CHAPTER 21

Chronic Effects

This chapter is a departure from the format and content of the other chapters in this manual. Rather than discussing signs and symptoms of acute poisoning, this chapter addresses chronic (also known as persistent) effects that have been associated with pesticide exposure. The information in this chapter is designed to provide the practitioner with evidence for the better-established inferences for chronic effects of pesticides. This will offer some facility in the basic knowledge of chronic effects, allowing an approach to such effects, aiding the practitioner in answering questions from patients and the public, and providing a basis for further inquiry into areas of interest. Knowledge of chronic effects of pesticide exposure is evolving rapidly and providers will need to be alert to new findings as they become available. The chapter is not intended to be a comprehensive review; such reviews are referenced when they are available.

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In some cases, persistent effects may be those lingering after an acute poisoning, while in other situations, persistent symptoms or demonstrable physiological alteration may be associated with chronic, low-level or subacute pesticide exposure over time. Evidence linking pesticide exposure to chronic health conditions relies on observational epidemiological studies and/or standard chronic toxicity testing using animal models. For obvious ethical reasons, experimental studies with purposeful dosing of pesticides are not conducted in humans. Therefore, while cause and effect is not proven with any one epidemiology study, several well designed studies in different populations, alone or combined with inferential evidence from animal exposures, can strongly support the likelihood that a given association is in fact causal in nature.

This chapter covers chronic health conditions that may have an association with pesticide exposure. Neurological effects, particularly neurodevelopmental abnormalities in children, have been implicated with exposure to insecticides that have toxicological activity on the central nervous system. Numerous studies have examined the effects of pesticides on the development of cancer in children and adults. Several classes of pesticides have properties that mimic endocrine hormones and may affect multiple organ systems and functions including reproductive health and cancer risk. Recently, data have emerged indicating a potential relationship between certain pesticides and asthma. Chronic, low-level arsenic exposure is associated with multiple chronic disease endpoints including skin disease, neuropathy and cancer.

Evaluating Epidemiological Findings

The conditions that are traditionally used to consider an established statistical association as causal in nature were clearly articulated by Sir Bradford Hill in relation to epidemiological and other research on smoking and lung cancer. While only rarely will all conditions be met, the more that are met, the more confident one can be in the truth of a causal connection. The most important condition that must be met is a temporal relationship (*i.e.,* exposure precedes outcome). Other supportive conditions include the strength of effect (described as the size of the effect – *e.g.*, high relative risk or odds ratio), dose-response relationship (more exposure = more effect), consistency (*i.e.*, multiple studies with similar outcomes), biological plausibility (*i.e.,* the outcome can be explained biologically), experimental support (usually done on animal models), and analogy (similar exposures produce similar outcomes).[1]

Supportive Conditions:

- ***temporal relationship (most important)***
- ***strength of effects***
- ***dose-response relationship***
- ***consistency***
- ***biological plausibility***
- ***experimental support***
- ***analogy***

One of the most important and major weaknesses of many epidemiological studies is adequacy and reliability of exposure assessment.

Disease processes with low incidence represent a particular challenge to evaluate using epidemiological methods. Although adult cancers are relatively common, cancer in childhood is rare. Consequently, to adequately study a disease with a low incidence, case-control studies rather than cohort designs provide adequate power, but they are subject to greater recall and classification bias. One of the most important and major weaknesses of many epidemiological studies is adequacy and reliability of exposure assessment.[2,3] Studies that incorporate pesticide-specific exposure assessment, markers of biological mechanisms, objective assessment of outcomes and consideration of the influence of timing of exposure across the lifespan are needed to better define the relationships.

Differences between Children and Adults

When evaluating the effect of chronic, low-level exposures in humans, important differences in exposure sources and patterns between children and adults stemming from differences in physiology and behavior must be considered. From a developmental standpoint, children in the first few years of life spend a considerable amount of time on the floor, where residues following indoor application of pesticides (or outdoor application that may be tracked inside) accumulate.[4,5,6] Children have more frequent hand-to-mouth activity, which can be an added source of oral exposure.[7,8] Children ingest a larger amount of food and water per body weight than adults. For example, in the first year of life, infants may take in 100-150 cc/kg/day of liquids. For a 70-kg adult to ingest an equivalent amount of fluid, he/she would need to drink six 2-liter bottles of fluids a day. Dietary composition for children differs from that for adults. For example, U.S. children are much more likely to routinely ingest a variety of apple-based products on a daily basis, thus ingesting a greater amount of pesticide residue from apples than would the typical adult.[9]

NEUROLOGICAL AND NEURODEVELOPMENTAL EFFECTS

Many registered pesticides are specifically toxic to the central nervous systems of target pests including insects and mammals such as rodents. Neurotoxicity to animals has been a useful attribute for the development of pesticides for use as insecticides and rodenticides. It is not surprising that these agents also have neurotoxic effects on large mammals including humans. However, many other pesticides, including herbicides, fumigants and fungicides, have human neurotoxicant properties. This section summarizes those effects that may persist following acute exposure, as well as describes subacute and chronic effects following long-term exposure.

Chronic Effects Following Acute Exposure

Acute pesticide intoxications may leave recovered individuals with residual neurologic impairment, particularly if they result in multiorgan failure or nervous system hypoxia. Such outcomes are noted for individual agents elsewhere in this document. Several studies document that patients with a history of a single acute organophosphate or other pesticide poisoning are at risk of neuropsychiatric sequelae when examined as long as 10 years after the episode. These show significantly impaired performance on a battery of validated neuro-behavioral tests and, and in some cases, compound-specific peripheral neuropathy. The findings are subtle and, in some cases, identified only through formal neuropsychologic testing rather than as frank abnormalities on clinical neurologic exam.[10,11,12]

Certain organophosphates have caused damage to the afferent fibers of peripheral and central nerves. The mechanism of this type of toxicity is the inhibition of "neuropathy target esterase" (NTE). This delayed syndrome has been termed organophosphate-induced delayed neuropathy (OPIDN) and is manifested chiefly by weakness or paralysis and paresthesias of the extremities. In addition to acute poisoning episodes and OPIDN, an intermediate syndrome has been described. This syndrome occurs after resolution of the acute cholinergic crisis, generally 24-96 hours after the acute exposure, with signs and symptoms lasting from several days to several weeks.[13] It is characterized by acute respiratory paresis and muscular weakness, primarily in the facial, neck and proximal limb muscles. In addition, it is often accompanied by cranial nerve palsies and depressed tendon reflexes. Both this syndrome and OPIDN lack muscarinic symptoms. The intermediate syndrome appears to result from a combined pre- and post-synaptic dysfunction of neuromuscular transmission. These syndromes are described in greater detail in **Chapter 5, *Organophosphates***.

Effects Following Low-Level, Chronic Exposure

Evidence of neurodevelopmental toxicity arising from chronic, low-level exposure in gestational or early postnatal life is accumulating.

The effects of chronic, low-level exposures to pesticides on the nervous system are less well understood, but consistent evidence of neurodevelopmental toxicity arising from chronic, low-level exposure in gestational or early postnatal life is accumulating. One well established example of such effects is arsenic exposure. Neurologic symptoms are also common with chronic exposure. Peripheral neuropathy, manifested by paresthesia, pain, anesthesia, paresis and ataxia, may be a prominent feature. These effects may begin with the sensory symptoms in the lower extremities and progress to muscular weakness and eventual paralysis and muscle wasting.[14,15,16] Central nervous system effects may also occur, including mood changes such as depression, irritability, anxiety and difficulty concentrating. Additional symptoms include insomnia, headaches and neurobehavioral impairment.[16]

Low-Level Insecticide Exposure

Research on insecticide toxicity to the developing brain and neurodevelopmental outcomes has been reviewed.[17,18] Most studies focus on exposure to organophosphates and organochlorines. Since these pesticides have historically been and/or currently are in wide usage for household or agricultural pest control, exposures to the child and pregnant mother have been common. Since these exposures have been common and widespread over many years, it is not surprising that they would be studied and that association of effects from these agents would be among the first documented in epidemiological research. Little or no research has been done on the neurodevelopmental effects of other common agents, such as pyrethroids commonly used in households and agriculture or exposures to herbicides and fungicides used extensively in agriculture. One published longitudinal cohort study assessed prenatal exposure to household permethrin and piperonyl butoxide by maternal air monitoring and examination of maternal and cord blood plasma. When assessing neurodevelopment at 36 months, significant adverse impacts were observed for exposure to piperonyl butoxide (PBO), the most common synergist used in household pyrethroid products. No adverse associations were observed with exposure to the active ingredient permethrin. The authors note the more challenging task of measuring permethrin in biological and environmental samples compared to assessment of PBO and the need for confirmatory studies to clarify the roles of pyrethroids and PBO.[19]

The following sections review some of the data available for neurological and neurodevelopmental effects by age group of the studied population.

Longitudinal Studies in Preschool Children

Two longitudinal birth cohorts have observed *in utero* organophosphate exposure associated with abnormal behavioral effects at birth. Using the Brazelton Neonatal Behavior Assessment Scale (BNBAS) in young infants born to mothers living and working in the Salinas Valley of California, a rich agricultural setting, increases in abnormal reflex functioning among the infants were associated with increases in maternal organophosphate urinary metabolite concentrations in pregnancy. The effects were not associated with early postnatal measurement of maternal urinary metabolite concentrations.[20] Using a similar design in a cohort of urban women, abnormal BNBAS responses in newborns were also related to maternal organophosphate metabolite levels during pregnancy. In this study, polychlorinated biphenyls (PCBs) and DDE (the primary metabolite of the organochlorine insecticide DDT) were also measured in maternal blood in the third trimester. There was no observed association between DDE and BNBAS scores and a very weak beneficial association between PCBs in one area of the BNBAS: "range of state."[21]

Assessment tools for preschool children include the Brazelton Neonatal Behavior Assessment Scale (BNBAS) and the Bayley Scales of Infant Development (BSID) Mental Development Index (MDI).

Another birth cohort residing adjacent to a PCB-contaminated harbor in Massachusetts evaluated the relationship between cord blood, PCBs and DDE and performance on the BNBAS. This study observed consistent inverse relationships between BNBAS measures of poor attention and levels of PCBs and DDE in the newborn

infants.[22] In contrast, a similar study in an agricultural community failed to show a relationship between prenatal DDT/DDE exposure and BNBAS.[23] Prospective follow-up of these birth cohorts suggests that prenatal exposure to pesticides has long-term effects on children's neurodevelopment.[24,25]

In a study of children exposed to hexachlorobenzene (HCB) during gestation, a relationship at 4 years of age between HCB exposure and the California Preschool Social Competence Scale and an ADHD scoring scale was demonstrated.[26] The greater the exposure, the worse the performance on the Social Competence Scale and the higher the ADHD scores. In the Salinas Valley agricultural cohort, effects of organophosphate insecticide exposure assessed based on maternal urinary metabolite monitoring during pregnancy and postnatal urinary levels assessed in young children has been investigated. Higher rates of symptoms associated with pervasive developmental disorder have been observed in association with both prenatal and postnatal exposure. Prenatal exposure was also associated with lower performance scores on the Bayley Scales of Infant Development (BSID) Mental Development Index (MDI). In contrast, the investigators report postnatal exposure associated with improved MDIs in this cohort. While the reason for this discrepancy is not clear, one hypothesis is that children with higher MDIs may have increased exploratory behavior that influences their postnatal exposure.[17]

In this cohort, increased prenatal DDT was associated with decreases in psychomotor developmental index (PDI) assessed at 6 and 12 months of age but not at 24 months. Prenatal DDE levels were also associated with decreased PDI, but only at 6 months of age. Decreases in MDI at ages 12 and 24 months were related to DDT levels. No significant relationship to DDE was noted on MDI.[27]

Similar studies of neurodevelopment in younger children have been performed in urban birth cohorts. These demonstrate consistent adverse impacts of prenatal chlorpyrifos exposure on neurodevelopmental function in both the motor and mental functional domains at 3 years of life.[28,29]

Chronic Effects in School-Age Children

A body of research associates pesticide exposure with ADHD and autism.

A rapidly increasing body of research associates pesticide exposure with behavioral disorders including Attention Deficit and Hyperactivity Disorder (ADHD) and autism spectrum disorder (ASD), which manifest in preschool and school-age children. A case-control analysis using State of California data on autism diagnosis and a spatial-temporal map of pesticide applications found the risk for ASD was consistently associated with residential proximity to organochlorine pesticide applications occurring around the period of CNS embryogenesis.[30]

Follow-up of the Massachusetts cohort discussed in the prior subsection showed an association between prenatal organochlorine exposure and higher rates of ADHD at school age. This association was consistent for both PCBs and DDE.[31] A cross-sectional analysis from the 2000–2004 National Health and Nutrition Examination Survey (NHANES) linked a representative sample of U.S. children's urinary OP metabolites with diagnoses of ADHD.[32] Increased measures of ADHD behavior using the child behavior checklist (CBCL) in the Salinas Valley cohort found prenatal OP exposure associated with a >70 percentile score on the ADHD confidence index, (OR = 5.1, 95% CI, 1.7-15.7) and the composite ADHD indicator (OR = 3.5, 95% CI, 1.1-10.7). Other measures were also positive but did not reach statistical significance.[33]

The relationship of pesticide exposure on stunting (poor growth) and abnormal neurodevelopment was investigated in school-age Ecuadorian children.[34] Seventy-two children less than 9 years of age in 2nd and 3rd grades were studied via detailed physical exam and neurodevelopmental testing. Prenatal exposure to pesticides was determined by maternal occupational history. Many of these mothers worked in flower production

activities leading to extensive pesticide exposure. Concurrent exposure in the children was assessed by measuring red blood cell acetylcholinesterase (ACHe) levels and urinary organophosphate metabolites. Many of the children suffered from stunting related to poor nutrition *in utero* and early life. Both stunting and pesticide exposure were associated with decreased performance on the Stanford-Binet copying test, and some of the best scores on the copying test were from children without stunting or pesticide exposure. The independent variables of stunting and pesticide exposure appeared to each contribute independently to the adverse effect. Concurrent exposure to organophosphates affected only simple reaction time. This study provides evidence that poor nutrition, common in many pesticide-exposed children in developing countries or agricultural settings, may increase the adverse effects of pesticide exposure.

Several studies of school-age children with prenatal exposure have been recently published. Though the results are not identical, these studies suggest adverse neurodevelopmental outcomes persist in both urban and agricultural environments in children followed in longitudinal cohorts.[24,25,35] One of these studies reported that adverse neurodevelopmental effects were related to prenatal but not postnatal exposure.[25] The other studies did not differentiate between prenatal and postnatal exposure so it is not clear whether or not postnatal exposure contributes to the neurodevelopmental effects.

Studies of school-age children with prenatal exposure suggest adverse neurodevelopmental outcomes in both urban and agricultural environments.

Chronic Effects in Adults Following Low-Level Exposure

In adults, there has been considerable interest in the effects on the nervous system from chronic, low-level exposure to pesticides. A recent review of the evidence regarding the association between pesticide exposure and neurologic dysfunction listed 38 publications reporting various neurologic outcomes of exposure.[36] The studies focused on low-level exposures in adults and can be grouped into two broad categories. The first category is cross-sectional and longitudinal studies of occupationally exposed individuals, observing for a wide range of outcomes. The second focuses on similar populations in relationship to specific disease outcomes, most notably in the neurological area, Parkinson's disease (PD).

Among the first category of studies, an older cross-sectional study evaluated neurotoxicity in pesticide applicators exposed to organophosphates. In this study an increase in vibration sense threshold was thought to represent a loss of peripheral nerve function.[37] A more recent study of termiticide applicators exposed to chlorpyrifos suggested some degree of adverse effects on neurologic function in a subset of tests, specifically pegboard turning and postural sway tests. There was a significant increase in self-reported symptoms in the exposed group. These differences were more marked in the individuals with longer exposure, suggesting a long-term cumulative effect.[38]

A study of farmworkers, as a proxy for pesticide exposure, observed that farmworkers had poorer performance on several neurobehavioral tests compared to nonfarmworker controls. Most notably, farmworkers performed worse with tapping (coefficient [linear regression] = 4.13, 95% CI, 0.0-8.27) and postural sway (coefficient = 4.74, 95% CI, -2.2-11.7). These effects were strongly related to duration of exposure, whether observed in current or former workers.[39] A 5-year prospective longitudinal study of licensed pesticide applicators, the Agricultural Health Study (AHS), reported

symptoms at enrollment were strongly correlated with prior pesticide exposure. The symptoms reported, such as headache, fatigue, insomnia, tension, irritability, dizziness, depression and numbness in the hands and feet, were related to duration of exposure to pesticides prior to enrollment. The relationship was still observed after excluding individuals with histories of acute pesticide poisoning or other isolated events with high personal exposure. The strongest associations were with fumigants, organophosphates and organochlorines.[40] This same study reported an association between physician-diagnosed depression and three patterns of exposure to pesticides: acute physician-diagnosed poisoning (OR 2.57 95% CI 1.74-3.79), a high pesticide exposure event (OR 1.65 95% CI 1.33-2.05), and high cumulative exposure (OR 1.54 95% CI 1.16-2.04). It is of interest that the two latter patterns were documented by the study in the absence of a physician-diagnosed acute poisoning episode.[41]

Several studies have examined the potential association between pesticide exposures and Parkinson's disease (PD). A cohort of 238 persons in Washington State who were occupationally exposed to pesticide was compared to 72 non-exposed individuals. In this study, an association between pesticide exposure and PD was reported in the highest tertile of years of exposure (prevalence ratio 2.0, 95% CI, 1.0-4.2).[42] The AHS evaluated the association between the prevalence of physician-diagnosed PD and pesticide usage. The cases were compared to a cohort who did not report PD. Associations were noted with cumulative days of exposure at initial enrollment, frequent personal use of pesticides, and with a few specific pesticides (dieldrin, maneb, paraquat and rotenone).[43] Several postmortem studies of persons with PD have reported a positive association between tissue levels of dieldrin and PD. An evaluation of the biological plausibility of causation concluded that there was sufficient evidence for causation to warrant further evaluation and specific mechanistic studies in animal models.[44] Systematic reviews of the evidence for the association between PD and pesticide exposure have generally concluded that there is evidence for an association. However, at the present time, there is insufficient evidence to conclude that specific pesticide exposures are causative of PD.[45,46]

Following these systematic reviews, several additional studies have evaluated the relationship between PD and pesticides. A multi-country case-control study of pesticide exposure and PD observed a significant exposure between interviewer-administered questionnaire results showing high pesticide exposure and PD (OR = 1.41, 95% CI, 1.06-1.88).[47] Another multi-site case-control study evaluated the risk for PD in various occupations where exposure to toxicants, including pesticides, may occur. Risk of PD was associated with any pesticide use (OR = 1.99, 95% CI, 1.12-3.21). Higher risk was also noted for any of 8 other pesticides selected a priori that have a mechanism that may be associated with PD (OR = 2.2, 95% CI, 1.02-4.75) and for the herbicide 2,4-D (OR = 2.59, 95% CI, 1.03-6.48).[48] To address the difficulty of exposure assessment, a case-control study was conducted using a geographic information system (GIS) that integrated past subject addresses and California pesticide agricultural spray records to characterize exposure. They found that subjects who lived within 500 meters of a field sprayed with paraquat and maneb during the period 1974–1989 were four times more likely to have Parkinson's disease than the control group (OR = 4.17, 95% CI, 1.15-15.16).[49]

Animal studies offer evidence for the basis of a mechanistic association with some pesticides and the development of PD or Parkinsonian features. Two fungicides, mancozeb and maneb, have dose-dependent toxicity on dopaminergic cells in rats. Both the organic component of the fungicide as well as the manganese ion contributed to the toxicity.[50] Additional pesticides of high interest in the relationship with PD include 2,4-D, paraquat, diquat, permethrin, dieldrin and rotenone.[48,51]

[in studies of farmworkers in the Agricultural Health Study]

Symptoms such as headache, fatigue, insomnia, tension, irritability, dizziness, depression and numbness in the hands and feet [in adults] were related to duration of exposure to pesticides.

CANCER

Epidemiological data support associations for both adult and childhood cancer,[2,3,52,53] with occupational exposure playing a role in cancer development for both adults and children. However, the most common types of cancer vary for children and adults, and as such, associations between pesticides and cancer are treated separately in this section. As noted at the beginning of this chapter, one common problem in evaluating cancer and pesticide relationships, particularly in children, is the relative rarity of cancer diagnoses.[3,53]

Several meta-analyses and systematic reviews have been published on the association between pesticide exposure and cancer. In most instances, these analyses and reviews serve as the primary source of information for the sections below on childhood and adult cancers.

Classification Systems for Carcinogenicity in Humans

All active ingredients in pesticides are required to be tested in animals or using *in vitro* tests for their likelihood of causing cancer. The Health Effects Division of the EPA's Pesticide Program performs an independent review of all the available evidence to classify active ingredients according to their potential to cause cancer. The classification systems have changed in the past 30 years from using a letter grade system originally issued in 1986 to a method that uses descriptive phrases based on the weight of evidence. Under the older letter grade system, a grade of "B" was a "probable carcinogen," "C" was equivalent to being classified as "possibly carcinogenic," "D" was "Not classifiable as to human carcinogenicity" and "E" was classified as having "Evidence for non-carcinogenicity for humans."

The current system was proposed in 1996, revised in 1999, and released as a final report, *Guidelines for Carcinogen Risk Assessment* in 2005 by the EPA. The report uses one of five specific phrases to designate carcinogenicity: "carcinogenic to humans," "likely to be carcinogenic to humans," "suggestive evidence of carcino-

Data support associations between occupational pesticide exposure and cancers in both adults and children.

CARCINOGEN CLASSIFICATION SYSTEMS AT A GLANCE

1986 EPA Classification System
- Group B: Probable human carcinogen
- Group C: Possible human carcinogen
- Group D: Not classifiable as to human carcinogenicity
- Group E: Evidence of non-carcinogenicity for humans

2005 EPA Classification System
- Carcinogenic: Carcinogenic to humans
- Likely: Likely to be carcinogenic to humans
- Suggestive: Suggestive evidence of carcinogenic potential
- Inadequate: Inadequate information to assess carcinogenic potential
- Not Likely: Not likely to be carcinogenic to humans

IARC Classification System
- Group 1: Carcinogenic to humans
- Group 2A: Probably carcinogenic to humans
- Group 2B: Possibly carcinogenic to humans
- Group 3: Not classifiable as to its carcinogenicity to humans
- Group 4: Probably not carcinogenic to humans

genic potential," "inadequate information to assess carcinogenic potential," and "not likely to be carcinogenic to humans." This information is available only via an emailed report from the EPA website *http://www.epa.gov/pesticides/carlist*. Although the new guidelines have been in place since 2005, not all pesticides have been evaluated under the 2005 cancer guidelines. Active ingredients in pesticides classified using the older letter designation could be reevaluated on a case-by-case basis.

Another classification system for potentially carcinogenic chemicals was established by the International Agency for Research on Cancer (IARC). This system classifies chemicals using a 1-4 grading system. A classification of 1 indicates the chemical is carcinogenic to humans. A category of 2 is split between 2A (probably carcinogenic to humans) and 2B (possibly carcinogenic to humans). A category of 3 indicates the chemical is not classifiable as to its carcinogenic potential. Generally, this category is used when there is inadequate evidence in humans or animals to establish a cancer-causing relationship. Group 4 indicates that the chemical is probably not carcinogenic to humans.

The table at the end of this chapter lists selected pesticides and their classification of carcinogenicity.

The table at the end of this chapter lists selected pesticides and their classification of carcinogenicity. The list is not meant to be all inclusive, but an attempt to list agents that are more commonly used or have a higher likelihood of being carcinogenic in humans. It includes a number of chemicals that were classified under both the newer and older EPA systems. The list includes some pyrethroid insecticides, the residential use of which has increased as many of the organophosphates have been phased out.

Associations between Childhood Cancer and Pesticides

Relationships between childhood cancers and pesticides were summarized in two review articles, the first by Zahm and Ward in 1998, and an update published in 2007 by Infante-Rivard. The pediatric cancer types with the most compelling evidence for an association with pesticides are leukemia and brain tumors. Of note, in most of the studies reviewed, all forms of leukemia were considered in one group because of insufficient numbers of certain types of leukemia − *e.g.*, acute lymphocytic leukemia (ALL) or acute myelocytic leukemia (AML). There were a few studies of sufficient size that were able to evaluate ALL separately. Brain tumors are also reported as a group rather than by individual tumor types as they are even rarer than childhood leukemia.[3,53]

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Childhood Leukemia

Thirteen of the 18 studies reviewed in the 1998 Zahm and Ward article found an increased risk of leukemia following pesticide exposure. The most common reported exposure was not related to agricultural production but rather household insecticide use during pregnancy or during the preconception period. As mentioned above, mixing leukemia types and recall bias were among the limitations of these earlier studies.[53]

Infante-Rivard reviewed 12 more recent studies in 2007.[3] Most of these studies were larger and used higher-quality exposure assessment methodologies. Five found statistically significant associations between leukemia and pesticide exposure.[54,55,56,57,58]

Two included a detailed exposure assessment and were able to demonstrate a dose-response effect.[56,58] The largest study included 491 subjects and limited the outcome to acute lymphocytic leukemia. In this study, maternal residential use during pregnancy of herbicides (OR = 1.84, 95% CI, 1.32, 2.57), plant insecticides (OR = 1.97, 95% CI, 1.32-2.94), and "pesticides for trees" (OR = 1.70, 95% CI, 1.12-2.59) were all associated with ALL. Childhood exposure (from birth to diagnosis of ALL) to plant insecticides (OR = 1.41, 95% CI, 1.06-1.86) and herbicides (OR = 1.82, 95% CI, 1.31-2.52) were also significantly associated.[56] Two studies by the same author did not find an association between child's residence near agriculture-related pesticide application and childhood leukemia,[59] nor maternal residence near agricultural pesticide application at the time of their child's birth and childhood leukemia.[60]

Two additional meta-analyses have been conducted that further explore associations between pesticides and leukemia and support the previously described associations. The first meta-analysis examined parental occupational exposure to pesticides and leukemia and the second focused on studies of pesticides in the home and garden.[61,62] In the first study, maternal occupational exposure was found to be associated with leukemia, the reported ORs were 2.09, 95% CI, 1.51-2.88 for overall pesticide exposure; 2.38, 95% CI, 1.56-3.62 for insecticide exposure; and 3.62, 95% CI, 1.28-10.3 for herbicide exposure. No associations were found for paternal occupational exposure.[62] In the meta-analysis focused on exposure through home and garden uses of pesticides, 15 studies were included and exposure during pregnancy to unspecified pesticides, insecticides and herbicides were all associated with leukemia (OR = 1.54, 95% CI,1.13-2.11; OR = 2.05, 95% CI, 1.80-2.32; and OR = 1.61, 95% CI, 1.2-2.16, respectively).[61]

Childhood Brain Tumors

In the 1998 Zahm and Ward review, 12 of the 16 studies presented evidence of an association between pesticide exposure and childhood brain tumors, and seven of these reached statistical significance. Similar to the findings with leukemia, household use by the parent (home and garden and on household pets) were the most commonly associated exposures. The number of children with brain tumors is even fewer than that of leukemia, so all types of brain tumors were used to define "cases."[53]

As noted with leukemia, the body of evidence estimating an association between brain tumors and pesticides since 1998 is more robust, with larger studies and improved exposure assessment. Nine of 10 studies in the 2007 Infante-Rivard review demonstrated an increased risk of brain tumors following maternal and/or paternal exposure, with three of the studies reaching statistical significance.[63,64,65] For all studies, it appeared that prenatal exposure to insecticides, particularly in the household, as well as both maternal and paternal occupational exposure before conception though birth represented the most consistent risk factors.[63,64,65,66,67,68,69,70,71] The largest case/control study (321 cases) limited the case definition to astrocytomas and noted an OR of 1.9, 95% CI, 1.1-3.3, following maternal preconceptual/prenatal exposure to insecticides.[65] One cohort study followed 235,635 children and found an association between all brain tumors and paternal exposure to pesticides immediately before conception (RR = 2.36, 95% CI, 1.27-4.39.[63]

In summary, there is relatively consistent evidence for an increased risk of developing some types of childhood cancers following preconception and/or prenatal exposure to pesticides. The strongest evidence appears to be for ALL, the most common form of childhood leukemia. Maternal exposure to insecticides and paternal occupational exposure appear to carry the greatest risk.

There is evidence for increased risk of developing some types of childhood cancers following preconception and/or prenatal exposure to pesticides.

Associations between Pesticides and Cancer in Adults

Bassil et al. conducted a systematic review of cancer and pesticides, which included studies of children and of adults. Each study was evaluated for methodological quality by two trained reviewers using a standardized assessment tool with a high inter-rater reliability. Only studies with a global rating of 4 or higher were included in the review.[2]

Many of the studies evaluating relationships between cancers in adults and pesticides are conducted in the occupational setting. Associations between pesticide exposure and the development of leukemia and non-Hodgkin lymphoma were noted in most studies. Solid tumors of the prostate, pancreas, kidney and breast were among the more consistently reported findings in studies of adults. As was noted in numerous studies of childhood outcomes, ascertainment of whether exposure actually occurred and the amount of exposure are recurring weaknesses in adult studies.

Tumors of the prostate, pancreas, kidney and breast have been among the more consistently reported findings.

Non-Hodgkin Lymphoma and Other Hematopoietic Cancers

Of the 27 studies on non-Hodgkin lymphoma (NHL) that met quality criteria in the Bassil review, 23 found positive associations. Almost half of these studies were conducted in adult cohorts of various occupational groups including farmers, pesticide applicators, landscapers and those who worked in pesticide manufacturing. Ten of the 12 cohort studies reported a positive association, with four reaching statistical significance. One of the larger cohort studies demonstrated a relative risk RR of 2.1, 95% CI, 1.1-3.9. Eleven of the 13 case-control studies (excludes one positive study in children) also demonstrated an association between occupational exposure and NHL, with 7 reaching statistical significance. Multiple classes of pesticides were implicated.[2]

A separate meta-analysis of case-control studies examining the relationship between pesticide exposure and hematopoietic cancers was published in 2007. The authors reviewed 36 case-control studies. After excluding studies with methodological flaws or data concerns, a study that included non-hematopoietic cancers and a study written in Italian, 13 studies remained for analysis. The cancers assessed in the meta-analysis were NHL, leukemia and multiple myeloma.[72] The overall meta-OR for NHL was 1.35, 95% CI, 1.2-1.5. An increased risk for leukemia and multiple myeloma was also demonstrated, though both were just short of reaching statistical significance (OR = 1.35, 95% CI, 0.9-1.2 and OR = 1.16, 95% CI, 0.99-1.36). The authors also conducted a meta-regression to account for the heterogeneity among the studies. They found that exposure for longer than 10 years increased the risk for all hematopoietic cancers (mOR = 2.18, 95% CI, 1.43-3.35) and for NHL (mOR = 1.65, 95% CI, 1.08-2.51).[72]

As with other cancer epidemiologic studies discussed above, the major limitation was the lack of sufficient exposure information in many of the studies. Additionally, the cohort studies in the above meta-analysis only listed the class of pesticide and the corresponding OR (herbicides or insecticides) rather than the individual pesticide.[72] Other individual studies have demonstrated risks from certain specific pesticides. One well-designed cohort study reported risks associated with mecoprop, a chlorophenoxy herbicide.[73] Another study demonstrated risks from another chlorophenoxy herbicide − methyl phenoxyacetic acid (MCPA) − and from glyphosate.[74] Another study demonstrated a significant increased risk of NHL for subjects exposed to 2,4-D.[75] The Agricultural Health Study demonstrated a risk of developing leukemia following exposure to diazinon.[76]

Prostate Cancer

It has been suspected that pesticide exposure may be associated with prostate cancer. This association may be related to hormonally active pesticides, known as endocrine

disruptors.[77] Of the eight studies included in the Bassil review, all showed positive associations between pesticide exposure and prostate cancer.[77,78,79,80,81,82,83,84] A particularly well-designed study from the Agriculture Health Cohort included 55,000 men in Iowa and North Carolina. The authors found that farmers who applied pesticides had a small but significant increase in prostate cancer compared to the general male population in Iowa and North Carolina (standardized prostate cancer incidence ratio of 1.14 (1.05-1.24)). The study also evaluated risk to specific pesticides by inquiring about 50 different pesticides to which the farmer was "ever exposed" and found positive associations with carbofuran, permethrin, aldrin and DDT. Each OR was in the range of 1.25 to 1.38, all with statistically significant 95% CIs. However, among those who were in the "highest exposure category," a risk estimate of 3.47, 95% CI, 1.37-8.76, was noted for the fumigant methyl bromide. In addition, six pesticides (chlorpyrifos, fonofos, coumaphos, phorate, permethrin and butylate) were positively associated with prostate cancer in men with a family history of prostate cancer.[83]

Around the same time as Bassil's review was published, Mink et al. conducted a separate review article on prostate cancer. The two authors reviewed and independently assessed each study for inclusion or exclusion, and discrepancies were reconciled. The authors included 13 studies (8 cohort, 5 case-control) in their final review; however, they did not report the total number of studies reviewed and excluded. Despite some scattered positive findings in some of the studies they reviewed, the authors concluded there was no causal link between pesticides and prostate cancer.[52]

Two case-control studies by Settimi et al. evaluated prostate cancer among agricultural workers and included a comprehensive questionnaire to evaluate exposures as well as potential confounders. The first study evaluated numerous types of cancers and demonstrated an excess risk of prostate cancer among farmers and farmworkers (OR = 1.4, 95% CI, 1.0-2.1). When the analysis was limited to those who applied pesticides, the OR = 1.7, 95% CI, 1.2-2.6.[85] Assessment of pesticide classes and individual pesticides within classes demonstrated risk specificity for organochlorine insecticides. Elevated ORs for prostate cancer were found for "ever being exposed" to all organochlorines, DDT and dicofol and tetradifon. All ORs were statistically significant, and were slightly higher for those who reported greater than 15 years of exposure compared to "ever exposed."[78]

Another case-control study included data on exposure, diet, lifestyle and occupational factors. A positive association was found for exposure to pesticides, but the 95% CIs were wide. This may have been attributable to the small size of the study − 40 cases − and fewer reporting exposure to pesticides.[86] Two other case-control studies found no association with prostate cancer and pesticide use.[87,88]

Tumors of the Kidney

A recent review article evaluated renal cancer in adults (primarily renal cell carcinoma) following occupational exposure to pesticides. This review included four studies, each of which observed positive associations between pesticides and renal cancer.[89,90,91,92]

Other Associations between Human Cancer and Pesticides

Several different agents used as wood preservatives are currently classified as probable carcinogens. Pentachlorophenol (PCP) has been classified as a B2 (probable human carcinogen). In humans, it has been associated with soft tissue sarcoma and kidney and GI tract cancers; however, a causal link has not been established.[89,93] In animal data submitted to the U.S. EPA in support of re-registration of PCP liver tumors, pheochromocytomas and hemangiosarcomas were noted, supporting the B2 classification.[94]

Arsenic is well established as a human carcinogen. Studies show that arsenic exposure can result in epigenetic dysregulation including DNA methylation, histone

modification and microRNA expression. These alterations may play a mechanistic role in cancer development, but long-term studies have not yet confirmed this.[95] Primary cancers caused by arsenic include tumors of the lung, bladder and skin. On occasion, the hyperkeratotic papules described above have undergone malignant transformation. Years after exposure, dermatologic findings include squamous cell and basal cell carcinoma, often in sun-protected areas.[96]

A recent review of lung cancer and arsenic evaluated nine cross-sectional studies, six cohort studies, and two case-control studies. Despite the limitations of some of the study designs, the risk ratios and standardized mortality ratios were consistently high on nearly all of the studies. The evidence was most consistent at high exposure levels. The evidence was weak or lacking for developing cancer from exposure to lower levels of arsenic via contaminated drinking water (<100 µg/L).[97]

ENVIRONMENTAL ENDOCRINE DISRUPTOR EFFECTS

Data relating human endocrine disruption has become progressively stronger in supporting a role of pesticides. Extensive research continues in this area of investigation.

Over the last 15 years there has been increasing interest in the ability of environmental chemicals to disrupt endocrine systems. Many pesticides, pesticide vehicles and contaminants have endocrine-disrupting properties based on *in vitro* and animal studies. While data on human effects remain somewhat fragmentary and inconclusive, the weight of evidence from multiple lines of investigation appears to support the concern for human effects. These effects are discussed briefly below, along with the literature that supports these assertions.

The cellular biology of endocrine disruption is very complex and has been extensively reviewed. While the details are beyond the scope of this manual, the reader is directed to one of several reviews for more specific information.[98,99,100] As a group, exogenous agents including pesticides that affect the endocrine system have been labeled endocrine disruptive chemicals (EDCs). Several basic mechanisms have been identified, including direct interaction with nuclear receptors (NR), disturbance of NR signaling and changes in hormone availability. *In vitro* evidence of the latter exists for several pesticides, by alteration of P450 enzyme activity that influences the availability of steroid hormones either by increasing or decreasing the rates of metabolism. For instance, methoxychlor has been shown to interfere with 5'deiodinase in the liver.[101]

Animal Toxicology

Animal studies conducted in the laboratory suggest that some pesticides may disrupt the endocrine systems of a variety of animals. Vinclozolin, a fungicide with low acute toxicity, has been shown to be strong antiandrogen in rats when exposure occurs *in utero*.[102] Exposure of female rats to DDT has been shown to lead to precocious puberty.[103] Lindane has been shown to affect adrenal steroid synthesis.[104] There is considerable evidence that a variety of chemicals, including some pesticides, affect thyroid function in animals.[105,106]

Further support for effects comes from observations in wildlife. These studies represent the most robust evidence base for various endocrine effects from many different pesticide classes. Only a few examples are mentioned because of space constraints. A strong antiandrogen effect was shown in alligators in a lake in Florida in response to heavy contamination with pesticides including dicofol, DDT and DDE.[107,108] Likewise, a relatively strong association has been shown between the biocide tributyltin (TBT) and pseudohermaphroditism in 150 species of snails.[109] Marine mammals have been noted to have high levels of contamination with a variety of chemicals including pesticides such as DDT, DDE, mirex, dieldrin and chlordane metabolites.[110] These contaminants have been potentially linked to reproductive failure and other effects due to their endocrine action. For example, PCBs in seals and polar bears have

been shown to affect thyroid function. Interestingly, levels of PCBs and organochlorine pesticides are negatively correlated with testosterone levels in male polar bears, but PCBs are positively correlated with testosterone in female polar bears. Each of these testosterone alterations may contribute to reproductive changes.[111]

Evidence of Human Effects of Endocrine Disruption

A systematic review by the Endocrine Society has led to a scientific statement on endocrine disrupting environmental toxicants and notes potential for a variety of human effects, including alteration in mammary gland development and possible carcinogenesis, alteration in male fertility and testicular cancer, male urogenital malformations, prostate cancer, thyroid disruption and obesity.[112] This is a rapidly evolving field of investigation.

Human Outcomes Related to Pesticides

Precocious Puberty. DDE has been linked to precocious puberty in one study of immigrant females in Belgium.[113] Though estrogenic pesticides have been proposed as a contributor to premature thelarche, the evidence to date is not conclusive.

Altered Lactation. A negative correlation has been shown in several cohorts between DDE and duration of lactation.[114]

Breast Cancer. There is considerable interest in this outcome because of animal studies and the estrogenic activities of pesticides such as DDT, DDE, endosulfan and atrazine. Though atrazine is not a direct mimicker of estrogen, in some models it induces aromatase formation, which converts testosterone to estradiol.[115] This effect is not consistent in all cell lines or animal models. Despite the evidence that estrogen is a promoter of breast cancer, the role of these pesticides in breast cancer remains unclear at this time. A U.S. EPA review in 1998 concluded that the association between organochlorines and PCBs was not sufficient to conclude that they were likely causes of breast cancer.[116] A review by The Endocrine Society in 2009 concluded there was sufficient evidence that endocrine disruptors altered mammary gland morphogenesis in humans, making them more prone to neoplastic development.[112]

Female Fertility. There is limited evidence that female fertility may be decreased in women occupationally exposed to pesticides.[117] However, this evidence has not been linked to specific pesticide exposures.

Semen Quality. Decreased semen quality has been noted in individuals exposed to dioxins and PCBs, which are persistent organic compounds considered related to organochlorine pesticides.[112] Two agents, chlordecone and DBPC (dibromochloropropane), have been shown to affect male fertility by direct testicular toxicity at high levels of exposure.[118,119] However, there is not strong evidence for a relationship between organochlorine pesticides and semen quality. On the other hand, there is significant evidence from epidemiology that non-persistent pesticides may alter semen quality. This has been documented by the relationship between pesticide metabolites measured in men and their semen quality. Among the compounds implicated, some with stronger evidence than others, are alachlor mercapturate, atrazine mercapturate and some metabolites of diazinon, chlorpyrifos and carbaryl.[112,120,121,122,123,124,125,126,127,128]

Male Urogenital Tract Malformations. There is limited evidence that exposure to chemicals, including DDT, is associated with increased rates of cryptorchidism and hypospadias. In some studies there appears to be a weak association between these entities and maternal serum concentrations of these chemicals. There is also epidemiological evidence suggesting a relationship between parental or community exposure to pesticides and these malformations without clear evidence for which pesticides are responsible.[112]

Prostate Cancer and Prostatic Hyperplasia. It is well accepted that endocrine status strongly affects the development of both prostate cancer and prostatic hyperplasia. Both androgens and estrogen have been shown to promote cancer and hyperplasia of the prostate. Likewise, antiandrogens and surgical castration can arrest or regress prostate cancer. It seems reasonable then that endocrine-active pesticides would play a role in recent increases in the rates of these problems. Epidemiologic studies have shown increased rates of prostate cancer in farmworkers. A direct link has been shown between methyl bromide exposure and prostate cancer in farmworkers.[83,129] In addition, though arsenical pesticides are in limited use today, arsenic has been associated with prostate cancer.[129] See the *Cancer* subsection of this chapter for additional information.

Antiandrogens. The active ingredients vinclozolin and DDT, along with DDE (the primary metabolite of DDT), are known to be antiandrogens. The effect of DDE and DDT on hypospadias and cryptorchidism is described above, but other antiandrogenic effects of these agents in humans are unclear at this time.

Reproductive Neuroendocrine Systems. There is a considerable amount of evidence in laboratory animals that pesticides may disrupt reproductive systems and affect sexual behavior. As noted above, vinclozolin has been shown to alter sexual behavior in rats. However, there are limited human data to support such effects in children or adults.[112]

Thyroid Function. In the Agricultural Health Study, an association was shown between pesticide exposure and thyroid disease in female spouses of farmworkers. Increased odds ratios ranging from 1.2-1.5 for hypothyroidism were seen with organochlorines including aldrin, DDT, heptachlor, lindane and chlordane, although only chlordane (OR = 1.3) was statistically significant. Benomyl (3.1) and paraquat (1.8) also had significantly elevated rates of hypothyroidism. Interestingly, maneb/mancozeb appeared to be related to both hypothyroidism and hyperthyroidism.[130] In a study of Inuit adults, negative associations were observed between some organochlorine pesticides and thyroid hormone levels.[131]

The science is rapidly advancing in this field, as most studies in human populations have been published relatively recently. Endocrine disruption continues to be the subject of intense research at a pace suggesting significant discovery in the coming decade.

ASTHMA

The role of pesticides in the development of and/or exacerbation of asthma has been hypothesized and is under investigation. Pyrethrins have some potential as an allergic sensitizing agent, with reports of contact dermatitis, asthma and anaphylactic reactions occurring following exposure.[132,133,134] Organophosphates appear to have mechanisms that could impact the development or exacerbation of asthma. Toxicological studies demonstrated that subcutaneous injection of the organophosphates chlorpyrifos, diazinon and parathion caused airway hyper reactivity in guinea pigs via inhibition of M2 muscarinic receptors.[135,136] Additional studies suggest an organophosphate exposure may induce lipid peroxidation, which will result in oxidative stress.[137,138] Organophosphates may also play a role in the immunological sensitization of individuals to asthma. In a cohort of women farmworkers and their infants, maternal agricultural work was associated with a 26% increase in proportion of T-helper 2 (TH-2) cells, the phenotype associated with atopic disease, in their 24-month-old infants' blood samples. The percentage of TH-2 cells was associated with both physician-diagnosed asthma and maternal report of wheeze in these infants.[139]

Pesticides and Asthma in Adults

Some epidemiological evidence supports an association between occupational exposure in adults and asthma. A case-control study conducted in Lebanon evaluated 407 subjects with asthma. Those with any exposure to pesticides exhibited an association with asthma (OR = 2.11, 95% CI, 1.47-3.02). Occupational use resulted in an even higher association (OR = 4.98, 95% CI, 1.07, 23.28), although as noted, the intervals were wide, but significant.[140]

Several examinations of the Agricultural Health Study (AHS, discussed in the previous subsection on cancer) evaluated the relationship of asthma to various exposures occurring in farming occupations.[141,142,143,144] In one of these AHS studies, organophosphate insecticides including chlorpyrifos, malathion and parathion were all positively associated with wheeze in farmers. Chlorpyrifos, dichlorvos and phorate were associated with wheeze in the commercial applicators. Chlorpyrifos had the strongest associations in both groups, with OR = 1.48, 95% CI, 1.00-2.19 for farmers and OR = 1.96, 95% CI, 1.05-3.66 for commercial applicators.[143] The same group of authors identified in an earlier paper that driving diesel tractors was also associated with wheezing (OR = 1.31, 95% CI, 1.13-1.52).[145] In order to control for such exposures unique to farmers, a second paper from the Agricultural Health Study cohort limited analysis to 2,255 commercial pesticide applicators. The authors continued to observe associations with organophosphates including chlorpyrifos (≥40 days per year; OR = 2.4, 95% CI, 1.24-4.65) and dichlorvos (OR = 2.48, 95% CI, 1.08-5.66). The herbicide chlorimuron ethyl was also associated with asthma (OR = 1.62, 95% CI, 1.25-2.1).[144] A third analysis evaluated risk factors for women who lived and grew up on a farm. In general, growing up on a farm was found to be protective for having atopic or non-atopic asthma (defined as "doctor diagnosed, after 19 years of age"). However, any use of pesticides was associated with atopic asthma (OR = 1.46, 95% CI, 1.14-1.87). Those women who grew up on a farm but did not apply pesticides had the greatest protection from asthma (OR = 0.41, 95% CI, 0.27-0.62).[141] As with most epidemiological studies, there were some limitations of exposure assessment, including self-reported behaviors and exposures and misclassification.

Other studies have not found an association between pesticide exposure and asthma. One case-control study evaluated exposure of aerial pesticide applicators and community controls. Self-reported asthma rates were similar in the two groups. There was a slight decrease in lung function among aerial applicators, forced expiratory volume in 1 second (FEV1) <80% predicted (8% v. 2%, p = .02), but otherwise there was no difference between cases and controls of other measures of asthma or asthma severity.[146] Two studies assessed emergency department visits for asthma and hospital admissions following insecticide application to control for mosquitoes potentially carrying West Nile virus (WNV) in New York City. One study evaluated visits at a single hospital in the South Bronx after malathion and resmethrin application during a 4-day period. Using the previous year as a reference point, there was no increase in the rate of ED visits or in the severity of asthma presentations.[147] Another study evaluated the rates of ED visits in all public NYC hospitals during the 14-month period of October 1999 to November 2000. The authors looked at asthma visits in a 3-day period before and after spraying events took place, but did not find an increase in daily ED visit rates that corresponded to pesticide spraying.[148] A multicenter prospective study in Europe did not find any association with asthma and exposure to the fungicide ethylene bis dithiocarbamate.[149]

The role of pesticides including pyrethrins and organophosphates with respect to asthma is under investigation.

Pesticide Exposure and Asthma in Children

The few epidemiologic studies on the association between pesticide exposure and respiratory health in children have reported mixed results. In a cohort of rural Iowan children, multiple farm-related exposures were studied for any associations with several asthma-related outcomes ranging from doctor-diagnosed asthma to cough with exercise. Any pesticide use in the previous year was not significantly associated with asthma symptoms and prevalence.[150]

A cross-sectional study of Lebanese children was conducted using a randomly selected sample from public schools. The authors found increased risks of chronic respiratory symptoms, including wheeze, among children with any pesticide exposure in the home, exposure related to parent's occupation, and use outside the home. For any exposure to pesticides, they found an association with asthma (OR = 1.73, 95% CI, 1.07-2.90). Residential exposure, defined as having regional exposure or living near a treated field, had a stronger association, OR = 2.47, 95% CI, 1.52-4.01. Finally, occupational use of pesticides by a family member had the strongest association, OR = 2.98, 95% CI, 1.58-5.56. In the researchers' multivariable model, parental exposure persisted as a risk factor (OR = 4.61, 95% CI, 2.06-10.29). However, within the study population of 3,291, 407 had chronic respiratory disease. Of those, only 84 had medically confirmed asthma.[151] Main shortcomings include the cross-sectional design and self-reported symptoms versus more objective outcome assessment.

A nested-case control study of the Southern California Children's Health Study was conducted to evaluate the relationship between multiple environmental exposures, early life experiences and the occurrence of asthma. Among environmental exposures in the first year of life, "herbicides" and "pesticides" both had a strong association with asthma diagnosis before age 5 years (OR = 4.58, 95% CI, 1.36-15.43 and OR = 2.39, 95% CI, 1.17-4.89, respectively). Of note, cockroach exposure in the first year and later was also associated with having any type of asthma (OR= 2.03, 95% CI, 1.03-4.02). There were also elevated ORs for cockroach exposure in the first year of life with early persistent asthma and late onset asthma; however, the findings did not reach statistical significance.[152] This relationship is potentially important, since cockroaches are known to exacerbate asthma, and pesticides are likely to be used in homes with cockroach infestation.

Similar studies addressing the respiratory health implications for children for specific pesticide chemical types or groups are rare. However, some evidence is emerging for a link between metabolites of DDT and asthma risk.[153,154] One study of 343 children in Germany found an association between DDE levels and asthma (OR= 3.71, 95% CI, 1.10-12.56) as well as DDE levels and IgE levels >200 kU/l (OR = 2.28, 95% CI, 1.2-4.31).[153] In a prospective cohort study of children in Spain, wheezing at 4 years of age increased with increasing levels of DDE at birth. The adjusted RR for the children with exposure in the highest quartile was 2.63, 95% CI, 1.19–4.69. The use of doctor-diagnosed asthma (occurring in 1.9% of children) instead of wheezing as the outcome variable also resulted in a positive association, although it was not statistically significant.[154]

In summary, the available data regarding chronic exposure to pesticides and asthma and other respiratory health effects provide some suggestion of effect but are limited in number with highly variant designs for exposure assessment and outcome determination.

SELECTED PESTICIDES AND THEIR CARCINOGENIC POTENTIAL			
Name of Pesticide	**EPA Cancer Classification***	**Notes**	**IARC Classi-fication****
Acephate	Group C		
Alachlor	Carcinogenic (High Doses); Not Likely		
Arsenic		Not listed by EPA, all pesticide uses canceled	1
Benomyl	Group C		
Bifenthrin	Group C		
Butachlor	Likely		
Captafol	Group B		2-A
Carbaryl	Likely		3
Chlordane			2-B
Chlordecone			2-B
Chlordimeform	Group B		3
Chloroaniline, p-	Group B		
Chlorophenoxy herbicides	2,4-D listed as Group D	Several are Group C (*e.g.*, DCPA) or Not Likely (*e.g.*, MCPA)	2-B
Chlorothalonil	Group B		2-B
Cypermethrin	Group C		
Dichlorvos	Suggestive		2-B
Diclofop-methyl	Likely		
Diuron	Likely		
Ethoprop	Likely		
Fenoxycarb	Likely		
Ferbam	Likely		3
Fipronil	Group C		
Furiazole	Likely		
Heptachlor			2-B
Hexachloroethane			2-B
Hexythiazox	Likely		
Iprodione	Likely		
Iprovalicarb	Likely		
Mancozeb	Group B		
Maneb	Group B		3
Metam sodium	Likely		
Metofluthrin	Likely		
Metolachlor	Group C		
Mirex			2-B
Nitrapyrin	Likely		
Oryzalin	Likely		

SELECTED PESTICIDES AND THEIR CARCINOGENIC POTENTIAL, CONT.			
Name of Pesticide	**EPA Cancer Classification***	**Notes**	**IARC Classi-fication****
Oxyfluorfen	Likely		
Parathion, ethyl-	Group C	Methyl parathion is “Not Likely”	3
Pentachlorophenol	Group B		2-B
Permethrin	Likely		3
Piperonyl butoxide	Group C		3
Pirimicarb	Likely		
Propachlor	Likely		
Propoxur	Group B		
Resmethrin	Likely		
Thiacloprid	Likely	The most commonly used neonicotinod, imidacloprid, is Group E	
Thiodicarb	Group B		
Tolyfluanid	Likely		
Toxaphene			2-B
Trifluralin	Group C		3
Triphenyltin hydroxide	Group B		
Vinclozolin	Group C		

* The most recent EPA classification, whether from the 1986 or the 2005 system

1986 Classification
- Group B: Probable human carcinogen
- Group C: Possible human carcinogen
- Group D: Not classifiable as to human carcinogenicity
- Group E: Evidence of non-carcinogenicity for humans

2005 Classification
- Carcinogenic: Carcinogenic to humans
- Likely: Likely to be carcinogenic to humans
- Suggestive: Suggestive evidence of carcinogenic potential
- Inadequate: Inadequate information to assess carcinogenic potential
- Not Likely: Not likely to be carcinogenic to humans

**IARC Classification

Group 1: Carcinogenic to humans
Group 2A: Probably carcinogenic to humans
Group 2B: Possibly carcinogenic to humans
Group 3: Not classifiable as to its carcinogenicity to humans
Group 4: Probably not carcinogenic to humans

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