure and sampling may also be an important factor in the development of effects. In some cases, sensory deficits were found in subjects who experienced past exposures but few peripheral nerve function effects were documented in subjects currently exposed (Lotti 2002). Differences in exposure assessment methodology, effects measurement protocols, and endpoints preclude a conclusive statement regarding the relationship between long-term low exposure to OPs and neurological effects.

The intent of this review is to present studies that have investigated a possible link between long-term exposures to OPs. Exposure information will be summarized when reported in the reviewed study. However, because of the difficulties discussed above regarding the level of exposure in humans, some studies include information regarding long-term effects resulting from an acute episode in addition to reporting effects from chronic exposure.

Neurological

The neurological effects noted in the literature include increased self-reported symptoms, impaired nerve function, decreased sensory and motor function, and changes in brain and muscle electrical activities.

Sensory and motor function

Several studies of workers with chronic exposure report increased long-term peripheral nerve function symptoms and these symptoms were more pronounced in workers from the highest exposure group. However, when neurological functions were tested using tests such as "vibration sensitivity, which evaluates peripheral somatosensory function" (Alavanja et al. 2004b) or tremor or grip strength which tests motor function, the results were inconsistent.

London et al. (1998) found that orchard sprayers reported more neurological symptoms including sleepiness, dizziness, and headache than non-applicators when exposure to OPs occurred recently or when worker had a previous acute episode but

not when life-time exposure was considered. However, no association was detected between neurological tests measuring vibration sensitivity or hand tremor or between neurobehaviorial effects and exposure (London et al. 1997; London et al. 1998). Using a job-exposure matrix based on days of exposure and job activity, no dose-response relationship was associated with long-term, life-time OP exposure and nervous system effects.

Pilkington et al. (2001) examined neurological symptoms and sensory deficits in sheep-dippers and found that dippers who directly handled the OP concentrate, thereby the highest exposed group, reported significantly more symptoms compared to other workers. Of these symptoms, sensory, rather than muscular or autonomic, were reported more frequently. No differences were noted for tests designed to test thermal thresholds and sensory sensitivity. It is not clear if effects data were collected immediately following an exposure event or if effects represent long-term health consequences. Cumulative exposure was evaluated from job information such as job task and days engaged in task combined with a dermal exposure model based on measured urinary metabolites.

Subtle sensory effects were detected in sheep dippers several months after exposure to OPs (Beach et al. 1996). Dippers reported on immediate neurological symptoms following a dipping procedure and from these results, the most and least symptomatic farmers were administered sensory and motor function tests several months after the event. The most symptomatic farmers had a significantly diminished ability to detect stimuli applied to the skin of the hand and foot. The authors surmise that while this result may indicate a peripheral nerve problem, the lack of effects demonstrated by additional sensory function tests make it difficult to make any formal conclusions. Cumulative exposure was measured by the number of sheep, number of dips per year, and number of years dipping with OPs.

Inversely, less reported symptoms were found in workers exposed to low-levels of OP pesticides but more subtle long-term sensory and motor function effects, as measured by neurological testing, were detected. Apple orchard pesticide applicators exposed seasonally to primarily guthion had significantly less sensitivity to vibration than controls indicating loss of peripheral nerve function (Stokes et al. 1995). It is uncertain if

this long-term effect could indicate permanent nerve damage. Workers' immediate symptoms to OP exposure were also assessed before and after a season of spraying. The only significant finding was an increase in headaches reported by the exposed workers compared to controls. ChE activities were not determined.

Two studies of pesticide production workers and farmers reported decreased ChE activities in plasma and blood but no peripheral nervous system effects. Dow chemical workers manufacturing chlorpyrifos assessed for symptom prevalence via interview and neurological deficits via neurological examination and nerve conduction testing had no detectable sensory or peripheral nervous system problems (Albers et al. 2004). Workers had significantly higher urinary metabolite levels and lower plasma BChE activities than controls but red-blood cell acetylcholinesterase (RBC AChE) did not differ between the groups.

No peripheral neurophysiological abnormalities were detected in apple thinners after a season of low-level exposure, via pruning activities rather than through direct pesticide handling, to residues of mainly azinphosmethyl, and phosmet and methylparathion (Engel et al. 1998). While RBC ChE activity was slightly but significantly decreased in workers compared to controls, results from nerve conduction, motor function, and neuromuscular function tests did not differ. Additionally, no trend was noted between exposure hours and nerve function measures. Exposure was determined via interview and considered detailed farm activity for the season, use of protective clothing, and home pesticide use. A subject was considered exposed if they worked >80 hours per season as a thinner.

Effects on postural sway were observed in workers recently exposed to OPs and in workers who had a past acute episode in addition to recent exposure (Sack et al. 1993; Steenland et al. 2000) and one study detected no effects (Ames et al. 1995). Postural sway assessments evaluate balance and vestibular sensory function (Alavanja et al. 2004b).

Pesticide applicators exposed to chlorpyrifos for > 1 year were given a battery of neurological tests intended to measure peripheral nerve function, postural stability, hand-eye coordination, sense of smell, motor function, and cognitive function (Steenland et al. 2000). For exposed subjects, significant deficits were noted with

postural sway and some motor function tests. Also, significantly more psychological and physical symptoms, such as memory disturbances, poor concentration, fatigue, dizziness, and loss of strength in the extremities, were reported. Additionally, subjects who reported a past acute episode, performed worse on postural sway tests and several cognitive function tests than workers who were only exposed at low levels. Workers with past acute exposure also reported more anger, fatigue, tension, confusion, and sleep problems. Exposure was measured by urinary OP metabolite (3,5,6-trichloro-2-pyridinol (TCP)) levels and all applicators had TCP levels higher than controls.

Sack et al. (1993) found increased postural sway significantly associated with recent OP exposure and lower plasma ChE activity in pesticide-exposed workers. Workers did not report adverse symptoms from pesticide exposure and there were no differences detected on other nerve conduction tests or neurological exams compared to controls.

No significant differences in postural sway tests or nerve conduction and neurobehavioral tests were detected in farmworkers with depressed ChE compared to controls (Ames et al. 1995). Farmworkers were exposed to OPs or carbamates and had “below-threshold” ChE values but exhibited no symptoms of cholinergic poisoning. “Below-threshold” values were defined as RBC ChE activities 70% or less of baseline or plasma ChE activity 60% or less of baseline.

Electrical activity

Electromyography (EMG) and sensory nerve conduction velocity tests provide a measure of muscle and nerve function. EMG measures electrical activity in muscles to determine muscle dysfunction whereas nerve conduction velocity tests investigate the function or loss of neuronal axons by testing the speed of an electrical impulse through the nerve (Krarup 1999). EMG measures and/or nerve conduction velocities were found to be abnormal in workers with decreased ChE activities, were correlated with symptoms during exposure to OPs, and were non-significant in workers with no measurable change in pre- and post- season ChE activity.

Reduced nerve conduction velocities were detected in pesticide applicators with decreased serum BChE activity following exposure to chlorpyrifos and other OPs (Gotoh et al. 2001).

EMG measures, in addition to upper and lower limb sensory and motor latency and conduction velocities, correlated with aerial spray worker's symptoms during exposure to parathion, moncrotophos, and chlorpyrifos (Ring et al. 1985). Latency measurements measured the time it took a nerve response to travel from the beginning of stimulus to the peak response and correlated positively with workers symptoms, while nerve conduction velocities correlated negatively. No correlations of EMG measurements with symptoms were detected 4 to 6 weeks after the spray season ended, possibly indicating EMG disturbance as a short-term effect. Additionally, motor conduction velocities were significantly reduced in workers with symptoms immediately after the start of the spraying season compared to workers with no symptoms. Workers symptoms ranged from visual complaints to gastrointestinal disturbances and fatigue. No other measures of exposure were evaluated.

Approximately 40% of Dutch agricultural workers exposed to mixtures of organochlorine, organophosphorus, and carbamate pesticides plus additional herbicides and fungicides were found to have abnormal EMG patterns (Drenth et al. 1972). Peripheral nerve EMG measures, blood ChE activities, and blood kidney and liver function tests were measured after the start and before the end of the spraying season. Ninety-five percent of the workers ChE activities were within the lower limits of what the authors considered normal ChE activities while the hepatic and renal tests were considered within normal range. ChE activities were not associated with EMG values.

No differences in EMG or ChE measurements were detected in agricultural workers with a low-level of exposure to OPs compared to unexposed controls (Jusic et al. 1980). Also, no differences in pre-exposure EMG or ChE measurements compared to post-exposure measurements were detected within the exposed workers. Intensity of exposure was determined by the type of work task, such as spraying pesticides or carrying bags of pesticides, and the duration of the task.

Experimental evidence using monkeys supports changes in brain electric potentials, as determined by electroencephalograph (EEG), in both high-dose and low-

dose exposures to OPs (reviewed in Duffy et al. 1979). Three studies from the 1970s and 1980s show disrupted brain electrical activity with both high and low level OP exposure.

Workers exposed either one time or 3 or more times to a cholinergic dose of sarin within 6 years preceding but not within one year of brain activity measurement showed increased beta activity and rapid eye movement (REM) sleep and decreased alpha activity compared to controls (Duffy et al. 1979). The authors concluded that long-term changes in brain function resulted from OP exposure. Savage et al. (1988) also measured electric potentials in the brain via EEG and found slightly abnormal activity in subjects who experienced an acute episode from OP exposure, however this difference was not significant.

Low-level exposures to OPs were found to disturb EEG measurements in the frontal lobe (Korsak and Sato 1977). Significant differences were also detected between subjects and controls on neuropsychologic tests designed to test dysfunction in the frontal lobe, a brain region important for sensory-motor functions. Impairment of brain function increased with increased duration of exposure. Plasma ChE activities did not differ with exposure duration. All subjects were considered to be asymptomatic.

Parkinsonism and Alzheimer's Disease

Extrapyramidal symptoms (parkinsonism) include tremors, rigidity, and slowness of movement and are associated with exposure to non-specific agricultural pesticides (Seidler et al. 1996; Gorell et al. 1998; Priyadarshi et al. 2000; Ritz and Yu 2000; Alavanja et al. 2004b). Risk appears to increase with increased duration of exposure. A study of male orchid growers in Washington State found a high risk of parkinsonism in workers exposed the greatest number of years to pesticides, although no association was made with specific pesticides (Engel et al. 2001). An increasing but non-significant trend in parkinsonism incidence was also associated with increasing years of exposure to a myriad of pesticides for Hawaiian pineapple and sugarcane plantation workers (Petrovitch et al. 2002).

While numerous studies have implicated a higher risk for parkinsonism with exposure to the fungicide, diethylthiocarbamate, and herbicides, roteneone and paraquat (reviewed in Di Monte et al. 2002; Vancore et al. 2002), only a few

epidemiological studies have implicated OPs as a risk factor. Exposure to parathion in particular resulted in a high odds ratio (OR = 8.08; 95% CI 0.92-70.85) for increased risk of parkinsonism in a Washington State population (Firestone et al. 2005). Exposure to diazinon (OR = 1.04; 95% CI 0.35-3.06) or malathion (OR = 1.01; 95% CI 0.37-2.72) was not associated with increased risk nor was occupational exposure or various home-based exposures to pesticides associated with increased risk. However, given the inconsistencies in results, the authors concluded that their "findings do not provide strong support for the hypothesis that pesticide exposure is a risk factor for [Parkinson's disease]."

Possible long-term parkinsonism was noted with long-term low-level exposure of Brazilian farm workers to chlorpyrifos (Salvi et al. 2003). Plasma AChE activity, psychiatric symptoms, cognitive ability, and parkinsonism were determined during a 3 month exposure period and after a 3 month unexposed period. Plasma AChE activities were within normal range and did not differ between exposure periods. Approximately 30% of the exposed workers had significant clinical signs of parkinsonism and while a significant decline in symptom severity was detected after the exposure period, the number of subjects that continued to exhibit symptoms remained high, indicating possible long-term effects. Psychiatric and anxiety disorders appeared more transient with a significant reduction in symptoms noted when exposure was discontinued.

Exposure to pesticides in general have been suggested for increased risk of Alzheimer's disease (Baldi et al. 2003; Kamel and Hoppin 2004). However, no significant relationship was detected between Alzheimer's disease and rural Canadian residents' long-term proximity to forest and agricultural land sprayed with a mixture of pesticides that included carbamates, OPs, organochlorines, and herbicides (Gauthier et al. 2001). While it was determined that residents were not exposed to compounds used on surrounding agro-forest lands, potential exposure may have existed from pesticides used in the agricultural sector. However a detailed exposure analysis was not conducted and exposure was determined by proximity of the residential areas to the total forest and agricultural areas that were sprayed from the 1970s to 1990s.

Neurobehavioral

In addition to neurophysiological effects, long-term neurobehavioral effects have been investigated. Subtle long-term neurobehavioral deficits in intellectual, and cognitive functions and increased symptoms of depression, memory problems, and task performance difficulties have been reported in people who sustained one or more acute exposure episodes with OPs (e. g. Savage et al. 1988; Rosenstock and Keifer 1991; McConnell et al. 1994; Brown and Brix 1998). Similar long-term psychological effects have been associated with low level exposure and with an increased duration of exposure.

Symptoms reported during or immediately after the exposure period do not always reflect the incidence of effects observed a period of time after the exposure. Stephens et al. (1996) found that long-term psychological effects may occur "independently of symptoms that might immediately follow acute OP exposure". Proximate effects from a recent (within 24 hours) OP dipping event were compared to ultimate effects seen after 2 months of no exposure in sub-group of sheep dippers from a chronic effects study (Stephens et al. 1995). Proximate, or "acute" effects, were determined by the change in cognitive symptoms reported by the workers before and 24-hours after exposure, while ultimate long-term, or "chronic" effects were determined at least 2 months after exposure by a battery of neuropsychological tests designed to evaluate cognitive function and mental health. A slight increase in immediate effects and a significant increase in long-term effects were detected in the sheep dippers compared to the controls (reported in Stephens et al. 1995). Within the sheep dipper group, no correlations were detected between "acute" effects and "chronic" effects indicating that long-term effects are not necessarily predicted by the presence of immediate effects. The sheep dips contained either diazinon or a mixture of diazinon with chlorfenvinphos or propetamphos.

A study of women greenhouse workers also found long-term but no short-term effects from seasonal exposure to dichlorvos, methamidophos, methidathion, and pirimiphos-methyl. A significant decrease in motor function and increased anxiety, depression, fatigue, and gastrointestinal distress was detected in workers approximately one month after a season of exposure compared to unexposed women (Bazylewicz-

Walczak et al. 1999). Within a season however, no pre- or immediate post-season differences were observed in mood or neurological performance tests in the exposed group and for some tests, improved performance indicated the ability to learn was not affected by exposure. Exposure was measured via air and dermal samples and was considered low based on a daily cumulative exposure that was below 0.01% toxic dose.

Subtle neurobehavioral effects were noted within a season or immediately preceding a season of exposure to OPs and with depressed ChE activity in some cases. Pesticide applicators exposed mainly to a low-level of azinphosmethyl while working in apple orchards reported little decrease in neuropsychological performance when preseason scores were compared to postseason, as well as when scores were compared to controls (Daniell et al. 1992). A significant effect was found on the Spanish language version of the symbol-digit substitution test which measures psychomotor function and concentration however the authors claim the result is "a minor, isolated finding which is unlikely to have clinical relevance." RBC ChE activities were slightly but not significantly depressed in the post-season compared to the pre-season values (Karr et al. 1992).

Rodnitzky (1975) detected significantly higher anxiety in pesticide applicators tested within two weeks of exposure to OPs compared to exposed farmers or unexposed controls. Subjects reflected "typical" occupational handlers of pesticides. Plasma ChE, but not RBC ChE activity, was significantly depressed in the exposed pesticide applicator group compared to controls but ChE activity was not depressed in the exposed farmers. No significant differences were detected in neurobehavioral tests used to measure memory, concentration, motor deficits, and language tasks. The authors were unclear if the higher anxiety in the applicators was an effect of OP exposure or job-related stress (Levin et al. 1976).

The risk of depressive symptoms was elevated in a sub-group of farmers who reported adverse effects such as eye irritation and chest discomfort immediately following exposure to OPs (Stallones and Beseler 2002). The authors stated that the findings do not appear to be confounded by other health or job-related stress factors. It is unclear if the depression was a long-term effect as no mention was made with

regards to the elapsed time between the high OP exposure event and psychiatric evaluation.

Neurobehavioral effects were observed several months after an exposure to OPs and were also associated with years of exposure to OPS. Reaction times on cognitive tests, but not memory or learning, were significantly affected in UK sheep-dippers two months after exposure to OPs compared to a control group (Stephens et al. 1995). Reaction times also increased as task difficulty increased. The farmers with the highest exposure performed the poorest on the hardest cognitive test, however there were no differences in tests designed to test short-term memory or learning. Cognitive and psychiatric tests were administered to farmers two months after their last exposure and exposure status confirmed by testing for urinary OP metabolites. All subjects were placed in a dose group based on the number of sheep dipped, number of dips administered per year, and number of years using OPs. The authors conclude that in general, sheep-dippers had more psychiatric disturbances; however these effects were not dose-related.

Deficits in concentration and task performance have been observed in workers with long-term exposures. South African fruit farmers exposed long term to OPs showed increased reaction times for two long-term memory tests and for information-processing (London et al. 1997).

New Jersey tree fruit farmers with seasonal, long-term exposure to OPs and no history of past acute exposure episodes, experienced slower motor function skills and poorer neuropsychological performance, specifically with concentration ability and dominant-hand response times, compared to blueberry/cranberry growers (controls) (Fiedler et al. 1997). In addition, farmers with high exposure, as determined by a "lifetime exposure metric" based on duration and extent of OP use, had slower dominant-hand reaction times than the low exposure group, however these results were confounded by age. Red blood cell cholinesterase activity fell within normal range for all subjects and indicated no current exposures. The author states that "long-term use of [OPs] without evidence of an acute poisoning episode appears to produce, at most, subtle changes in neuropsychological performance."

Risk for deficits in perceptive and visumotor function and task performance increased with an increased cumulative measure of exposure, defined as “years working with pesticides”, in greenhouse workers in southeastern Spain cumulatively exposed to mainly OPs and carbamates (Roldan-Tapia et al. 2005). Exposures were considered “subsymptomatic” with no association with plasma cholinesterase activity which was used as a measure of recent exposure.

Long-term neurobehavioral effects were also observed after an acute exposure episode. A study of 100 people who sustained one or more OP poisoning exposures, mostly through occupationally-related events, observed subtle long-term neurological deficits in motor skills involving speed and coordination, intellectual skills, and flexibility of thinking in the exposed workers compared with controls (Savage et al. 1988). Exposed workers also reported more symptoms of depression, problems with memory, and difficulty performing tasks. Participants were not to have used pesticides for 3 months before the study but poisoning event(s) could have occurred at any time prior to 3 months pre-testing. Plasma and RBC ChE activity levels were analyzed as well as organochlorine residue levels. All ChE activities were within normal baseline values and did not differ between subjects and controls. Blood organochlorine levels were about 2 times higher in exposed workers than controls however no association was detected between residue levels and neuropsychological tests cognitive, sensory, motor function, intellectual function, or psychological tests. The authors concluded that the long-term effects of an acute OP exposure are subtle cognitive difficulties that are only evident through neuropsychological testing (Brown and Brix 1998).

1.2 Children

Very few studies have examined the neurological and neurobehavioral effects of ChE-inhibiting compounds on children. Experimental studies show that developing animals exhibit subtle and delayed behavioral deficits after exposure to low-levels of OPs (reviewed in Weiss 1997; Schettler 2001; Garry 2004; Slotkin 2004) and are more sensitive to lower doses of OPs compared to adults (Vidair 2004; reviewed in Slotkin 2004). Additionally, AChE and other esterases may play a role in neural development suggesting a potential for interference from exposure to anti-ChE compounds (reviewed in Brimijoin and Koenigsberger 1999; Garry 2004). We are aware of one study that

evaluated the neurological effects of OPs on children. In a unique group of cases where methyl parathion was sprayed illegally in the homes of children in Mississippi and Ohio, Ruckart et al. (2004) detected increased behavioral problems and poorer performance on neurobehaviorial tests measuring short-term memory and attention in the exposed compared to the unexposed children. The child's exposure status was determined by the level of chemical residue found in house wipe samples and the level of metabolites in urine samples from any member of the household, not necessarily the child. Wipe samples contained $\geq$150 ug methylparathion/100cm^2 or $\geq$133 ug methylparathion/cm^2 for Mississippi and Ohio, respectively, while urine para-nitrophenol levels were $\geq$100 ppb. Exposure occurred when children were $\geq$6 years old and unexposed and exposed children completed the battery of neurobehavioral tests 2.5 to 6 years after exposure. The authors state that interpretation of results should be made with caution as effects were not found consistently between the Mississippi and Ohio study sites.

Research Needs. Given the variability in subtle neuropsychological effects from high-level acute exposure, well designed studies with appropriate endpoints, large sample sizes, and well characterized exposure assessments are required in order to detect effects from low-level exposure (Brown and Brix 1998; Karalliedde et al. 2000; He 2000; Lotti 2002; Kamel and Hoppin 2004; Alavanja et al. 2004b). More detailed exposure assessments will also help to clarify effects from acute episodes and chronic exposures with or without one or more acute episodes (Brown and Brix 1998; Kamel and Hoppin 2004). Additionally, follow-up studies are needed to determine the longevity of effects after both acute episodes and chronic low-level exposures (He 2000). Brown and Brix (1998) suggest that a threshold exposure level may exist for subtle effects to occur since within some studies effects are only noted at the higher levels of exposure. More research as to this possible threshold may be helpful in preventing long-term neurological deficits.

2 Genotoxic effects

2.1 Adult

Cytogenetic damage is considered a primary risk factor in the initiation of the carcinogenic process (Bolognesi 2003). Genetic damage can be evaluated by measuring chromosomal aberrations, frequency of micronuclei, and sister-chromatid exchanges. Micronucleus assays measure the frequency of the occurrence of micronuclei which are pieces of DNA that have been cast out of the nucleus and sister-chromatid exchanges evaluate the amount of breakage of the DNA strands and exchanges of DNA segments between sister-chromatids. Sister-chromatid exchange analysis is considered less sensitive at detecting genotoxic effects than measurement of chromosomal aberrations.

In general, individual agrochemicals are considered to have low genotoxic potential based on genotoxicity screening tests (Bolognesi 2003). However, there is evidence that technical grade malathion has genotoxic potential in both experimental animals and cultured human cells (Flessel et al. 1993). The few studies focused on anti-ChE compounds and cytogenetic damage in humans have had mixed findings.

Chromosomal aberrations and fragile sites were detected in Australian farmers after a season of low-level exposure to OP compounds (Webster et al. 2002). Significant increases in Howell-Jolly bodies and induced and non-induced chromosomal gaps and breaks were found in post-exposure farmers compared to controls and pre-exposure farmer blood samples. No differences in plasma ChE levels were observed between post-exposed farmers and controls. This study's overall aim was to examine the link between OP exposure and bladder cancer which may be indicated by the presence of DNA gaps and breaks and Howell-Jolly bodies. The authors acknowledge that "the link between fragile sites and chromosomal aberrations seen in [bladder cancer] has yet to be established" however, this study does indicate that genetic damage occurs even at non-cholinergic levels of exposure.

On the contrary, no difference in the frequency of micronuclei was detected in malathion-exposed pesticide sprayers compared to controls (TitenkoHolland et al. 1997). Additionally, no difference in micronuclei frequency was detected in a subgroup of workers with measurable levels of malathion metabolites compared to workers with

no measurable metabolites. Exposure to malathion was considered to be “relatively low” based on urine metabolite levels.

Confounding factors and exposure to pesticide mixtures make it difficult to determine if effects are a result of exposure to single compounds. Studies that have considered exposure to pesticide mixtures that included OPs, carbamates, pyrethroids, and organochlorines have reported positive effects on chromosomal aberrations and mixed results with micronuclei frequency and sister-chromatid exchanges (reviewed in Flessel et al. 1993; Bolognesi 2003). The overall conclusions from these studies are that 1) an association exists between exposure to pesticide mixtures and cytogenetic damage, 2) damage depends on the degree of exposure with no effects noted at low levels of exposure, 3) occupational exposure, such as chemical plant and greenhouse workers and agricultural pesticide sprayers, has been associated with cytogenetic effects.

Three studies not included in the above reviews by Flessel et al. (1993) and Bolognesi (2003) have reported increased risk for aneuploidy, higher levels of chromosomal aberrations, and increased frequency of micronuclei with OP-containing pesticide mixtures. Risk tended to increase with higher exposure levels. A small study of Mexican men exposed occupationally mainly to methyl parathion, metamidophos, endosulfan, and dimethoate showed significant associations between OP urinary metabolites and sex null aneuploidy and frequencies of total aneuploidies (abnormal number of chromosomes) in sperm (Recio et al. 2001). Frequency of sperm aneuploidies increased with increased OP concentration. Relative risk between sex null aneuploidy and concentration of urinary diethylphosphate (DEP) was 1.28 (95% CI 1.01-1.43) during crop preparation when small amounts of pesticides were used. Risk increased to 2.59 (95% CI 1.59-2.71) during the heavier spray season. Smaller but significant risks were also associated with dimethylthiophosphate (DMTP) and total dialkylphosphates and sex null aneuploidy as well as with total aneuploidy.

Green house workers in Ecuador exposed to a mixture of pesticides, including substantial exposure to anti-ChEs as evidenced by significantly lower red-blood cell ChE activities, had higher levels of cytogenic damage compared to controls (Paz-y-Mino et al. 2002). The overall percentage of chromosomal aberrations was higher in exposed

workers (21%) compared to controls (3%) and the frequency of chromosomal aberrations was significantly higher in workers with the highest exposures.

Marquez et al. (2005) documented a significant increase in frequency of micronuclei in Chilean women exposed to a mixture of pesticides while pruning, harvesting, and packing, but not spraying, fruits. The cytokinesis block proliferation index, an indicator of effects on the cell's proliferation kinetics, also decreased . Workers were exposed for 5 months to mainly OPs, carbamates, and pyrethroids and cytogenetic testing was done several weeks after the end of the work season. The results, therefore, suggest that the lymphocyte damage is "relatively persistent".

2.2 Children (no information)

Research Needs. The significance of chromosomal aberrations on human health requires further study (Flessel et al. 1993). As the role of mutations in the causation of cancer becomes apparent, the role of chromosomal damage as an indicator of mutation will become more relevant. The frequency of certain chromosomal aberrations have been shown to differ between females and males, therefore more studies investigating the effects of pesticides on cytogenetic damage in both sexes as well as in a variety of ethnic groups is recommended (Davies et al. 1998). Additionally, more accurate exposure assessments are required.

3 Immunotoxic Effects

3.1 Adult

General Immune System

Reviewers of the literature pertaining to the immunotoxicity of ChE-inhibiting pesticides generally agree that the overall experimental evidence demonstrates a variety of effects such as immunosuppression, immune system stimulation at low doses, indirect effects via alteration of the nervous system or metabolism, and effects on the developing immune system from exposure to OPs and carbamates (Banerjee 1999; Voccia et al. 1999; Colosio et al. 1999; Luebke 2002; Galloway and Handy 2003). Human epidemiological data also reveals immune function impairment in humans

although it is difficult to link effects to a specific compound and few studies define a dose-response relationship thus resulting in uncertainty regarding low dose and/or long duration effects.

The majority of human studies have measured cell-mediated immune components that provide information about the activation of immune processes under T-lymphocyte control and about the extent of oxidative stress on the system (Hoffman et al. 2003; Kaiser 2005). These components include the following: CD4 and/or CD8 surface molecule subsets of T-lymphocytes that play a role in recognizing endogenous and exogenous antigens; tumor necrosing factor (TNF), a cytokine involved in the inflammatory process; neopterin, a compound that possibly has a role in modulating reactive oxygen and nitrogen species; and neutrophils that are phagocytic white blood cells that reflect the innate immune system. The cell-mediated immune system activates cells or stimulates secretions that activate cells to achieve a immune response while humoral immunity involves antibody production.

Continuously exposed indoor pesticide applicators and intermittently exposed agricultural workers had impaired humoral and cell-mediated immune responses compared with controls (Stiller-Winkler et al. 1999). Both groups were exposed to mixtures of OPs, carbamates, phenoxy herbicides and pyrethroids. For both applicators and agricultural workers, a negative correlation was observed between exposure duration and immunoglobulin (IgM) indicating decreased humoral defenses. Neopterin and soluble tumor necrosing factor receptor (sTNF) odds ratios increased with increased duration of exposure in agricultural workers but decreased with duration in the indoor pesticide applicators (Stiller-Winkler et al. 1999; Galloway and Handy 2003). The authors suggest that the constant exposure to compounds by the pesticide applicators, in contrast with intermittent exposure by agricultural workers, may result in chronic immune system impairment (Stiller-Winkler et al. 1999). This study also investigated immune system markers in agricultural workers before and after a season of exposure. Decreased immunoglobins and sTNF after exposure indicated decreased humoral and cellular immune functions. The authors state that "this implies that recent exposure as well as permanent exposure, [as shown for the indoor applicators], is associated with an impairment of humoral and cellular immune function."

An alteration in T-cell levels was found in women with long term exposure to aldicarb contaminated groundwater (Fiore et al. 1986). Exposed women had significantly increased absolute numbers of CD8 (T8) cells, increased percentage of total CD8 cells, a decreased percentage of total CD4 (T4) cells, and a decreased CD4:CD8 ratio compared to unexposed controls. CD8 T-cells or cytotoxic T-cells work to destroy foreign cells in the body while CD4 or helper T-cells work to induce cell-mediated and antibody-mediated immunity (Kimball 2005). A dose-response relationship revealed a negative correlation between the CD4:CD8 ratio values and household well aldicarb levels and between the ratio values and daily aldicarb ingestion values. Aldicarb ingestion was estimated using values from daily tap water ingestion logs filled out by the women and aldicarb residue results from household well samples. The ingested mean daily concentration of aldicarb was 0.087 ug aldicarb /kg body weight/day and ranged from 0.001 to 0.65 ug/kg/day (Mirkin et al. 1990) and exposure duration was at least 4 years. Additionally, exposed women "showed an elevated stimulation assay response" to the *Candida* antigen (Fiore et al. 1986). The significance of these findings is unknown however as comparison of physician and health records indicated no clinical symptoms or adverse health problems in the exposed compared to unexposed women (Fiore et al. 1986; Mirkin et al. 1990; Colosio et al. 1999).

In a follow-up study of the participants in the Fiore (1986) study, 5 women continued to be exposed to aldicarb through their groundwater although at a decreased dosage of 0.022 ug/kg/day (Mirkin et al. 1990). The exposed women had increased values for total lymphocytes, percentage of lymphocytes, CD2 T-cells and CD8 T-cells compared to the unexposed women, including those women who were exposed in 1985 but no longer exposed in 1987. Additionally, IgG levels were higher in the aldicarb-exposed compared to the unexposed. Sample sizes were small and the authors suggest that conclusions regarding the lack of clinical effects seen with aldicarb exposure "must be made cautiously".

Impairment of neutrophil function and a high rate of recurrent upper respiratory infections was found in Polish OP pesticide production workers with low, medium, and high levels of exposure to the compounds (Hermanowicz and Kossman 1984). Exposure levels were determined by job type with technicians and janitors at the lowest

level and pesticide formulators at the highest level of exposure. Exposure was confirmed by level (dose)-dependent serum and blood ChE activity. All exposure groups had decreased ChE activity compared to the control group. Neutrophil chemotaxis and adhesion, which measure neutrophil function, were the same between the exposed groups regardless of exposure level yet significantly decreased from the controls. Recurrent respiratory infection rates increased with the number of years workers were on the job yet rates did not differ between exposure levels. The authors state that the role of airborne inhalants in these results can not be ruled out.

One study suggested that exposure to pesticides may affect neutrophil function by interfering with myeloperoxidase (MPO) (Queiroz et al. 1999). In people with a genetic MPO-deficiency, neutrophils are able to ingest *C.albicans* but are unable to kill the fungus (Lehrer and Cline 1969). Queiroz et al. (1999) had a similar finding with Brazilian farmers exposed to mixtures mainly of OPs and carbamates -- neutrophils were able to phagocytize but not kill the fungi, indicating a possible impairment in MPO. Klucinski et al. (1996) also documented low MPO levels in chemical plant workers exposed to a combination of pesticides including OPs and carbamates.

Autoimmune

"Autoimmune diseases are those produced by a failure of the immune system to recognize and tolerate self-antigens" (Fox, SI 1984), a result of the production of autoantibodies and immune responses directed towards the self. While evidence from experimental animal studies indicates that OPs can suppress or enhance immune function (Cooper et al. 2002), few studies have investigated the possible association between exposure to anti-ChEs and prevalence of autoimmune disease in humans.

In one study focused specifically on exposure to OPs, elevated autoantibodies were found in subjects exposed to undetermined or varying amounts of chlorpyrifos compared with control subjects (Thrasher et al. 1993; Thrasher et al. 2002). Significant differences in odds ratios for the presence of autoantibodies against antibrush border (Thrasher et al. 1993), nucleic acids/nucleoproteins , smooth muscle and parietal cells (Thrasher et al. 2002) compared to unexposed controls, but not different from positive controls, were detected. Additionally, the investigators detected a significantly decreased percentage of CD5 and an increased percentage of CD26 lymphocyte

phenotypes. Exposure resulted from accidental spills or puddles from home pesticide application or contact with chlorpyrifos-treated lumber. Chlorpyrifos concentrations were measured in some of the spills and ranged from 0.013 to 190 mg/kg. It is unknown if subjects experienced cholinergic involvement at the time of exposure. Subjects were referred to the study because of chronic health problems that started after exposure to the chlorpyrifos.

Antinuclear antibodies (ANA) are a group of autoantibodies that attack the nucleus of all cells and are used as biomarkers of autoimmune disease (Fox, SI 1984). The presence of ANA was significantly associated with lifetime exposure to insecticide use (OR =2.64; 95% CI 1.32-5.30), including carbamate use (OR = 2.29; 95% CI 1.12-4.67), among pesticides users in rural Canadian communities (Rosenberg et al. 1999). Subjects were recruited from several rural areas, lifetime exposure was assessed and the presence of ANA was tested. In addition to carbamates, significant associations were found specifically with pyrethroids, some organochlorines, and phenoxyacids but the prevalence of ANA was not significantly associated with subjects' use (26.2% ANA positive) or nonuse (23.2% ANA positive) of pesticides in general (Holsapple 2002).

Oxidative stress

Oxidative stress describes an imbalance between production of reactive oxygen species and anti-oxidant defense (Ranjbar et al. 2002; Abdollahi et al. 2004b). Reactive oxygen species include free radicals and peroxides that can damage the integrity of proteins, lipids, carbohydrates and nucleic acids while trying to obtain electrons. Inactivation of free radicals occurs by antioxidant defenses and imbalance in the system can have deleterious health consequences. OPs have been shown to induce oxidative stress in experimental studies (Kourakis et al. 1996; Abdollahi et al. 2004a) as well as acute poisoning cases in humans (e.g. Banerjee et al. 1999; Seth et al. 2001).

Oxidative stress from long-term exposure to OPs has been documented in occupationally-exposed workers. Increased oxidative stress markers and decreased antioxidant capacity were found in Iranian pesticide formulators exposed to OPs (Ranjbar et al. 2002). Increased oxidative stress was demonstrated in the OP formulators via increased thiobarbituric acid-reactive substances that indicated lipid peroxidation, and decreased ferric-reducing ability of the plasma in addition to

decreased thiol groups that reflected suppressed anti-oxidant capacity of the blood. However, no significant decrease in the antioxidant, gamma glutamyl trans peptidase was detected. The formulator's AChE activity was inhibited 44% compared to controls and the decreased AChE activity correlated with the increased thiobarbituric acid-reactive substance levels.

3.2 Children (no studies)

Research Needs. Little information exists on the sensitivity of the developing immune system and early life exposures to pesticides or the risk factors that increase vulnerability to pesticide effects (Banerjee 1999; Luebke 2002). Little information exists regarding the effects of pesticides on autoimmunity (Banerjee 1999; Holsapple 2002). Given that the effects of some pesticides have been shown to contribute to autoimmunity, there is a need for further screening at the development stage of the compound with further testing for autoimmunogenicity to be conducted when a pesticide's toxicity profile suggests key parameters that may be predictive of an autoimmune effect. Additionally, this model needs to be validated using compounds that are known to be associated with autoimmune disease. There is also a need for agreement on the biomarkers, endpoints and animal models to be considered in the evaluation of compound on immune system effects as the multiple functions of the immune system necessitate that several parameters and models be considered for a comprehensive assessment of immune system status and that these biomarkers be relevant for the determination of subtle immune changes (Vial et al. 1996; Banerjee 1999; Voccia et al. 1999).

4 Carcinogenic effects

4.1 Adult

In general, occupations considered to have the highest exposures to pesticides are farmers and pesticide applicators. Despite methodological difficulties such as confounding variables and lifetime exposure to numerous pesticides, most reviews and meta-analyses (but not all, see Acquavella et al. 1998) of cancer studies in farmers from the 1960s to 1990s identify increased risk for non-Hodgkin's lymphoma (NHL),

Hodgkin's lymphoma, multiple myeloma, leukemias, and cancers of the skin, lip, stomach and prostate with the occupation (Pearce and Reif 1990; Blair et al. 1992; Zahm and Blair 1993; Davis et al. 1993a; Keller-Byrne et al. 1995; Blair and Zahm 1995; Wiklund and Dich 1995; Khuder and Mutgi 1997; Dich et al. 1997; Khuder et al. 1999; Fleming et al. 2003; Alavanja et al. 2004b). While pesticides are implicated in the etiology of these cancers, the role of the ChE-inhibiting compound is less clear.

Non-Hodgkin's Lymphoma

Non-Hodgkin's lymphoma (NHL) is a cancer of the lymphatic system (American Cancer Society 2005) and has been found to have a weak association with occupational exposure as a farmer (Cantor et al. 1992; reviewed in Davis et al. 1993a; Wiklund and Dich 1995; Dich et al. 1997) although this view is not supported by all (Blair et al. 1992; Acquavella et al. 1998).

While it is difficult to link cancers with a specific pesticide, several studies have shown an increased risk for NHL corresponding with specific exposure to ChE-inhibiting compounds. Exposure to diazinon, coumaphos, and fonofos was associated with increased risk of NHL in Midwestern farmers (diazinon OR = 1.7; coumaphos OR = 1.7; fonofos OR = 1.5) (De Roos et al. 2003). No exposure durations were reported. Interestingly, analyses of combined exposures of atrazine with a ChE-inhibitor, for example atrazine and carbofuran and atrazine and diazinon, estimated synergistic effects.

Another study of Midwestern farmers found farmers who reported exposure to OPs had a 50% increased risk of NHL than non-farmers (Waddell et al. 2001). However, the risk for NHL was not evident when only direct and not proxy respondent information was used exclusively. Direct respondents tend to have a better recall regarding the types of pesticides used than proxy respondents who are answering on the subjects' behalf when the subject has deceased. Excess risk for small lymphocytic subtype was significant with diazinon use (OR = 2.8; 95% CI 1.1 – 7.3) when using direct respondents only.

Risk for NHL was elevated in farm workers exposed to OPs used on livestock (OR=1.5, 95% CI 1.0-2.1), especially with halogenated aromatic OPs (OR= 2.0, 95% CI 1.1-3.7) such as chlorpyrifos, coumaphos, and tetrachlorvinphos (Cantor et al. 1992).

Separating NHL into the subtypes follicular, diffuse, small lymphocytic, and unclassified, the following associations between subtype and OPs were detected: increased risk for diffuse NHL and OPs in general (OR= 2.3, 95% CI 1.4-3.8) and non-halogenated aliphatic OPs specifically, such as malathion, phorate, and dimethoate (OR= 2.2, 95% CI 1.3-3.8); small lymphocytic NHL and halogenated aromatic OPs (OR= 5.2, 95% CI 1.9-14.3); and unclassified NHL and halogenated aliphatic OPs, such as chlorethoxyfos (OR= 2.3, 95% CI 1.0-5.3). There were no associations detected between any pesticide and follicular NHL. Cases were diagnosed in the 1980s, therefore, due to a long latency for NHL, about 15-20 years after exposure, risk of handling pesticides before 1965 was also investigated. Exposure to malathion (OR= 2.9, 95% CI 1.1-7.4), diazinon (OR= 2.6, 95% CI 1.2-5.9), and carbaryl (OR=3.8, 95% CI 1.1-13.6) used on crops was associated with increased risk of NHL when handled before 1965. Study bias could have resulted from proxy responses, misclassification of exposure, and mixtures.

Significant associations were found in Canadian men between NHL and more than 10 hours per year exposure to OPs and carbamates (McDuffie et al. 2001). Specifically, exposure to malathion (OR=1.83; 95% CI 1.31-2.55) and carbaryl (OR=2.1; 95% CI 1.2-3.7) were significantly associated with NHL. No associations were detected with diazinon, dimethoate, carbofuran, or methomyl.

The use of carbaryl was associated with increased risk for NHL (Zheng et al. 2001). Odd ratios were increased in farmers who directly handled the product (OR=1.8; 95% CI 1.1-2.8) or for whom it had been $\geq$ 20 years since they first used carbaryl (OR=1.8; 95% CI 0.9-3.7). No significant associations were found with exposure to carbofuran, butylate, and EPTC (a thiocarbamate herbicide).

In a study of women's use of pesticides and risk for NHL, significantly increased risk was found when OPs were directly handled by the women (OR= 4.5, 95% CI= 1.1-17.9) (Zahm et al. 1993). The OPs handled included chlorpyrifos, diazinon, dichlorvos, famphur, fonofos, malathion, and terbufos. Insignificant increased associations were detected when carbamates (OR= 1.6, 95% CI= 0.6-2.5) and OPs (OR= 1.2, 95% CI=0.6-2.5) were used on the farms but not handled directed by the workers.

Farmers with additional health concerns may have increased risk for NHL with exposure to OPs. Risk of NHL after exposure to fonofos was 3.7-fold greater for

asthmatic farmers (95% CI 1.3-10.9) and 1.6-fold greater for nonasthmatic farmers (95% CI 1.0-2.4) compared to nonfarmers without asthma (Lee et al. 2004a). Asthmatic farmers tended to have larger odds ratios for NHL risk with exposure to carbaryl, carbofuran, diazinon, and malathion than the nonasthmatic farmers had although both groups had larger odds ratios for these compounds compared to the nonfarmers. Asthma-induced immune system dysfunction was postulated as a mechanism.

An association with NHL and pesticide applicators has also been documented. Zahm (1997) found that male applicators exposed to a variety of pesticides, including carbamates and OPs, had an increased risk of mortality from NHL (OR= 7.11, 95% CI= 1.78-28.42). This study was limited by a young cohort with a short duration of employment thereby reducing the power to detect effects such as other cancer types which may have a longer latency period. Effects from herbicides such as 2, 4-D, or mixtures of herbicides and OPs were not ruled out.

Hodgkin's Disease

A weak association has been reported for risk of Hodgkin's disease (HD) in farmers. Meta-analyses indicated increased relative risk of 1.23 (95% CI 0.99-1.53) for acquiring Hodgkin's disease (Khuder et al. 1999) and an increased relative mortality in farmers from Hodgkin's disease (MRR= 1.16, 95% CI= 1.03-1.29) (Blair et al. 1992). No specific information on pesticide use or class was given. To our knowledge, there are no studies that have investigated Hodgkin's disease and anti-ChE pesticide use.

Other Blood Cancers

Multiple myeloma is a cancer of the plasma cell (Multiple Myeloma Research Foundation 2005). Agricultural occupations appear to have a higher-than-average chance for developing multiple myeloma. As with NHL, possible etiologies of the disease include exposure to chemicals (pesticides, herbicides), a zoonotic disease agent, and/or prolonged allergen exposure (Khuder and Mutgi 1997). While a meta-analysis of multiple myeloma and farming in the US observed that 28 out of 32 studies reported a positive association between multiple myeloma and farming, the meta-analysis risk indicated a weak association (Blair et al. 1992; Wiklund and Dich 1995; Khuder and Mutgi 1997).

One study that examined exposure to OP pesticides and risk for multiple myeloma found non-significantly elevated odds ratios for farmers who reported personally handling coumaphos, dichlorvos, carbaryl, malathion, and terbufos (Brown et al. 1993). Risk was not elevated for OPs in general when considered as a pesticide class.

Very little has also been published regarding the risk of developing leukemia after exposure to OPs although a weak positive association exists for leukemia and farming (Blair et al. 1992; Keller-Byrne et al. 1995). One study reported elevated risks for leukemia subtypes with exposure to OPs and carbamates and with exposure over time (Brown et al. 1990). Risk for the chronic lymphocytic leukemia subtype was increased with exposure to carbamates used on crops and animals (crops: OR=2.0; 95% CI 1.1-3.5; animals: OR=3.1; 95% CI 1.0-9.3). Risk for chronic lymphocytic leukemia and chronic myelogenous leukemia subtypes were increased with exposure to dichlorvos with ORs of 2.2 (95% CI 1.0-4.6) and 3.3 (95% CI 1.0-10.6), respectively. Risk for leukemia in general was elevated for workers who first used carbaryl, malathion, dichlorvos, and famphur $\geq$20 years prior to the study.

It is worth noting that in a study of enclosed-space pesticide applicators in Minnesota, two out of three subjects with leukemia had hairy cell leukemia, a rare hemeopetic cancer (Garry et al. 1994). However, the small sample size and mixed exposures to a variety of compounds precludes any association with ChE-inhibitors. No known follow-up work has been published.

Breast Cancer

Some experimental studies indicate that OPs can induce changes in breast cells (e. g. Cabello et al. 2001; Cabello et al. 2003a; Cabello et al. 2003b) however, only a few studies examined the association between breast cancer and ChE-inhibiting chemicals. A recent study of farmer's wives in Iowa and North Carolina reported mixed results in associations between women and breast cancer and exposure to OPs and carbamates (Engel et al. 2005). Risk for cancer was increased in women whose husbands used OPs in general (RR=1.9; 95% CI 0.9-4.0) and used malathion (RR = 1.4; 95% CI 1.0-2.0) or carbaryl (RR=1.4; 95% CI 1.0-2.0) in particular. Examination of the data by menopausal status indicated increased risk when premenopausal women

directly handled chlorpyrifos (RR= 2.2; 95% CI 1.0-4.9), dichlorvos (RR=2.3; 95% CI 1.0-5.3) and terbufos (RR=2.6; 95% CI 1.1-5.9). In contrast, postmenopausal women had greater risk for the cancer when their husbands handled chlorpyrifos (1.6; 95% CI 1.1-2.4), diazinon (1.5; 95% CI 0.9-2.3), and dichlorvos (1.4; 95% CI 0.7-2.6). There was no apparent increased risk when postmenopausal women handled the compounds directly. Additionally, risk was increased with a woman's direct handling of diazinon when the family had a history of cancer.

A study of woman greenhouse workers on Crete exposed mainly to OPs and carbamates showed increased risk for benign breast lesions that may play a role as markers for subsequent breast cancer (Dolapsakis et al. 2001). Exposure dose was not measured but the authors state that "…[farmer's work] involves spraying various pesticides for 2-3 hours per week for 9 months per year" and the study chose women who worked for at least 10 years in greenhouses. The breast lesions were categorized by their risk for predicting subsequent breast cancer. Of the lesions associated with occupational pesticides, "moderately increased" risk was found for fibroadenoma, "slightly increased" risk for sclerosing adenosis, gross cystic disease, and fibrocystic changes plus ductal hyperplasia, while "no increased" risk was found for inflammatory mastitis, and ductal hyperplasia. Exposed women were 4.9 times more likely to develop fibroadenoma than unexposed women and risk ranged from 1.4 to 1.9 times for the cancers in the "slightly increased' category.

A suggestion of increased risk for breast cancer with exposure to "less persistent current-use" pesticides (including malathion, carbaryl, and other carbamates) used between 1975 and 1995 was found in a study of breast cancer on Cape Cod, Massachusetts (Brody et al. 2004). Risk was associated with agricultural areas (excluding cranberry cultivation) and areas sprayed for tree pests. No trends in exposure duration were noted, although sample size was small.

Residential proximity to anti-ChEs used in agriculture was not associated with increased risk for breast cancer in California (Reynolds et al. 2004). "Exposed" women were defined as living in areas with a pesticide use or pesticide class use density of $\geq$1 lb/mi^2.

Lung

Few studies investigated lung cancer and exposure to pesticides. Blair et al (1983) reported that risk of mortality from lung cancer increased with increased years of pesticide applicator licensure and non-mutually exclusive work controlling a variety of pests such as termites and wood infesting insects, general household pests, rodents, and lawn and ornamental pests. Specific pesticides were not investigated in this study. However, in a follow up study, Pesatori et al. (1994) analyzed risk by pesticide class and found a significant increase for lung cancer with exposure to carbamates (OR=16.3. 95% CI 2.2-122.5) and a non-significant increase for OPs (OR=2.2; 95% CI 0.8-5.8). Among individual compounds, increased risk was noted for carbaryl, propoxur, and parathion. Results should be viewed with caution as the use of live and proxy controls may bias outcomes. The authors also point out that exposure to mixtures may confound results.

Increased lifetime use of chlorpyrifos or diazinon was associated with a significantly increased risk of lung cancer in a North Carolina and Iowa farmer cohort study (Alavanja et al. 2004a). Data was adjusted for smoking and other confounding factors. Interestingly, a lower cancer risk was noted for the lowest exposure group for carbofuran, chlorpyrifos, and diazinon compared to the never used pesticides group, a finding that the authors say may be explained by unidentified factors in the unexposed group or by hormesis.

Prostate

Farmers (Blair et al. 1992; Keller-Byrne et al. 1997) and commercial pesticide applicators (farmers and nursery workers) (Van Maele-Fabry and Willems 2003; Van Maele-Fabry and Willems 2004) had a small but significant increase in risk for prostate cancer than the general population.

Exposure to the OP, dichlorvos, was weakly associated with increased risk of prostate cancer (OR=1.35, 95% CI= .93-1.96) in Hispanic farm workers in California when compared with cancer-free workers (Mills and Yang 2003). Data were collected from pesticide use reports submitted by farmers to agricultural commissioners and "...the total number of pounds of pesticides active ingredient applied in a given county in a given year was summed and used as a surrogate measure of potential exposure." .

This study was limited by a reduction in sample size from loss of farm workers due to migration, a generally low incidence of prostate cancer in Hispanics compared to general population, and uncertainty in exposure.

Increased risk of prostate cancer was detected when the applicator had a family history of prostate cancer and used the thiocarbamate butylate (OR=1.93; 95% CI 1.119-3.11), or the OPs coumaphos (OR=2.58; 95% CI 1.29-5.18), fonophos (OR=2.04; 95% CI 1.21-3.44), chlorpyrifos (OR=1.65; 95% CI 1.02-2.66), and phorate (OR=1.64; 95% CI 1.02-2.63) (Alavanja et al. 2003). Several elevated but nonsignifiant odds ratios were noted with the thiocarbamate, EPTC, the OPs terbufos and dichlorvos, and the carbamates aldicarb and carbofuran.

Brain Cancer

Athough most studies reported increased mortality from brain cancer in farmers meta-analysis relative risk was not significantly increased except when analyses were confined to United States (Blair et al. 1992; Khuder et al. 1998). Bohnen and Kurland (1995), in a review the epidemiologic literature concerning exposure to pesticides and the risk of developing brain cancer, conclude that the current studies do not "support an etiologic role from specific pesticides in the pathogenesis of primary brain tumor in adults" however they concede that the studies are poor and difficult to compare.

While the following two studies do not specifically implicate pesticides as risk factors, they do argue for further investigation. Investigation of the incidence of cancers with regards to subject's proximity to cranberry bogs on Cape Cod, Massachusetts found elevated relative risks for brain cancers (RR = 2.5; 95% CI 1.2-5.1), especially astrocytomas (Aschengrau et al. 1996). Risk remained elevated when data was adjusted for confounding factors such as proximity to a military base. Increased risk was not associated with other cancers such as lung, breast, or bladder cancer. Pesticides used in the cranberry industry in the past century include the anti-ChEs, carbaryl, acephate, azinphos-methyl, chlorpyrifos, and diazinon in addition to organochlorines and metals (University of Massachusetts - Cranberry Experiment Station 2000).

In Italy, Musicco et al. (1982) found increased risk for farmers for gliomas compared to nonfarmers, especially when the farmers worked after 1960. The authors

suggest this may be due to possible risk factors such as OPs, organochlorines, herbicides, and fertilizers whose use increased in Italy after 1960.

Other Cancer

Increased risk of bladder cancer from exposure to OPs has been suggested. Webster et al. (2002) argues that the presence of chromosomal aberrations in Australian farmers may provide preliminary evidence of increased risk for bladder cancer from exposure to OPs, but no follow-up study has been published (see Genotoxicity Section for details).

Meta-analysis reported an increase in farmer mortality due to stomach cancer (MRR= 1.12, 95% CI= 1.09-1.14) (Blair et al. 1992). However, in the one study found that considered exposure to pesticides, increased risk for stomach (OR= 0.7, 95% CI 0.4-1.3) or esophageal cancers (OR= 0.8, 95% CI 0.4-1.5) was not detected in farmers who used carbamates or OPs (stomach: OR= 0.9, 95% CI= 0.5-1.5; esophageal cancers: OR= 0.6, 95% CI=0.3-1.2) (Lee et al. 2004b).

4.2 Children

Children are unique from adults in that they have increased vulnerably to toxic insults. Most studies that investigated the relationship between childhood cancers and pesticides in general reported positive associations between cancer risk and home pesticide exposure, suggested that risk for cancer tended to be higher in exposed children compared to exposed adults, and indicated that a parent's occupational exposure to pesticides increased the risk of cancer in their children (O'Leary et al. 1991; Daniels et al. 1997; Zahm and Ward 1998; Baldwin and Preston-Martin 2004). Other studies reported increased risk when exposure occurred to the mother during pregnancy (Pogoda and Preston-Martin 1997). Few studies evaluated the risk of childhood cancers and exposure to anti-ChEs,.

Brain Cancer

Childhood brain cancer was positively associated with exposure to OP garden insecticides and pet flea collars (Davis et al. 1993b). Risk increased in children when exposure occurred within age two categories, birth to 6 months of age and seven months to diagnosis, with garden use of carbaryl (OR=2.4; 95% CI 1.1-5.6) and

diazinon (OR=4.6; 95%CI 1.2-17.9). Risk was associated with exposure only from birth to 6 months of age for flea collars used on pets (OR=4.8). Dichlorovos was a common active agent in flea collars during estimated exposure time.

Pogoda and Preston-Martin (1997) found significantly increased risk for pediatric brain tumor with prenatal exposure to flea and tick products while less risk was associated with childhood exposure to these products. The flea and tick products contained a mixture of compounds that included OPs, carbamates, pyrethrins, and pyrethroids.

Two of the three following studies use “pesticide-class” rather than chemical type to classify exposure and are included because they were conducted in the late 1980’s to 1990’s when OP pesticides were common ingredients in home and agricultural pest control products.

Home and garden pesticide use were both moderately associated with childhood neuroblastomas in a study conducted from 1992 to 1994 in the United States and Canada (Daniels et al. 2001). In lieu of pesticide chemical type, pesticide type-of-use was reported and positive associations with childhood cancer were detected for home ant and roach control chemicals (OR = 1.8; 95% CI 1.0-3.1), garden herbicides (OR = 1.9; 95% CI 1.1-3.2), and a weak association with garden insecticides (OR = 1.3; 95% CI 0.7-2.3). Risk for childhood cancer increased when garden pesticides were applied by the mother (OR = 2.2; 95% CI 1.3-3.8). Additionally, risks were increased for children over 1 year old which the authors surmise may reflect longer exposure duration, greater opportunity for contact with pesticide as older children may move around more, or a disease etiology that results in an older age at diagnosis.

Some studies found slightly increased risk associated with parental occupational exposure and childhood cancer but no association with pesticide use specifically. Flower et al. (2004) found increased incidence of childhood cancer, especially lymphoma, in children whose parents worked as private pesticide applicators (farmers) or commercial pesticide applicators. Risk increased when the father did not use protective gloves to handle pesticides (OR = 1.98; 95% CI 1.05-3.76). However, no difference in risk was reported with the father or mother’s direct handling of pesticides,

frequency of pesticide use, or use of OPs in general or with malathion, chlorpyrifos, or dichlorvos, specifically.

A study of parental occupational exposure and risk of childhood brain cancer cases between 1986 and 1989 suggests a slightly increased risk for astrocytoma with mother's occupational exposure to insecticides and herbicides (van Wijingaarden et al. 2003). General categories of pesticides were analyzed: insecticides, herbicides, and agricultural and nonagricultural fungicides and the resultant risk associations were noted after adjustments for all categories were made. For all four pesticide categories, odds ratios ranged from 1.3 to 1.6 (excluding agricultural fungicides) for maternal exposure (van Wijingaarden et al. 2003; Baldwin and Preston-Martin 2004). Mothers exposed to insecticides were predominantly food service workers and no significant association was detected with parental employment as an agricultural worker.

Other Cancers

A study of risk for childhood acute lymphoblastic leukemia suggests increased risk with exposure to home use insecticides, including OPs and carbamates (Infante-Rivard et al. 1999). Odds ratios for pre-and post-natal exposure to insecticides against "cockroaches, ants, flies, bees, and wasps", moths, termites, and insects ranged from 1.27 to 2.99 and remained elevated when only application by the mother was considered. Odds increased for exposed children with polymorphisms of the P450 enzyme. Compounds most likely used included "chlorpyrifos, diazinon, dichlorvos, malathion, cygon, propoxur and carbaryl in addition to some organochlorines and phenoxy herbicides".

Increased risk for leukemias and exposure to dichlorvos-containing pest strips and for lymphomas and childhood exposure to home pest extermination pesticides including diazinon, chlorpyrifos, and organochorines was detected (Leiss and Savitz 1995). Exposure was based on whether or not the child was *ever* or *never* exposed to the various pesticide treatments.

Maternal residential proximity to agricultural OP and carbamate pesticide use and risk of childhood leukemia and central nervous system cancers was not found to be significant (Reynolds et al. 2005). The authors caution that small sample sizes and difficulties in assessing exposure may have influenced results.

Research Needs. One method of assessing exposure is to use proximity to the potential risk. Future studies are needed "…to evaluate how well proximity to agricultural pesticide use estimates exposure and to determine other significant predictor variables" (Reynolds et al. 2005). Exposure assessments in general as well as information on timing of exposure in children require improvement (Davis et al. 1993b; Zahm and Ward 1998). Critical developmental periods may make children more susceptible to effects from pesticide exposures and an understanding of vulnerable periods may help to prevent deleterious effects from exposure. Additionally, subgroups of adults and children with genetic polymorphisms or mutations that may alter their susceptibility to cancer require further study (Zahm and Ward 1998).

Increased understanding of risk associated with mixtures of chemicals is needed. Pogoda and Preston-Martin (1997) call for increased understanding of the risk for pediatric brain tumors and exposure to nitroso-containing compounds. Efforts are needed to increase study sample sizes to increase statistical power as many cancer studies, especially those considering children, have a small number of cases. Additionally, use of methods for minimizing confounding variables and bias are important (Bohnen and Kurland 1995).

5 Reproductive effects

5.1 Adult and 5.2 Children

Occupational studies have shown significant associations between maternal, as well as paternal, exposure to pesticides in general and adverse reproductive outcomes (reviewed in Savitz et al. 1994; Nurminen 1995; Pastore et al. 1997; Garcia 1998). However, most reviewers agree that the paucity of high quality studies with adequate exposure assessments preclude definitive comments regarding the significance of pesticides on reproductive outcomes or the specific compounds responsible (Nurminen 1995; Garcia 1998; Figa-Talamanca et al. 2001; Hanke and Jurewicz 2004).

Regardless, with regard to specific pesticides, anti-ChE compounds have been implicated in adverse outcomes such as increased risk of infertility, spontaneous abortion, stillbirth, preterm delivery, and birth defects (reviewed in Figa-Talamanca et al.

2001; Sheiner et al. 2003; Hanke and Jurewicz 2004). Changes in hormone levels, impaired semen quality, and altered birth parameters have also been reported. Animal studies have reported reproductive effects such as premature ovulation, endocrine disruption, and congenital abnormalities from exposure to OPs (Sharara et al. 1998; Akingbemi and Hardy 2001; Garcia et al. 2003) and some specifically show estrogenic and antiandrogenic effects (e. g. Tamura et al. 2001) while other studies do not (e. g. Chen et al. 2002).

Increased odds of longer menstrual cycles (OR=2.1; 95% CI 1.1-3.7) and decreased odds of irregular cycles (OR=0.38, 95% CI 0.19-0.77) were associated with exposure to carbamates (Farr et al. 2004). While no effects on the menstrual cycle were detected with exposure specifically to OPs, use of "probable or possible hormonally active-, ovarian-, or estrous- cycle-disrupting pesticides", a category that included parathion, increased the odds of longer cycles, missed periods, and intermenstrual bleeding compared to women who never used pesticides.

Sperm Quality

Impaired semen quality was detected in Japanese indoor pesticide applicators during the active spraying season when the most frequently used compounds were the OPs, fenitrothion, dichlorvos, and chlorpyrifos, and a mixture of fenitrothion and dichlorvos. (Kamijima et al. 2004). Sperm motility was significantly decreased and sperm morphology defects increased in applicators compared to controls during the spray season but not during the off season. A non-significant decrease in testicular volume was also noticed during the spraying season. No differences were found in lutenizing hormone or follicle-stimulating hormone levels. Erythrocyte ChE was significantly lower in the applicators compared to the controls during the active season and decreased in a dose-dependent manner (Kamijima et al. 2004). No dose-dependent trend was noted with the serum indices. The authors caution that the effects of protective clothing (e.g. thick, hot pants increasing scrotal temperature) can not be ruled out. Patients who suffered acute OP poisoning also had no change in lutenizing hormone but a decrease in follicle-stimulating hormone was documented (Guven et al. 1999).

A study of sperm quality in Mexican workers exposed to methyl parathion, metamidophos, dimethoate, diazinon, and endosulfan in agricultural fields found altered sperm chromatin structure and DNA denaturation positively associated with concentrations of the urinary OP metabolite, diethylthiophosphate (DETP) (Sanchez-Pena et al. 2004). Other sperm quality measures such as motility, viability, morphology, concentration, and volume were within normal ranges except that a higher percentage of the agricultural worker samples contained immature germinal cells compared to World Health Organization guidelines.

Decreased semen quality, especially decreased semen concentration, was associated with metabolite levels of 2-isopropoxy-4-methyl-pyrimidinol (IMPY- a urinary metabolite of diazinon) in men exposed to environmental background levels of OPs and herbicides in a rural area of Missouri (Swan 2003). Cases were defined as men with low sperm counts while controls had high sperm counts. Both cases and controls in rural Missouri and an urban area of Minnesota had pregnant partners. Both cases and controls reported similar levels of occupational and home pesticide use with only 3.4% of all subjects occupationally exposed to pesticides. A greater percentage of subjects in the rural area had higher pesticide metabolite levels compared to those in the urban area. Also in the rural area, IMPY, alachlor, and atrazine urine levels were significantly higher in men with low sperm count compared to those with high sperm count while in the urban area, no difference was found in pesticide levels between cases and controls. The risk of low semen quality was elevated 17-fold (95% CI 2.8-98.0) with higher concentrations of IMPY. Semen quality comprised the following parameters: semen concentration, morphology and motility. 3,5 6-tirchloropyridinol and 1-naphthol, metabolites of chlorpyrifos and carbaryl, respectively, were also detected and elevated in Missouri but were not significantly associated with sperm parameters. The significance on reproduction is uncertain as all cases and controls had pregnant partners.

Meeker et al. (2004) found significant associations between sperm concentration and motility and metabolite levels of chlorpyrifos and carbaryl. Exposure to these OPs was assumed to be due to environmental background levels as no cases reported occupational exposure to the compounds. Risk was significantly increased for lower

sperm concentration and decreased sperm motility with “medium” and “high” concentrations of 1-Napthol (a metabolite of carbaryl and naphthalene) while risk was of borderline-significance for 3, 5, 6 – trichloro-2-pyridinol (TCPY) and sperm concentration and motility.

Sperm quality was decreased in parathion-exposed Chinese pesticide formulators (Padungtod et al. 1999). Interestingly, there was no difference in the magnitude of the effects between workers with normal paraoxonase and those with paraoxonase polymorphisms. See further discussion in the Miscellaneous Effects section.

Conception

Time to pregnancy is usually defined as “the time interval between the start of unprotected intercourse and a clinically recognizable pregnancy” (Petrelli and Mantovani 2002). Time to pregnancy was delayed for women who were exposed to OPs and carbamates either indirectly through a spouse’s exposure or through direct exposure.

The odds for delayed time to pregnancy was increased (OR=2.4; 95% CI 1.2-5.1) for couples where the male was a greenhouse worker with high (>100 hours) exposure to a mixture of pesticides including carbaryl and dichlorvos (Petrelli and Figa-Talamanaca 2001). Decreased fecundability was also indicated for Finnish male greenhouse workers who were insufficiently protected from exposure to OPs and carbamates (Sallmen et al. 2003).

Women who engaged in farm activity when a mixture of pesticides including OPs were used on the farm had a higher risk for delayed time to pregnancy (Conditional fecundibility ratio (CFR) 0.75; 95% CI 0.51- 1.10) (Curtis et al. 1999). On the contrary, the CFR was $\geq$1 when only men reported farm activity with pesticide use or when no spouse was engaged in farm activity regardless of whether pesticides were used on the farm or not. Since men reported farm activity most every time their wives did, it was not possible to examine the effects of pesticides on women alone. No biological endpoints or dose was monitored and information from farm operators on pesticide use allowed researchers to create pesticide history charts to estimate exposure during time to

pregnancy. The authors only used subjects that eventually conceived, excluding sterile couples and couples with long term fertility problems.

Spontaneous Abortion

Evidence of increased risk of miscarriage and fetal abnormalities has been associated with paternal exposure to anti-ChE compounds. “Spontaneous abortion” is defined as the loss of a fetus during pregnancy due to natural causes. Specifically, the term "miscarriage" is the spontaneous termination of a pregnancy before fetal development has reached 20 weeks. Pregnancy losses after the 20th week are categorized as “preterm deliveries” (MedlinePlus 2005) or “fetal death”.

The risk of spontaneous abortion was increased (OR=3.8; 95% CI 1.2-12.0) for wives of pesticide applicators exposed to mixtures of organochlorines, rodenticides, carbamates, and OPs, including fenthion and malathion (Petrelli et al. 2000). The abortion rate was 28% for pesticide applicators compared to 7% for the controls.

Increased risk of miscarriage was also associated with paternal exposure to carbaryl when combined with a mixture of crop insecticides and fungicides (OR = 2.1; 95% CI 1.1-4.1) or when combined with crop herbicides (OR = 1.9; 95% CI 1.1-3.1) such as glyphosate and atrazine (Savitz et al. 1997). Similar results were noted for thiocarbamates and herbicide application. An odds ratio of 2.7 (95% CI 0.7-11.0) was associated with preterm delivery and paternal use of livestock chemicals in combination with OPs. Risk of smaller birth weights for gestational age with exposure to pesticides was not detected.

Increased risk for miscarriage may result from exposure to carbamates and thiocarbamates during a critical period of conception. Paternal and indirect maternal exposure to thiocarbamate or carbaryl compounds three months before conception to within one month after conception increased the risks of spontaneous abortion in women over 35 years old (Arbuckle et al. 2001). In general, women over 35 years of age were 2.6 times more likely to abort than younger women. However, when exposed to carbaryl before conception, women >35 years old were 4 times more likely to have a miscarriage compared to unexposed older women while women >35 years old and exposed to carbaryl in combination with 2,4-D were 27 times more likely to abort compared to the women exposed only to carbaryl. Risk was also increased when older

women were exposed to triazines and thiocarbamates before conception or just to thiocarbamates during the first trimester. Couples lived on farms year-round but occupational exposure was primarily through the male.

Birth Parameters

Birth parameters were found to be affected by indoor application of organophosphates. Levels of chlorpyrifos, diazinon and propoxur in umbilical cord blood were determined and birth weight and length collected from 250 newborns delivered between 1998 and 2002 in a study of minority women in New York City (Perera et al. 2003; Whyatt et al. 2004). Birth weight and length were significantly inversely correlated with cord levels of chlorpyrifos, with levels of chlorpyrifos plus diazinon (after conversion into chlorpyrifos equivalents) and, to a lesser extent, with levels of propoxur. On average, the chlorpyrifos concentration in cord blood was 7.6 pg/g and was detected in 94% of the cases (Perera et al. 2003). Cases were then grouped by the concentration of OPs found in the cord blood (Whyatt et al. 2004). In the cord blood group with the highest concentration of chlorpyrifos, birth weight and length averaged 150 g (95% CI -288 to -12.5 g; $p = 0.03$) and 0.75 cm less than (95% CI -1.6 to -0.06 g; $p = 0.07$) these parameters in the lowest concentration group. Similar significant differences were noted between high and low concentrations in the chlorpyrifos combined with diazinon (adjusted to chlorpyrifos-equivalents) groups but only nonsignificant decreases were noted between the propoxur cord blood concentration groups. Interestingly, the above significant effects were not noted in newborns born after January 2001. This result is thought to be due to the phase out of chorpyrifos and diazinon for residential uses. OP residue levels were also detected in personal air monitoring devices worn by the women in the last trimester of pregnancy but these levels did not correlate with the birth parameters.

In contrast, no differences in newborn size parameters with exposure to OPs were detected in minority women living in a California agricultural community (Eskenazi et al. 2004). Exposure was measured by urinary metabolites and cholinesterase activity in maternal and cord blood. Urinary metabolites were analyzed twice during the pregnancy and ChE activity in the cord blood determined once during the pregnancy and just before delivery. No significant associations were detected with levels of whole

blood ChE activity and fetal growth parameters however, an increase in urinary OP metabolites was significantly associated with an increase in head circumference, an unexplainable finding. Additionally, an increased risk of preterm birth was associated with increased exposure levels when exposure occurred later in the term. The increase in exposure was determined by decreased levels of cord blood ChE and increased levels of urinary dimethyl phosphate metabolites.

Intrauterine growth retardation or restriction (IUGR) is “a condition which the fetus is undernourished for gestational age” (Gilbert and Danielson 2003). IUGR has been related to neonatal death, morbidity, limited growth, and several disease conditions in adult life. The relationship between infants with IUGR and pesticide exposure was evaluated in Mexican women who were exposed to OPs either through residing in a community where pesticides were applied or through contact with a family member or spouse who handled the compounds or worked in agriculture (Levario-Carillo et al. 2004). Infants with lower blood AChE ($\geq$20% lower than community baseline) or who had mothers with lower blood AChE were at greater risk for IUGR than those who did not show positive exposure (OR = 2.3; 95% CI 1.0-5.3). Among the infants, those with IUGR had significantly lower AChE levels than those without IUGR.

In general, congenital abnormalities have been associated with maternal and paternal occupational exposures to pesticides as well as maternal exposure via pesticides applied in the home (Chia and Shi 2002). Women exposed through agricultural or horticultural occupations or residence on farms had higher risks for spina bifida, orofacial cleft, neural tube defects, and limb abnormalities. Application of pesticides by the mother or professionally applied to household gardens or in the home resulted in increased risk of neural tube defects, heart defects, cleft lip with or without cleft palate, and limb defects (Shaw et al. 1999). Risk of fetal death from congential abnormalities was elevated when offspring, with fathers occupationally exposed to agricultural pesticides, were conceived during periods of heaviest pesticide use (Regidor et al. 2004).

Exposure to OPs during organogenesis, the 3rd through 8th weeks of pregnancy,increased risk of congenital birth defects leading to fetal death (Bell et al. 2001). Slightly increased risk for fetal death due to congenital anomalies during

organogenesis (weeks 3-8 of pregnancy) was associated with application of OPs (OR=1.4, 95% CI= 0.8- 2.5) and carbamates (OR=1.7, 95% CI=0.9- 3.2) within 9 square miles of maternal residence. When application occurred within one square mile of residence, the risk increased for both OPs (OR= 2.9 CI 1.3- 6.4) and carbamates (OR=2.3 CI 0.9- 6.4). When congenital anomalies as cause of fetal death were removed from the analyses, a slight risk of fetal death from other causes was observed when proximity to carbamate ChE-inhibitors occurred between the 12th and 16th weeks of pregnancy. Exposure to the mother during different stages of pregnancy was determined through the state Pesticide Use Report database, which reports the type, amount, date, and location of applications.

Thomas et al. (1992) investigated aerially-applied malathion as a risk factor for spontaneous abortion, intrauterine growth retardation, congenital anomalies, and stillbirth. Exposure indices were determined by classifying the proximity of maternal residence to an aerial spray "corridor" and combining the number of weekly applications per corridor. An increased risk of gastrointestinal anomalies was detected with malathion exposure during the second trimester and residence within an active corridor (RR= 4.14, 95% CI 1.01-16.6). Positive, but non-significant, associations between exposure and stillbirths, limb and orofacial anomalies, and spontaneous abortion were also observed with direct exposure (Thomas et al. 1992; Arbuckle and Sever 1998). In contrast, a Chilean study reported no differences in rates of stillbirth between pre-and post-malathion fumigation (reviewed in Arbuckle and Sever 1998).

Increased risk for birth defects in infants of female industrial workers and increased risk of fetal death in wives of industrial workers exposed to chronic low doses of OPs has been reported (Arbuckle and Sever 1998). Additionally, increased risk for spontaneous abortion and stillbirth has been observed in Indian cotton workers exposed to mixtures of pesticides that included OPs.

Decreased paraoxoanse activity in conjunction with maternal OP exposure may also contribute to adverse effects on fetal growth parameters (Berkowitz et al. 2004). See further discussion in the Miscellaneous Effects section.

Research Needs. Epidemiological studies are expensive and suspect if the study design is flawed. Therefore, it is important that optimal strategies for collecting data be defined. Prioritization of hazardous substances is necessary and use of research generated for wildlife species can assist in this procedure (Sharara et al. 1998; Moline et al. 2000). Reproductive endpoints and biomarkers need to be identified and classified across countries (Sharara et al. 1998; Moline et al. 2000; Chia and Shi 2002). Development of adequate methodology, comprehensive exposure assessments, increased sample sizes (Sharara et al. 1998), and proper handling of confounding factors are important (Garcia 1998; Chia and Shi 2002; Hanke and Jurewicz 2004). Documentation of genetic variations, elective termination of fetus with birth defects, and differences in reproductive history also need to be taken into account.

With regard to particular areas of study, more research on occupational studies that focus on specific occupations to better identify causative agents (Chia and Shi 2002), studies on the "gene-environment interaction and male-mediated effects" (Garcia 1998; Hanke and Jurewicz 2004) in addition to the influence of environmental exposures on the endocrine and immune system and the subsequent reproductive effects (Guven et al. 1999; Hanke and Jurewicz 2004), and studies on the relationship between congenital malformations and pesticide exposure, focusing on specific chemicals and/or chemical classes (Garcia 1998) would greatly increase knowledge regarding reproductive effects.

6 Metabolic Effects

6.1 Adult

Thermoregulation

In contrast with experimental animals and wildlife that suffer from hypothermia induced by exposure to OPs, hyperthermia or fever is a commonly reported clinical symptom in humans exposed to poisoning doses of anti-ChEs and can last a period of time after the acute poisoning effects have resolved (Gordon 1994; Grue et al. 1997). Less is known about the effects from chronic or low-level exposure to these compounds.

Anti-ChEs have been shown to affect the ability to dissipate heat, therefore the effects of chronic exposure to these compounds while working or exercising may stress the thermoregulatory system. Gordon (1994) reviewed two studies that investigated the effects of exercise on humans orally exposed to the carbamate, pyridostigmine bromide, and reported variable results. Decreased core temperature and skin blood flow with exercise was reported in one study leading to the conclusion that the "reduction in cutaneous blood flow could be a major factor in limiting heat dissipation during exercise in the heat". A second study observed an increase in temperature plus sweating with exercise, a finding that suggested central nervous system effects, while Shibasaki and Crandall (Shibasaki and Crandall 2001) observed that inhibition of AChE caused a decrease in sweat rate in humans, indicating that AChE plays a role in sweat gland modulation in humans.

Research Needs. Other possible thermoregulatory effects that have not been investigated thoroughly in humans are the effects of long-term anti-ChE exposure on the ability to adapt to changing environmental temperatures, the possible augmentation of effects from anti-ChEs in humans with elevated body temperatures due to exposure, and the role of genetic variability on the ability of the thermoregulatory system to modulate itself.

6.2 Children (no information)

7 Respiratory effects

7.1 Adult

Pesticide production workers and farmers exposed to OPs and carbamates are reported to have significantly decreased pulmonary function, increased wheezing, and increased risk for asthma compared to controls. Workers employed in the manufacture of chlorfenvinphos experienced decreased pulmonary function and weakened respiratory muscles compared to controls (Konieczny et al. 1999). Elevated thoracic gas volume, decreased air conductance and maximal and expiratory pressure indicated possible decreased lung elasticity and impairments in the muscles and nervous system.

Exposed workers had similar red blood cell AChE activities compared to controls. Mean air chlorfenvinphos concentrations were below maximum allowable concentrations and ranged from 0.0008-0.0018 mg/m^3.

Exposure to carbamates and organophosphates has been associated with asthma and allergy in pesticide applicators and farm workers (Eskenazi et al. 1999). An increase in wheezing was associated with use of chlorpyrifos, malathion, and parathion and further analyses revealed a significant positive dose-response trend for parathion and chlorpyrifos (Hoppin et al. 2002). Odds ratios ranged from 1.12 to 1.50 for chlorpyrifos and parathion, respectively. Additionally, subjects who wheezed were more likely to have doctor-diagnosed asthma or have allergic reactions (as determined by a history of hay fever or eczema). The extent of adjustments made for confounding factors, such as exposure to animals, was unclear (Ernst 2002).

A study of Canadian farmers reported significant risk for asthma with use of carbamate insecticides (OR=1.8; 95% CI 1.1 - 3.1) compared to non-asthmatic farmers (Senthilselvan et al. 1992). Asthmatic farmers showed increased symptoms and lower pulmonary function values that indicated lung dysfunction and thus verified the claim of clinical asthma. Carbofuran, methomyl, and carbaryl were the most common carbamates used.

7.2 Children (no information)

8 Dermatological effects

8.1 Adult and 8.2 Children

Exposure to ChE-inhibiting compounds may result from contact of the chemical with skin. Numerous case studies document allergic contact dermatitis, erythema multiforme, and skin hypopigmentation occurring as the result of dermal exposure to OPs and carbamates, (Bhargava et al. 1977; Spiewak 2001; Spiewak and Stojek 2003).

Contact dermatitis can be classified as either an irritant or allergic syndrome. Classic symptoms such as redness, thickening of skin, flaking or blistering (Rice and Cohen 1996) are observed with both syndromes but allergic dermatitis is characterized by immune system responses. Farmers tended to have a higher prevalence for contact

allergy to carbamates than controls (reviewed in Spiewak 2001) and the OP, parathion, was experimentally shown to have a “very high allergising potential.” Studies, however, have indicated that sensitivity responses to low concentrations of pesticides may be uncommon with reactions occurring mainly in heavily exposed workers and risk may be higher for children.

Lisi et al. (1987) found that for people in agricultural, previous agricultural, and non-agricultural occupations, irritant and allergic reactions to OPs and the carbamate, carbaryl, were rare when exposed by patch test to 0.5 to 1% concentrations of the anti-ChEs. With higher concentrations of OPs, experimental studies on humans found that a patch test with a 10% dilution of malathion induced a contact dermatitis in 45% of the subjects and that individuals with the highest sensitivity to the 10% solution also reacted strongly to subsequently weaker concentrations (Milby and Epstein 1964).

In a field study of mosquito control workers occupationally exposed to malathion, few cases of sensitization were reported and those that did react were considered to be the most heavily exposed occupationally, according to the study’s exposure classifications (Milby and Epstein 1964). Additionally, IgE-mediated hypersensitivity reactions to malathion were not observed in California residents potentially exposed to a low dose of aerially applied malathion (applied at a rate of 2 mg malathion per square foot) during a medfly eradication program (Schanker et al. 1992). Antibody responses were not observed following standard skin patch tests with malathion and malathion-petroleum mixture however, irritant responses were noted in children at doses below the maximal amount of chemical applied. Low sample size (N=10) precludes conclusions regarding this study arguing that further study into widespread spraying regimes would be warranted. Additionally, all studies point out that reactions to contaminants in the pesticide application as well as carrier vehicles such as corn syrup may also contribute to contact dermatitis reactions and further study is warranted.

In addition to contact dermatitis, cases of erythema multiforme, a hypersensitivity reaction characterized by skin lesions, with exposure to the OPs, dimethoate and methyl parathion, have been reported (Spiewak 2001). In a study of cutaneous vascular reactions to a dermal application of malathion on humans, Boutsiouki et. al (2001) found that a prolonged cutaneous vascular response is produced on the skin and

is confined to the treatment area after a short-term and long-term exposure to a single low-dose of the OP. The authors suggest that this prolonged modulation of vasodilatory effects may be due to increased tissue levels of acetylcholine due to inhibition of AChE (Boutsiouki et al. 2001; Boutsiouki and Clough 2004).

9 Miscellaneous Effects

9.1 Adult

Bone

Cancellous or "spongy" bone area and biomarkers of bone formation were reduced in sheep dippers exposed long-term to organophosphates (Compston et al. 1999). Significant increases were noted in the eroded perimeter and significant decreases detected in mineral apposition rate and bone formation rate. The authors suggest that low bone formation may have implications in bone strength later in life. This study was part of a larger study that found bone density to be lower in sheep dippers than for controls (see Stephen et al. 1998). Experimental evidence has demonstrated the expression of AChE by osteoblasts and suggested that ACHE plays a role in bone formation (Genever et al. 1999). Exposure information from the Stephen et al. (1998) study as well as a study examining the bone formation and resorption by Vedi et al. (2000) were not available for this review.

Paraoxonase polymorphism

Serum paraoxonases are phosphotriesterase enzymes involved in the detoxification of OPs (Sogorb and Vilanova 2002) and are named according to the substrate chemicals they hydrolyze. Polymorphisms in the serum paraoxonase gene (PON1) can result in failure to detoxify paraoxon, a metabolite of parathion. Several polymorphisms occur in the promoter and coding regions of the gene (Humbert et al. 1993). A glutamine (Gln) substitution in coding region position 192 (the Gln homozygote) is one PON1 genotype associated with low paraoxonase activity because it metabolizes and detoxifies paraoxon slower than the Arg homozygote or Arg/Gln

heterozygote (Sogorb and Vilanova 2002) however, the Gln phenotype hydrolyzes diazoxon faster than the Arg phenotypes (Davies et al. 1996; Hernandez et al. 2003).

Paraoxonase activities were non-significantly decreased in greenhouse pesticide applicators exposed long-term to OPs compared to non-applicators (Hernandez et al. 2004). Decreased cholinesterase activity and increased acid phosphatase and beta-glucuronidase levels were also associated with pesticide exposure (Lee et al. 2003).

Chlorpyrifos-exposed farm workers with the Gln homozygote had a greater prevalence of symptoms associated with chronic toxicity than workers with the Arg homozygote genotype (Cherry et al. 2002). Plasma ChE activity and past acute exposure to OPs did not predict symptoms of chronic toxicity. Gastrointestinal distress, dizziness, headache, fatigue, and limb numbness and pain were considered symptoms of chronic exposure to OPs.

The PON1 Arg and Arg/Gln genotypes at coding region 192 were more frequent in farmers that reported ill health possibly from exposure to OPs via sheep dipping practices than healthy farmers (Steenland et al. 2000). Additionally, ill farmers were more likely to have decreased hydrolytic activity towards diazoxon, the metabolite of diazinon. Diazinon is mainly used in sheep dipping in the UK.

Termitacide applicators with a homozygous paraoxonase genotype at amino acid position 54 responsible for a low level of paraoxonase did not appear to have any significant differences in postural sway, motor or sensory function tests from the other subjects (Steenland et al. 1994). These subjects had two differences upon clinical examination, an abnormal gastroc soleus reflex and an abnormal Romberg test, which test the sensory systems involved in balance.

Experimental evidence has shown that paraoxon affects sperm quality and fertilization *in vitro*. A study of polymorphisms of PON1 detected decreased sperm quality in Chinese pesticide formulators exposed to ethyl-, methyl-parathion, and methamidophos and reproductive outcomes (Padungtod et al. 1999). The Arg homozygote, Gln homozygote, and Arg/Gln heterozygote genotypes were determined in the workers and exposure was measured by urinary metabolites and serum AChE activity. Parathion exposed workers, regardless of genotype, had significantly decreased sperm quality than unexposed workers. Within the exposed group, workers

with the Arg/Gln heterozygote and Arg homozygote had significantly lower sperm count, lower percentage of sperm with normal morphology, and lower sperm concentration compared to a reference population. The Gln homozygote also had decreased sperm concentration compared to controls. The exposed Gln homozygote had significantly higher sperm counts compared to the other exposed genotypes, a finding contrary to the hypothesis. The authors suggest several possibilities for this result such as a "healthy worker effect" eliminating Gln homozygotes that have experienced other types of health effects, small sample size, or additional polymorphisms that interact to influence sperm quality. A second finding was that exposed Arg homozygote and Arg/Gln heterozygote genotype workers had significantly higher serum and urinary LH levels than the unexposed Arg workers.

Decreased PON1 activity may also contribute to adverse effects of maternal OP exposure on fetal growth parameters (Berkowitz et al. 2004). A significant positive trend was observed for maternal PON1 activity and fetal head circumference in women with levels >11ug/L of the chlorpyrifos urinary metabolite, 3,5,6-trichloro-2-pyridinol (TCBy) indicating a small but significant decrease in head circumference with low PON1 activity and detectable urinary metabolite levels. No significant effects were found with PON1 activity or PON1 polymorphisms and birth weight. The authors point out that head circumference is correlated with brain size and both parameters are "predictive of IQ and cognitive ability."

Other enzymes

A higher frequency of "mildly poisoned" farmers had BChE variants compared to farmers with no clinical poisoning signs (reviewed in Lockridge and Masson 2000). "Poisoning" was determined by decreased red blood cell AChE. BChE is thought to provide a protective effect in humans by scavenging low doses of OPs.

Lymphocyte NTE was used in one study to assess the neurological effects of the cotton defoliants, merphos and DEF (S,S,S-tributylphosphorotrithioate), on farm workers (Lotti et al. 1983). Lymphocyte NTE was inhibited 40 to 60% however, whole blood AChE and plasma BChE remained within pre-exposure values after several weeks of exposure. No significant differences were detected in nerve conduction tests

designed to assess peripheral nerve function or in sensory tests. It was not known if or how lymphocyte NTE activity predicts NTE activity in nervous tissue.

Chronic fatigue

An association between chronic fatigue syndrome and exposure to OPs was determined in sheep dippers (Tahmaz et al. 2003). High levels of chronic fatigue syndrome symptoms were associated with higher exposure to OPs. Exposure was determined mainly from dermal exposure estimates for each dipping task, job task, and length of time on job. Symptoms were self-reported and included fatigue, depression, headache, muscle pain and weakness, memory impairment, confusion, and sleep disorder. Some subjects with low exposure had high symptom scores which the authors state may indicate multi-causal nature of the syndrome.

9.1 Children (no information)

Research Needs. Limited proof exists suggesting a hypersusceptibility of individuals with paraoxonase polymorphism to OP neurotoxicity (Lotti 2002). More research that takes polymorphisms into account is needed to clarify the risk for individuals with these differences to OP exposure (Brown and Brix 1998; He 2000; Lotti 2002; Kamel and Hoppin 2004; Alavanja et al. 2004b). Further research is needed to investigate the cause of chronic fatigue among farmers exposed to pesticides.

10 Ecological effects (no information)

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APPENDIX 2

Sublethal Effects of Exposure to Cholinesterase-inhibiting Pesticides: Vertebrate Wildlife

1 Neurological effects

1.1 Mammals

Grue et al. (1991) reviewed the cholinergic effects in mammals that result from pesticide-inhibited brain cholinesterase. In general, brain cholinesterase recovers to pre-exposure levels at a rate slower than plasma ChE; extent and rate of recovery depends on the specific compound to which the animal was exposed and the maximum level of enzyme inhibition. Sheets et al. (1997) investigated the effects of organophosphates (a spectrum of chemicals representing a 60-fold potency range) on tissue cholinesterase in rats and found clear dose-response enzyme inhibition in red blood cells (most sensitive), brain (least sensitive) and plasma. Females were more sensitive than males.

Information on sublethal effects of anti-cholinesterases in mammals derives largely from the human health literature. Symptoms of intoxication in wild mammals include vocalization, salivation, rapid heart beat, rapid breathing, tremors, induced tranquility, incoordination, difficult breathing, uncoordinated muscle contraction, lethargy, contraction of pupils, and head nodding (Grue et al. 1991).

Extensive studies with laboratory rodents indicate that impacts to learning, cognition, memory processes, circadian rhythms, sensory perception and brain activity result from depressed brain cholinesterase (Grue et al. 1991). Brain activity and sleep were disrupted in dosed monkeys; impacts lasted over a year. Neural damage was documented in rats leading to tremors, convulsions, and epileptic-type seizures. One study discovered a novel neurological lesion which involved minimal demyelination in spinal nerve roots. The lesion was believed not to be cholinergic in origin (Sheets et al. 1997).

The impact of cholinesterase inhibition on complex memory processes was unclear but differences apparently exist between effects on reference and working

memory. The authors suggested that even short-lived disruption of memory could have significant consequences to survival in wild mammals (Grue et al. 1991).

Large dose, single exposure leads to overall reduction in activity termed "behavioral slumps" which are sometimes followed by episodes of hyperactivity. Nostrandt et al. (1997) compared biochemical and behavioral endpoints in a dosed rat study and identified a threshold level of brain acetylcholinesterase inhibition (>60-70%) at which behavioral alterations including gait changes, depressed motor activity, and hypothermia were observed. This level of brain cholinesterase inhibition was not associated with overt symptoms of acute cholinergic toxicity (lacrimation, salivation, etc). Chronic exposure to anti-cholinesterases often produces a “tolerance” phenomenon which results from the down regulation of the hippocampal muscarinic acetylcholinesterase receptors (Bushnell et al. 1991).

Other documented behavioral endpoints include reduction in food and water intake (possibly mediated by prey aversion), and increased (cat study) or decreased (pine vole study) aggression (Grue et al. 1991). The authors concluded that the extensive physiological and behavioral literature developed by the early 1990s indicated the most important sublethal effects of cholinesterase inhibition were decreased food intake, hypothermia, and altered levels of reproductive hormones. In a later review, Sheffield and Lochmiller (2001) reported that “small mammals exposed sublethally to diazinon may face increased predation and experience aberrant behavior, learning disabilities, decreased endurance, motor coordination and immunocompetence, anorexia, and vision and hearing impairment in addition to hypothermia, cholinesterase inhibition, pathologic changes and reproductive impairments.”

Research Needs. Grue et al. (1991) report on the many studies linking brain cholinesterase inhibition with physiological and behavioral effects. Research using laboratory rodents has shown that there is reasonable agreement between physiological and behavioral effects and the degree of brain cholinesterase inhibition in the early phases of large dose, single exposure. Much effort has been invested in identifying "critical" levels of inhibition (inhibition below which animals tolerate without observable adverse effects) to predict effects in free-living wildlife. Later studies have found that

this approach may be of limited usefulness due to the variability in cholinesterase levels resulting from exposure, and the possibility of “hidden” (ie unobservable) effects.

Specific information needs include determining whether circadian disruption, known to occur in laboratory rodents, also occurs in wild mammals. In addition, more work is needed on the effect of cholinesterase inhibition on memory. Because OPs are not an homogeneous group of chemicals, Nostrandt et al. (1997) proposed a model research design to undertake a systematic evaluation of compounds and their effects on the relationship between cholinesterase and behavior. Specifically, investigations of anti-cholinesterases and neurobehavioral alterations that include variable test measures, tissues, doses and time assessments are needed.

1.2 Birds

Grue et al. (1997) reviewed acute, sublethal effects of OP and CB pesticides likely to reduce free-living populations of non-target wildlife in treated areas. These include hypothermia, effects on food consumption, and effects on reproduction. In addition to these specific effects, “depression,” “behavioral slumps,” and, in some cases, hyperactivity caused by exposure to OPs and CBs can also affect a “wide variety of behavioral outputs” (Grue et. al 1997:372), many of which have not been studied in relation to ecological effects.

Effects of cholinesterase-inhibiting compounds on predator-avoidance behavior have also been found. In a controlled laboratory study, Galindo et al. (1985) dosed bobwhite *Colinus virginianus* with methyl parathion and found lower brain acetylcholinesterase (AChE) activity in dosed quail that were subsequently captured by a domestic cat than in dosed bobwhite that avoided capture. Buerger et al. (1991) found greater predation on free-living dosed bobwhite than on controls. House sparrows *Passer domesticus* exposed to fenthion were captured by American kestrels *Falco sparverius* more frequently than non-exposed controls within the same flock (Hunt et al. 1992). Parsons et al. (2000, 2001) found cholinesterase levels were reduced and predation rates higher in birds using estuarine habitats in agricultural landscapes compared to birds in urban landscapes.

Gastrointestinal distress symptoms are common with OP/CB poisoning, and birds and mammals consequently reduce their food intake and lose weight. This may

be due to inability to eat (pesticide-induced anorexia; Grue 1982), avoidance of contaminated food (Grue 1982; Bennett 1989a; Bennett 1989b; Bennett 1994), or both. Food intake may be decreased due to reduced ability to perform food-providing behaviors (e.g. reduced nestling begging; Grue and Shipley 1984). Because cholinesterase-inhibitors can affect vision, learning, and memory (Grue et al. 1991), foraging behavior in the wild may be altered.

Migratory behavior, in particular spatial reference memory, can be altered by exposure to cholinesterase-inhibiting compounds. For example, adult white-throated sparrow *Zonottrichia albicollis* migratory behavior was impaired through sub-lethal dietary ingestion of acephate, while juvenile behavior was not, indicating that the effect was on memory (Vyas et al. 1995). There are reports of decreased singing behavior in both wild birds in treated areas (reviewed in Grue and Shipley 1984) and in captive males dosed with insecticides (Grue and Shipley 1984), as well as alterations in aggressive behavior (McEwen and Brown 1966).

1.3 Reptiles

A review by Pauli and Money (2000) found reptiles to be similar to birds and mammals in relative sensitivity to cholinesterase-inhibiting pesticides. Organophosphate insecticides significantly inhibited brain AChE and serum BChE in a dosing study with anoles. Intoxication included muscle twitching, tremors, irregular movements, quivering, convulsions, wriggling, gasping, and blinking. More than 30 days were required for brain cholinesterase to recover to pre-exposure levels. As poikilotherms, reptiles are more sensitive to exposure at certain times of day as activity is influenced by body temperature (Sanchez-Hernandez 2001). The authors speculate that the activation and detoxification systems of cold-blooded lizards are mediated through metabolic processes and thus effects are generally temperature dependent.

Bain et al. (2004) documented the prevalence of BChE in lizard plasma (75%), higher total cholinesterase levels in males than females, and detected no size or age effects on enzyme levels. Low dose exposure was associated with rapid enzyme recovery compared to high doses which required more than three weeks to return to pre-exposure levels. Dosed and control lizards showed similar capture rates, but the

strike rate of dosed lizards was greater than controls. The physiological basis for this result was not determined.

Research Needs. Several authors have advocated increasing the use of reptiles in ecotoxicological study of pesticide effects. Reptilian serum enzymes recover very slowly following exposure which constitutes a “stable” response conducive to non-destructive field monitoring (Sanchez-Hernandez 2001). Good concurrence between brain and blood enzyme thresholds has been shown in reptiles in studies explicitly linking exposure and effect.

Pauli and Money (2000) stressed the need for additional field studies to monitor effects in free-living animals, laboratory dose-response experiments, and observational studies. There are limited residue data from the field and virtually no information on carbamate effects. The most useful studies to date have combined experimental dose-response trials with field verification. High inter-individual variation in cholinesterase complicates ability to establish benchmark activity levels to which field cholinesterase levels can be compared. However reactivation analysis of tissue samples is proposed as a way to circumvent this problem using proportional effects on AChE and BChE (Bain et al. 2004).

1.4 Amphibians

A review of the amphibian ecotoxicological literature was performed recently by Cowman and Mazanti (2000). There is documented evidence that organophosphates reduce acetyl- and butyryl-cholinesterase in amphibians, cause paralysis, are myotoxic, have varying life stage effects, disrupt behaviors, and reduce activity. As with other vertebrates, amphibian plasma BChE appears more sensitive to pesticide exposure than brain AChE (Sparling et al. 1996). In Sanchez-Hernandez’s review (2001), evidence suggests that amphibians are more resistant to OP toxicity than mammals as a result of “intrinsic cholinesterase properties."

Research Needs. In general, there are a limited number of investigations on the toxicological effects of exposure to cholinesterase-inhibiting pesticides in amphibians (Sanchez-Hernandez 2001). The amphibian ecotoxicological literature reveals

substantial inter-specific variability in response to exposure which limits the ability to extrapolate across species on the basis of few studies. Larval frogs have been recently included in ecotoxicological laboratory assays (FETAX) stimulating additional research interest in ecotoxicology of amphibians. Specific research needs include quantifying the recovery time of enzyme activity following exposure, identifying serum esterases, quantifying enzyme responses to pesticide exposure and characterizing the mechanisms of activation and detoxification of pesticides in amphibians (Sanchez-Hernandez 2001).

1.5 Fish

A review of cholinesterase inhibition in fish by Zinkl et al. (1991) reports general effects of muscle paralysis (fin, operculum, respiratory), hyperactivity, equilibrium loss, flared pectoral fins, exaggerated opercular movements, overreaction to stimuli, terminal tetany and convulsions. In addition, decreased locomotion, disrupted stream positioning and feeding hierarchies, inhibited feeding, reduced predator avoidance and territorial behaviors (fewer fish defending territories) have been documented. Laboratory studies have shown that behavioral deficits also include inhibition of learning, and "depression." Brain AChE inhibition may persist for 40+ days after exposure.

Recent studies have shown that brain AChE inhibition at 70-90% is associated with mortality indicating that some species are able to tolerate high levels of inhibition (Fulton and Key 2001). Recovery for some species was greater than two months. Effects on swimming stamina have been observed when inhibition is greater than 80%. The expression of enzyme inhibition varies in different tissues. Anti-cholinesterases may inhibit neurite outgrowth and thereby adversely affect neurological development (studies reviewed in Fulton and Key 2001).

Fish muscle BChE was found to be much more sensitive to organophosphates than brain and muscle AChE (Sanchez-Hernandez 2001). Brain cholinesterase was also less sensitive to OP toxicity than plasma cholinesterase. Fish have relatively low levels of carboxylesterase which is thought to buffer animals to cholinesterase inhibitors. The relatively slow synthesis of new enzyme accounts for the documented slow recovery of brain AChE following exposure. Low level exposure resulted in decreased growth rate,

food consumption, food conversion efficiency, swimming activity, swimming speed, swimming distance, and disrupted activity budgets in fish (reviewed in Sanchez-Hernandez 2001).

A recent study by Sandahl et al. (2005) showed that exposure of juvenile coho salmon *Oncorhynchus kisutch* to chlorpyrifos resulted in altered swimming rates (spontaneous and feeding), latency to first strike, and total food strikes. Several of these effects correlated with brain AChE levels. The authors recommend using a benchmark concentration approach rather than traditional LOECs and NOECs to determine critical exposure thresholds. They found that chlorpyrifos significantly inhibits salmon brain AChE at <1ppb. OP mixtures are likely to be additive in effect and recovery may take up to 6 wk. Lethargy documented in salmon may be related to decreased feeding and possible resultant effects on growth, which is an important concern for commercial species (Sandahl et al. 2005).

Research Needs. Zinkl et al. (1991) provide many specific recommendations for collecting and interpreting fish exposure and effects data. They point to the need to establish the usefulness of AChE monitoring in tissues other than brain to diagnose pesticide poisoning. Fulton and Key (2001) suggest that brain AChE inhibition is an appropriate indicator for low level exposure because significant inhibition can be detected well below levels associated with mortality. They also recommend that a relatively simple 24-hr laboratory exposure model would work well in predicting field effects. Information needs include determining the relationship between AChE inhibition in various tissues and exposure, the significance of BChE inhibition, and the impact of AChE inhibition on neurological development (Fulton and Key 2001). Sanchez-Hernandez (2001) emphasizes the need for field validation of laboratory methods using enzyme biomarkers. Fish brain AChE is potentially useful as an indicator because the response is "stable" (i.e. recovery is in days to weeks). Another area that needs further investigation is the importance of sediment as a potentially highly significant route of exposure for some species (Sanchez-Hernandez 2001). To characterize low level exposure and sublethal effects, Sandahl et al. (2005) recommends controlled laboratory studies of behavior, low-level exposure and biochemical investigations of enzyme

activity. They emphasize the advantage of using behavior as an integrative response for determining the toxicological effects of pesticides, however this approach is limited by a lack of standardized behavioral endpoints.

2 Genotoxic effects

2.1 Mammals (no information)

2.2 Birds (no information)

2.3 Reptiles (no information)

2.4 Amphibians

Pesticide mixtures caused DNA profile changes in amphibians, and carbofuran specifically has been shown to be genotoxic (reviewed in Cowman and Mazanti 2000). The authors refer to genotoxic effects as being "hidden."

2.5 Fish

According to studies reviewed in Barr et al. (2004), carbaryl (study on Asian cichlid) and malathion (study on mammals) have documented genotoxic effects in fish. Significant DNA strand breakage occurred in the Sacramento sucker *Catostomus occidentalis* as a result of pesticide exposure. These field results were confirmed by mutagenicity tests with water collected after agricultural runoff events. The authors were unable to determine definitively what component of runoff caused DNA damage. They speculate that the components of run-off in their study most likely to have caused genotoxic effects are not OPs although carbaryl and malathion were detected (Barr et al. 2004).

3 Immunotoxic Effects

3.1 Mammals

In a review by Sheffield and Lochmiller (2001), research has shown mice to undergo disruptions in immunoglobulin concentrations in serum as a result of being exposed either *in utero* or through lactation to cholinesterase-inhibiting pesticides.

3.2 **Birds** (no information)

3.3 **Reptiles** (no information)

3.4 **Amphibians** (no information)

3.5 **Fish** (no information)

4 Carcinogenic effects

4.1 **Mammals** (no information)

4.2 **Birds** (no information)

4.3 **Reptiles** (no information)

4.4 **Amphibians** (no information)

4.5 **Fish** (no information)

5 Reproductive effects

5.1 Mammals

A review by Grue et al. (1991) identified that the effects of cholinesterase-inhibiting pesticides to the mammalian endocrine system ramify to metabolic effects. In addition, brain cholinesterase inhibition, neurotoxic effects and disruption of plasma glucose levels have been reported. In dosed mice, luteinizing hormone was reduced and evidence of stress associated with decreased food intake may lead to skewed sex ratio and decreased litter size (Grue et al. 1991).

Sheffield and Lochmiller (2001) provide a rather comprehensive review of the literature on reproduction and community/population effects of anti-cholinesterases on field and lab mammals. In laboratory rodents, OPs cause alterations to testes and sperm, altered sperm capacitation, and inhibited fertilization. Physiological mechanisms included “alteration of seminiferous epithelium and Leydig cells, decreased testicular weight, increased spermatid degeneration and reduced total sperm counts, decreased testicular sperm density, steroidogenesis, and enzyme activity, along with damage to the spermatogenic cells." In addition, "maternal weight loss and toxicity, decreased

birth and weanling weights, embryonic cholinesterase inhibition, an increase in stillbirths and neonatal deaths accompanied by a reduction in juvenile weight gain, slightly decreased uterine and ovary weights and mean number of embryos per female and significant decrease in stage of pregnancy, and significant mortality of pups before weaning." Transfer of OPs across the placenta, bioconcentration in fetal tissues, and lactational transfer of OPs have been documented. Hormone alterations include reduced follicle-stimulating hormone, luteinizing hormone, and testosterone. Additionally, reduced cholesteryl esterification has been documented with possible important adverse effects on steroid hormone production (Sheffield and Lochmiller 2001).

Research Needs. Grue et al. (1991) pointed out that little is known about the effects of cholinesterase inhibition on the reproductive hormones of wild mammals. In addition, more laboratory and field studies of reproductive effects following low level exposure are needed. Many studies have shown effects of cholinesterase inhibition resulting from high dose exposures, but few follow-up studies have attempted to discriminate effects based on lower doses. Consequently, little is known about the impact of sublethal cholinesterase inhibition on reproduction and survival.

5.2 Birds

Egg-laying can be reduced through exposure to cholinesterase-inhibiting compounds, through decreases in food consumption (Stromborg 1986; Bennett et al. 1991) and potentially through altered hormone levels (Rattner et al. 1982). Parental behavior can be altered through exposure, such as decreased nest attentiveness and defense. Studies in which only one parent was dosed showed that altered behavior in one mate can be compensated for by the other, and that effects of a single dose are temporary (Robel et al. 1983; King et al. 1984; Meyers et al. 1990). However, low level, chronic exposure may result in more severe effects, including nest abandonment and reduced hatching success (Bennett et al. 1991). These effects may increase if both mates are exposed. Post-fledging survival has not been studied often. In a study of European starling *Sturnus vulgaris*, differences in post-fledging survival were not detected between unexposed and birds exposed to a single, low level dose of

dicrotophos (Stromborg et al. 1988), even though dosed fledging weights were 4% below controls.

In the field, even in controlled dosing studies (e. g. Grue and Rattner 1993), effects of OP exposure on nestling survival can be difficult to determine. Most studies have not detected effects; however, two studies (Patnode and White 1991; Fluetsch and Sparling 1994) found population parameters reduced in songbird populations exposed to multiple pesticide applications.

Body weight at fledging can be affected by food intake as a nestling and is probably dependent on the frequency and intensity of exposure; some studies have failed to detect differences in fledge weights after dosing with OPs (Grue and Shipley 1984); others have found differences (Powell and Gray 1980). In addition to fledge weight, time to fledging can also be increased (Martin et al. 1991), a concern for migratory birds.

5.3 Reptiles

According to a review by Pauli and Money (2000), parathion has been found to accumulate in the eggs of lizards.

5.4 Amphibians

A review of the relevant literature by Cowman and Mazanti (2000) found that exposure to malathion adversely affects morphogenesis. Parathion and OP oxons can cause skeletal deformities. Cholinesterase-inhibiting insecticides are known to adversely affect development through neurotoxic effects to the circulatory system (carbaryl, carbofuran), myotoxicity (oxamyl), and metabolic pathways (primicarb).

5.5 Fish

According to Zinkl et al. (1991) fish exposed to diazinon at levels not affecting adult survival nevertheless experienced decreased egg production, inhibited ovarian development and reduced fry production. Other studies found decreased egg hatchability.

6 Metabolic Effects

6.1 Mammals

Cholinergic pathways in mammals mediate heat loss and production and therefore studies with laboratory rodents have shown adverse effects on thermoregulation as a result of cholinesterase inhibition (reviewed in Grue et al. 1991). There is evidence that anti-cholinesterases elicit a greater response when animals are not at rest; that activity exacerbates the response. According to Gordon (1994), human thermoregulatory response to anti-cholinesterases is hyperthermic rather than hypothermic which is the prevalent response in most other mammals including laboratory rodents.

6.2 Birds

Grue et al. (1997) reviewed numerous sublethal effects of cholinesterase inhibiting pesticides that could reduce wildlife populations. Hypothermia (reduction in body temperature) was associated with marked reduction in brain cholinesterase activity after OP/CB exposure in laboratory rats and humans (Gordon 1994). Hypothermia may be accentuated in birds by colder ambient temperatures (Maguire and Williams 1987; Martin and Solomon 1991) although lowered brain cholinesterase activity after OP exposure can also be accentuated by heat stress (Rattner et al. 1987). While hypothermia may actually decrease the rate of metabolism and therefore decrease amounts of toxic metabolites, it may also decrease an organism's ability to combat cold (Martin and Solomon 1991).

6.3 Reptiles

Bain et al. (2004) reported no metabolic endpoints during a dose-response study with lizards, although an increase in daytime body temperature may indicate a febrile response. Appetite was apparently unaffected by exposure potentially increasing risk of lizards in treated habitats; feeding would continue despite exposure.

6.4 Amphibians

Cowman and Mazanti (2000) that exposure to some anti-cholinesterases (including chlorpyrifos, malathion, temephos, and some OP mixtures) reduces temperature tolerance in amphibians. In addition, malathion reduces digestive

efficiency and carbaryl causes metabolic and digestive effects. Exposure to primicarb may cause adverse effects to the liver through hormone impacts and metabolic activation of liver enzyme systems.

6.5 Fish

Many studies have found no evidence that low cholinesterase inhibits growth in fish (reviewed in Zinkl et al. 1991). However, fish with low acetyl-cholinesterase have reduced stamina.

7 Respiratory effects

7.1 Mammals (no information)

7.2 Birds (no information)

7.3 Reptiles (no information)

7.4 Amphibians (no information)

7.5 Fish

Acute exposure of fish to pesticides results in gill muscle paralysis and asphyxiation (Zinkl et al. 1991). Other symptoms of respiratory distress as a result of cholinesterase inhibition include increased amplitude of respiration, bradycardia, and increased vascular resistance.

8 Dermatological effects

8.1 Mammals (no information)

8.2 Birds (no information)

8.3 Reptiles

Phosphamidon has been shown to cause body scales to shed and change in body color in agamas (reviewed in Pauli and Money 2000).

8.4 Amphibians

Cowman and Mazanti (2000) reported the following dematological symptoms in amphibians resulting from pesticide exposure: damage to melanophores (dimethoate), adverse effects on palate epithelium (chlorpyrifos), blisters (OP oxons), degeneration of gill epithelium (primicarb), pigmentation effects (propoxur).

8.5 Fish (no information)

9 Cytological Effects

9.1 Mammals

Knopper and Mineau (2004) investigated many physiological and reproductive endpoints and found no evidence for cytological effects although a subsequent power analysis revealed that sample sizes were too small to conclude that golf course pesticides cause no effects to resident small mammals. According to Grue et al. (1991), muscle necrosis occurs in mammals exposed to anti-cholinesterases, however this symptom is often reversible. Muscle fasciculation and weakness was associated with muscle necrosis.

9.2 Birds (no information)

9.3 Reptiles (no information)

9.4 Amphibians

Cytological effects in amphibians exposed to anti-cholinesterases included reduction of white and red blood cell numbers (fenitrothion), edema (OP oxons), and liver cell abnormalities (primicarb) (Cowman and Mazanti 2000).

9.5 Fish

According to Fulton and Key (2001), chlorpyrifos may affect bone strength in fish.

10 Ecological effects

10.1 Mammals

Sheffield and Lochmiller (2001) reviewed studies that indicate several cholinesterase-inhibiting insecticides (carbaryl, dimethoate, malathion, azinphos-methyl) exert adverse effects on mammal populations and communities including inhibited reproduction, population size reduction, and increased population turnover rates. Schauber et al. (1997) determined that recruitment, body growth and survival were all negatively impacted by field-applied azinphos-methyl. Field studies of the effects of diazinon on arthropods, vegetation, primary production and overall species diversity show that organophosphate insecticides can adversely affect ecosystem components and processes. Some authors suggest that broad-scale shifts of small mammal populations to favor herbivores over omnivores may be related to insecticide use.

Barrett (1988) found that carbaryl affected dominance relationships in small mammal communities through an effect on reproduction--one species experienced a delay in reproductive activity. In a related study, carbaryl altered sex ratios, increased interspecific competition, decreased weight of newborn mammals, and affected population growth rates. Sheffield and Lochmiller (2001) found that exposure to diazinon decreased the incidence of reproductive condition (especially in females) and thus decreased productivity of females. Diazinon severely reduced the occurrence of arthropods in treated plots. Other studies have shown an increase in weakened or dead arthropods in the diet of shrews and other mammals in exposed plots revealing a tendency to prey on affected arthropods, and thereby increasing risk of further exposure.

Research Needs. Sheffield and Lochmiller (2001) characterized the need to understand the impacts of chronic, low-level exposures to wild mammals as "urgent." Specifically, the authors recommend field studies designed to evaluate population, community, and ecosystem level responses to the subtle, sublethal effects of pesticide exposure.

10.2 Birds

Population-level sublethal effects are difficult to study, because the effects may be removed in time from applications and are more difficult to document than mortality events. Many studies show few if any effects of low level exposures in free-living wildlife populations (reviewed in Grue et al. 1997). However, a few have tracked populations and documented effects related to pesticide application over time. Patnode and White (1991) found reduced survival of eggs and hatchlings in passerines inhabiting orchards which were exposed to multiple applications of several chemicals. Fluetsch and Sparling (1994) found reduced nest success in mourning doves *Zenaida macrocoura* and American robins *Turdus migratorius* in conventional apple orchards compared to organic orchards.

10.3 Reptiles (no information)

10.4 Amphibians

Cowman and Mazanti (2000) report on habitat-mediated effects of pesticide exposure on amphibians in lentic versus lotic stream systems.

10.5 Fish (no information)

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