Invited Commentary

Pesticides and Human Reproduction

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Pesticides are potent molecules specifically designed to kill living organisms. They include insecticides, rodenticides, fungicides, and herbicides. More than 600 unique pesticide chemicals and thousands of commercial formulations are currently on the market, and more than 450 million kg are applied each year in the United States, 75% in agriculture.[1] Use of some highly toxic and environmentally persistent older pesticides such as lead arsenate, dichlorodiphenyltrichloroethane (DDT), and lindane has declined. However, use of newer pesticides such as the neurotoxic neonicotinoid insecticides, and the herbicide glyphosate—determined by the International Agency for Research on Cancer to be a "probable human carcinogen"[2]—has increased sharply. Glyphosate use in the United States has increased more than 250-fold, from 0.4 million kg in 1974 to 113 million kg in 2014, and further increases are projected as herbicide-resistant weeds continue to proliferate. Measurable levels of multiple pesticides are found in the bodies of nearly all Americans.[3] Consumption of pesticide-treated fruits and vegetables is the principal route of exposure.

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Acute, high-dose pesticide exposures have been known for decades to cause clinically obvious and sometimes fatal poisoning; the World Health Organization estimates that as many as 25 million agricultural workers worldwide experience unintentional pesticide poisonings each year.[1] More recently, understanding has increased that acute poisoning is only the visible tip of a large iceberg and that pesticides are capable of causing a wide range of asymptomatic effects at levels of exposure too low to produce overt signs and symptoms. This concept of *subclinical toxicity* had its origins in studies of asymptomatic losses of intelligence and alterations of behavior in children with low elevated blood levels of lead.[4] It is based on the recognition that there exists a dose-related continuum of toxic effects ranging from clinically obvious poisoning at high exposure levels down to functional alterations at lower exposures. The number of persons affected by subclinical toxicity is typically much larger than the number who experience acute poisoning.

Recognition of the subclinical toxicity of pesticides has been made possible by advances in laboratory science and epidemiology. Laboratory advances have led to development of increasingly sensitive and specific biomarkers of exposures and health outcomes. And beginning with the Framingham Heart Study, epidemiologists have become skilled at conducting multiyear prospective studies that observe persons with varying levels of exposure and examine them repeatedly over long periods. In these studies, each participant serves as his or her own control and slight decrements in function can be measured with great reliability. A further advantage is that environmental exposures can be measured in real time as they actually occur. The subclinical effects of pesticide exposure that to date have been most carefully evaluated in prospective studies are deficits in neurobehavioral development associated with in utero exposures to chlorpyrifos, a widely used organophosphate pesticide.[5]

Although subclinical effects can be subtle and their links to environmental exposures detected only through specialized testing in well-designed studies, they can nonetheless cause serious and lasting damage. Moreover, when subclinical toxicity is widespread, it can impair the health of entire populations. The classic example of the societal impact of widespread subclinical toxicity is seen in the 3- to 5-point reduction in population mean IQ and the lifelong disruptions of behavior in the millions of American children exposed to lead between 1922 and 1975 when thousands of tons of lead were added each year to gasoline in the United States.[4]

Reproductive injury is a dimension of pesticide toxicity that has come under increasing scrutiny. High-dose exposures to certain highly toxic, older-generation pesticides such as chlordecone (Kepone) and 1,2-dibromo-3-chloropropane (DBCP) were recognized decades ago to be capable of causing severe reproductive injury with infertility and azoospermia in occupationally exposed males.[6] Direct injury to the gonads was the apparent mechanism. More recently, a range of sensitive and specific markers of reproductive function have been developed. These new markers allow sophisticated analyses of the effects of pesticides on reproduction at low exposure levels.[7] Some of the recently recognized reproductive effects of pesticides reflect direct injury to the testes and ovaries. Others appear to be mediated through endocrine disruption by pesticide chemicals that can mimic or block the actions of naturally occurring hormones.[8] DDT is an example of a potent endocrine disruptor that nearly caused extinction of the bald eagle and the osprey through interference with estrogen function.

The study in this issue of *JAMA Internal Medicine* by Chiu et al[9] of the association between dietary pesticide exposure and decreased female fertility is an elegant example of a prospective epidemiological study that uses sophisticated biological markers to identify a subclinical effect of pesticide exposure on human health. In this study of women attending a fertility clinic, the authors found that regular consumption of conventionally grown, pesticide-treated fruits and vegetables was associated with increased risk of pregnancy loss, while consumption of organic fruits and vegetables significantly reduced risk of pregnancy loss and increased fertility. A range of potentially confounding factors was considered, and none changed the study outcome. All dietary pesticide levels were within the range of typical American exposure.

What are the implications of this study? It comes at a time when multiple lines of evidence suggest that human fertility is on the decline and that the frequency of reproductive impairment is increasing. Sperm counts in Western countries have

fallen by 54% since 1973.[10] The Centers for Disease Control and Prevention reports that incidence of hypospadias has more than doubled. Incidence of testicular cancer has increased by 55% in the United States since 1970. These changes are too rapid to be of genetic origin. They are clinically obvious findings, and thus improved diagnostic recognition is not a likely explanation. Environmental exposures are therefore almost certainly involved. To be sure, this study does not claim that pesticides actually caused increased rates of reproductive loss in women. Nor does it identify a specific pesticide or class of pesticides responsible for decreased female fertility.

The observations made in this study send a warning that our current laissez-faire attitude toward the regulation of pesticides is failing us. We can no longer afford to assume that new pesticides are harmless until they are definitively proven to cause injury to human health. We need to overcome the strident objections of the pesticide manufacturing industry, recognize the hidden costs of deregulation, and strengthen requirements for both premarket testing of new pesticides, as well as postmarketing surveillance of exposed populations—exactly as we do for another class of potent, biologically active molecules—drugs.

How should physicians respond to these findings? The answer is to educate. Educate our patients about the hidden dangers of pesticides in the modern environment and urge reductions in exposure wherever possible. Encourage our patients to eat organic. And educate elected officials and other policy makers about the hazards of pesticides—make them realize that pesticides are not merely a regulatory issue or an environmental problem, but that in fact these potent chemicals can have powerful effects on human health that need to be intelligently confronted.

ARTICLE INFORMATION

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