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PESTICIDES MATTER

A PRIMER FOR REPRODUCTIVE HEALTH PHYSICIANS



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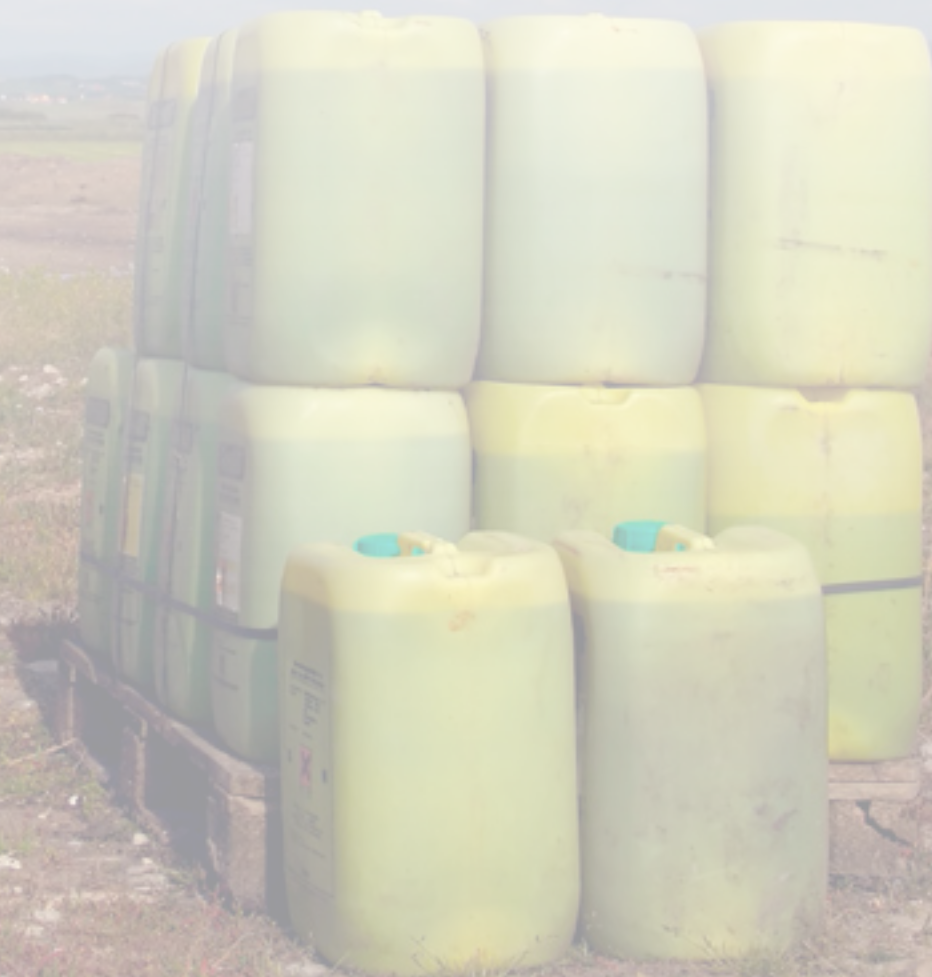
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ABSTRACT

Pesticides are substances or mixtures intended to prevent, destroy, repel, or mitigate pests. They are also widespread environmental chemicals found in food, water, air, dust, and soil. Virtually every pregnant woman in the U.S. has measurable levels of pesticides in her body.(1) Everyone of reproductive age is potentially vulnerable to pesticide-related adverse health consequences, and women and men exposed at work and in agricultural communities are at even greater risk.

Pesticide exposure is linked to adverse reproductive and developmental health outcomes that can occur throughout the life course of males and females. Pesticide exposures can interfere with all developmental stages of reproductive function in adult females, and have been associated with sterility in males, spontaneous abortion, diminished fetal growth and survival, as well as childhood and adult cancers. This paper summarizes recent comprehensive reviews of the evidence for these and other adverse reproductive health outcomes that have been associated with exposure to pesticides and provides an overview of mechanisms of pesticide toxicity.

The adverse reproductive and developmental health consequences of pesticide exposure can be prevented. This paper provides guidance to reproductive health care professionals about how to recognize, diagnose and report pesticide illnesses and advise patients how to avoid pesticides whenever possible. To this end, a patient brochure accompanies this white paper. The paper also offers recommendations for how reproductive health professionals can advocate for improved institutional and public policy that will help reduce pesticide exposures for the whole population.



DEFINITION OF PESTICIDES

Pesticides are substances or mixtures intended to prevent, destroy, repel, or mitigate pests. Pests are defined as living organisms that inhabit where they are not wanted or that cause damage to crops, humans or other animals.(2) According to the U.S. Environmental Protection Agency (USEPA) there are currently 1,234 active pesticide ingredients and 19,881 pesticide products (including restricted use¹) registered for use in the U.S.(3)

Pesticides are categorized according to chemical class and target organism. For example, atrazine, widely used on corn, is a triazine and an herbicide (weeds). Chlorpyrifos, also used on corn, is an organophosphate and insecticide (insects). Permethrin, a synthetic pyrethroid, is a multipurpose insecticide, acaricide (mites), pediculicide (lice) and insect repellent. Every chemical class of pesticides has at least one agent capable of affecting a reproductive or developmental endpoint in laboratory animals or people.(4)

Pesticide compounds are combinations of “active” and “inert” ingredients. Active ingredients are the components of the formulation intended to kill, repel, attract, mitigate, or control the target organism. The USEPA regulates pesticide usage based on the toxicity of the active ingredients. “Inert” ingredients are defined as any other product ingredients that are not the “active” ingredients. Inert ingredients are used to enhance the efficacy, absorption, or shelf life of the active compound (i.e., solvents, stabilizers, spreaders or stickers, preservatives, surfactants, defoamers, etc.). Inert does not imply non-toxic. In fact, inert ingredients can increase the toxicity of pesticide formulations. For example, animal studies have demonstrated that some inert chemicals are toxic to placental cells and can decrease heart rate, blood pressure, and liver mitochondrial activity.(5) Toxicity testing has also shown that the active and inert ingredients of the popular pesticide product Roundup® work synergistically and have greater endocrine disrupting effects than the active ingredient, glyphosate, alone.(6)

PESTICIDE USAGE

Pesticides are applied in large quantities in agricultural, community and household settings. In 2007, over 1.1 billion pounds of pesticide active ingredients were used in the U.S.(7) Agriculture accounts for approximately 75 percent of U.S. pesticide usage.(8) As of 2007, glyphosate, atrazine and metam sodium were the top three most widely used pesticides in agriculture by pounds applied.(7) Non-agricultural household and community uses of pesticides include weed, insect, and rodent control around homes, gardens, parks, golf courses, along roads and rights-of-way, and in commercial or industrial areas.(9) Some pesticides approved for agricultural use are also used to treat human ailments such as head lice or scabies. The USEPA estimates that almost 75 percent of U.S. households use pesticides.(7)

The types and diversity of toxic chemicals used as pesticides has changed and expanded over time. The use of chemical pesticides began in the 19th century with sulfur compounds, and near the end of the 19th century the first arsenical compounds were introduced.(10) In the 1940s environmentally persistent chlorinated hydrocarbons such as dichlorodiphenyltrichloroethane (DDT) were introduced. In 1972, DDT was banned in the U.S., and organophosphates, carbamates, and synthetic pyrethroids replaced the organochlorines for U.S. residential insect control.(10) Beginning in 2000, the USEPA restricted household use and retail sales of widely used organophosphate pesticides based on its finding that chlorpyrifos and diazinon were an exposure risk to children.(11,12) The use of synthetic pyrethroids for household pest control subsequently increased and these chemicals are currently widely available to consumers. However, synthetic pyrethroids have not been reevaluated under safety standards developed in the mid-1990s,(13-16) and they have recently been linked to adverse child neurodevelopmental health outcomes.(17)

1. The “Restricted Use” classification restricts a product, or its uses, to use by a certificated pesticide applicator or under the direct supervision of a certified applicator. See: <http://www.epa.gov/opprd001/rup/>

PESTICIDE EXPOSURE

Pathways

Pesticides can be ingested, inhaled, or dermally absorbed through contact with treated surfaces. The pathways of pesticide exposure include food, water, air, dust, and soil.

For example:

- **Food** - Pesticides are commonly present in food. In 2006, the U.S. Department of Agriculture (USDA) measured pesticide residues in 62.1 percent of fruits and vegetables, 30 percent of peanut butter samples and 19 percent of bottled water samples tested.(18) Two or more pesticides were detected in more than one in four (26.2%) food samples tested by the USDA. Typical U.S. food consumption patterns can result in potentially high cumulative exposure to pesticides. Pesticide residues in the types and amounts of foods and beverages typically consumed by the U.S. population can lead over time to exposures that are high enough to increase the chance of children developing cancer and other chronic diseases.(19) It is estimated that 40 percent of U.S. children have enough cumulative exposure to pesticides to potentially impact their brains and nervous systems.(20)
- **Air** - Pesticides drift away from the site of application and can travel great distances in the air. A 2003 analysis of California Department of Pesticide Regulation and the California Air Resources Board pesticide air monitoring data documented that several widely used pesticides are regularly found far beyond their agricultural application sites. Specifically, the report found that pesticide air concentrations near application sites (within 30–500 feet) exceeded acute Reference Exposure Levels (RELs) for methyl isothiocyanate (MITC), chlorpyrifos, and diazinon for adults and children, and molinate for children. Ambient, seasonal concentrations in areas of high use but not adjacent to an application site surpassed sub-chronic RELs for methyl bromide and MITC for adults and children, and for chlorpyrifos, diazinon, and molinate for children.(22)
- **Water** - A comprehensive and representative water quality assessment conducted by the U.S. Geological Survey between 1992 and 2001 detected one or more pesticides 90 percent of the time in streams draining watersheds with agricultural, urban, and mixed land uses; 20 percent of the time at least ten pesticides were detected.(9) A 2010 report by the Natural Resources Defense Council found that 80 percent of drinking water samples from 153 public water systems in the U.S. were contaminated with the pesticide atrazine.(21) Furthermore, of the 20 watersheds sampled in 2007 and 2008, all were contaminated with atrazine and 16 had average concentrations above the level of harm for plants and animals.(21)
- **Household surfaces and dust** - Recent research shows widespread household presence of pesticides, many of which have been banned for decades. For example, 74, 42, and 13 percent of 500 American homes randomly sampled between 2005 and 2006 had detectable levels of chlordane (banned 1988), DDT (banned 1972), and heptachlor (banned for commercial sale 1988), respectively.(23) Other studies from Ohio and North Carolina found pyrethroid pesticides in every dust sample collected from homes and day care centers.(24, 25)

Documentation of widespread environmental exposure is reinforced by population-based studies of pesticides that have found virtually every pregnant woman in the U.S. has measurable levels of pesticides in her blood.(1) Pesticides have also been detected in urine, (26) semen,(27) breast milk,(28, 29) ovarian follicular fluid,(30, 31) cord blood,(32, 33) and amniotic fluid.(34, 35)

Vulnerable Populations

Pesticide exposure is a two-fold reproductive and developmental health concern: (1) exposure is ubiquitous among pregnant women (Figure 1) and (2) the fetus, infants, children, and exposed workers bear a disproportionate burden of exposure.(10, 36) Populations that can be at particularly high risk of exposure are:

Pregnant women, infants and children who live in poverty in densely populated inner cities. The majority (85%) of pregnant women in an urban cohort of 571 Dominican and African American women in New York City reported using some form of pest control during pregnancy,(37, 38) and 54 percent reported using higher-toxicity methods, such as canned sprays, pest bombs, and sprays used by exterminators. (39) Moreover, among infants in this cohort born before the residential ban of chlorpyrifos in the U.S., the amount of chlorpyrifos in umbilical cord blood at birth was significantly inversely associated with the baby's birth weight and length,(40) and the child's mental and motor development at 3 years of age,(41) independent of neighborhood context.(42)

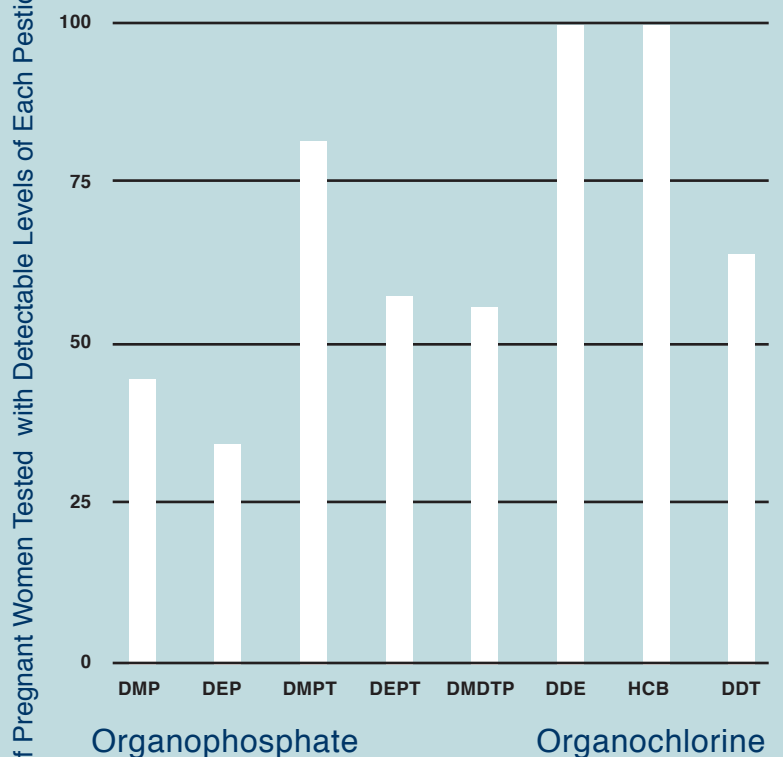
Pregnant women, infants and children who reside in agricultural communities. Pregnant women in a largely agricultural cohort in the Salinas Valley of California had substantially higher levels of pesticides in blood and urine compared to levels measured in non-pregnant women 20 years or older in the U.S. population overall.(43) Studies of the children of these women documented adverse impacts of prenatal pesticide exposure on child mental development. (44-46) Other studies of women who were exposed to pesticides during pregnancy further confirm the neurodevelopmental toxicity of pesticide exposure. (17, 47)

Occupationally exposed women and men. Measured levels of organophosphate pesticide metabolites among occupationally exposed populations exceeded the levels seen in the general population by 50 to 100 fold.(48) A 2008 study documented that 73 fieldworkers picking strawberries three days after the fruit had been sprayed with malathion had median creatinine-adjusted malathion metabolite levels

that were 60 to 395 times higher than U.S. national averages for adults, depending on the sampling day. (49) These levels occurred despite adherence to the re-entry interval (12 hours post application) and overall use of protective gear recommended by the Worker Protection Standard. The importance of preventing workplace exposures to pesticides and other substances with reproductive and developmental toxicity is underscored by the fact that more than two-thirds of working men and women are of reproductive age, and recent trends show a majority of U.S. children are born to working mothers.(50)

Figure 1.

Pesticide Exposure Among Pregnant Women in the U.S. (1)



Data for pesticide analytes from a subsample of 268 pregnant women in NHANES 2003-2004, a nationally representative sample of the US population.

DMP Dimethylphosphate	DMDTP.... Dimethyldiophosphate
DEP Diethylphosphate	DDE Dichlorodiphenyldichloroethylene
DMPT Dimethylthiophosphate	HCB Hexachlorobenzene
DEPT Diethylphosphate	DDT Dichlorodiphenyltrichloroethane

REPRODUCTIVE HEALTH OUTCOMES OF PESTICIDE EXPOSURE

Pesticide toxicity can manifest in a wide range of adverse reproductive health outcomes that can occur throughout the life course of both men and women (See Box 1, which describes the evidence). California's Proposition 65, a list of chemicals known to the state of California to cause reproductive or developmental effects, includes 42 pesticides.(51)

The weight of the epidemiologic evidence linking adverse reproductive health outcomes and pesticide exposure presented here is synthesized from two meta-analyses,(52, 53) and three comprehensive literature reviews conducted between 2007 and 2009.(54-56)

The health effects data presented below represent the combined contribution of all five papers and are organized into three sections: health outcomes in children, adult males, and adult females.

Prenatal and Early Life Pesticide Exposure and Health Outcomes in Children

In 2008 Wigle et al. reviewed the epidemiological evidence of relationships between prenatal and early life pesticide exposure and reproductive and child health outcomes (Table 2, pg. 18-19).(54) For many of the outcomes, the epidemiologic studies were limited in number and quality (e.g., small studies, ecological studies, limited control of potential confounders), had inconsistent results, or found little to no evidence of exposure-risk relationships. However, three outcomes each had several human studies and showed fairly consistent associations and evidence of exposure-risk relationships after control for potential confounders: [1] adverse impacts to fetal growth and survival with prenatal exposure to DDT and its metabolite, dichloro diphenyl dichloroethylene (DDE); [2] spontaneous abortion with prenatal exposure to ethylene oxide; and [3] childhood cancers (leukemia, lymphoma, brain and bone) with prenatal and paternal exposure to a variety of pesticides.

Evidence for the relationship between prenatal and early life exposure and childhood cancers is particularly strong. The 2008 in-depth review by Infante-Rivard and Weichenthal of the studies linking pesticide

exposure and childhood cancer concluded, "one can confidently state that there is at least some association between pesticide exposure and childhood cancer. Furthermore ...recent epidemiological studies suggest that this relationship may be causal due to the repeated finding of pesticide exposures significantly increasing the risk of childhood cancer."(56) Similarly, the 2009 systematic review and meta-analysis by Wigle et al. found that childhood leukemia was associated with prenatal maternal occupational pesticide exposure in analyses of all the studies combined and in several subgroups.(52) These findings were confirmed by another systematic review and meta-analysis published in 2010.(57)

The systematic review and meta-analysis by Turner et al. found exposure during pregnancy to unspecified residential pesticides, insecticides and herbicides were positively associated with childhood leukemia. (53) Exposure to unspecified residential pesticides and insecticides during childhood were also positively associated with childhood leukemia, but there was no association with herbicides. Associations with paternal occupational pesticide exposures were weaker and less consistent.

Box 1. The Evidence

The evidence linking pesticide exposure to adverse reproductive and developmental effects is from human observational studies and in vitro and in vivo toxicological testing.

Non-Human Evidence

Animal data serve as essential early warning systems and are the fundamental experimental evidence basis of pesticide regulation. Whereas it can take 20 years to get a result from a human observational study about a chronic health endpoint like cancer, an animal study can provide comparable evidence in two years.⁽⁵⁸⁾ Animal data on the carcinogenicity of a variety of chemicals have preceded as well as predicted later epidemiological observations in humans, and strong evidence exists that experimental results can be extrapolated qualitatively to human subjects.⁽⁵⁸⁾

The history of the pesticide dibromochloropropane (DBCP) is illustrative of the role that animal data can play in timely prevention, as well as the role that studies of occupationally exposed populations can play in elucidating the links between environmental exposures and adverse health outcomes. DBCP is a nematocide (roundworms) that was widely used in the U.S. to treat citrus, grapes, peaches, pineapples, soybeans, and tomatoes. By 1961 testicular atrophy due to DBCP had been documented in three rodent species.⁽⁵⁹⁾

Sixteen years later, a small group of agricultural chemical workers in California became aware that none had fathered children recently. The ensuing investigation of this sentinel cohort and, subsequently, other groups of male workers documented profound, and in many cases permanent, effects on spermatogenesis due to exposure to DBCP.^(60,61) While the use of DBCP was banned from all food crops in the U.S. by 1985, its export was not. Until recently the use of DBCP continued in banana and pineapple plantations in less developed countries, and resulted in epidemics of sterility among exposed male workers.⁽⁶²⁾

Human Evidence

For ethical reasons, experimental human evidence is not part of the evidence stream in the realm of environmental health. Human observational studies are used to assess the relationship between exposure and adverse health outcomes. As above, occupationally exposed populations generally provide the first human evidence of harmful health effects. At that point, however, prevention has failed.

By virtue of the time lag between an environmental exposure and a chronic health outcome there are relatively few human studies of long-term reproductive health consequences of thousands of currently used pesticides. As of 2002, there were 257 studies and reports of reproductive and developmental effects of pesticides in humans, most of which addressed banned or restricted use pesticides.⁽⁶³⁾

Human observational data generally lack the capacity to unequivocally prove causal relationships. This problem is compounded in environmental health science because most people are exposed to a mixture of chemicals, and health problems that may be associated with these exposures are often delayed by years or decades after exposure. Reproductive health outcomes are also couple-dependent, varied, and emerge from a complex web of factors such as dose, timing and duration of exposure, and individual susceptibility.⁽⁵⁵⁾ In general, few if any epidemiological studies have successfully incorporated the full complement of relevant considerations (e.g. assessing mixtures, life stage of exposure, the possibility of differential individual genetic susceptibility) into study design.⁽⁶⁴⁾

Nevertheless, the human studies linking pesticide exposure and adverse reproductive health outcomes are compelling given that the general direction of bias in such human observational studies is to demonstrate “no effect.” This tendency to underestimate risk is because of the challenge of getting precise estimates of exposure and health outcomes.^(55, 65-67) Moreover, because exposure is ubiquitous, even small risks can translate into large numbers of adverse events.

REPRODUCTIVE HEALTH OUTCOMES OF PESTICIDE EXPOSURE *continued*

Prenatal and Early Life Pesticide Exposure and Health Outcomes in Children *continued*

Recent studies continue to strengthen the association between prenatal pesticide exposures and the range of adverse childhood and adult outcomes. Increased seasonal levels of agrichemicals (nitrites, atrazine, and other pesticides) in surface water have been found to be associated with greater risk of birth defects from live births having the last menstrual period during the same time span (April-July).(68) For instance, spring conceptions, when use of atrazine for agriculture is highest, were associated with the highest rates of gastroschisis in the state of Washington.(69) Similarly, neural tube defects, particularly anencephaly, in a Mexican-American population in Texas were more likely to occur when there was residential prenatal pesticide exposure, such as those living geographically near cultivated fields, and those with a partner who had occupational pesticide exposure.(70)

Additionally, neurodevelopmental harm, specifically attention-deficit/hyperactivity disorder (ADHD) was associated with higher urinary organophosphate metabolite levels prenatally(71) and during childhood.(72) Finally, in a prospective study, maternal post-natal serum DDT metabolite levels were associated with a son's risk of developing testicular cancer in later years.(73)

Adult Male Pesticide Exposure and Health Outcomes

Sterility and Altered Semen Quality

In the 30 years since the first report of human sterility due to exposure to the pesticide DBCP, scientific concern regarding whether the use of pesticides or other chemicals alters semen quality has grown substantially. A large body of data suggests that sperm counts have been declining in Europe and the United States but the data do not currently allow for a definitive conclusion on whether adult pesticide exposure, at background environmental levels, alters semen quality.(74,75) Swan and colleagues have demonstrated that some currently used pesticides are significantly associated with reduced sperm concentration by linking pesticide concentration in men's urine to results of their semen analysis.(74)

Prostate Cancer

The 2009 Endocrine Society Scientific Statement on Endocrine Disrupters, (see Endocrine Disrupters, pg. 13) a literature review paper and consensus opinion, concluded that there are compelling data from a large epidemiological study (Agricultural Health Study) from North Carolina and Iowa demonstrating a link between increased prostate cancer rates and 55,000 pesticide applicators and the fumigant, methyl bromide, although the mechanism of action is unknown.(76) Additionally, exposure to six other pesticides (chlorpyrifos, fonofos, coumaphos, phorate, permethrin, and butylate) showed significant correlation with increased prostate cancer rates in those with a family history of the disease, suggesting a gene-environment interaction. The mechanism of action of some of these pesticides may be by inhibition of the p450 hepatic enzymes that metabolize testosterone, estradiol, and estrone.

Postnatal Pesticide Exposure and Health Outcomes in Adult Females

Human and animal data indicate postnatal pesticide exposures can interfere with all developmental stages of reproductive function in adult females, including puberty, menstruation and ovulation, fertility and fecundity, and menopause. A review by Mendola et al. of relevant human data and key animal studies published between 1999 and 2007 summarized these impacts as follows:(55)

Puberty

DDT/ DDE is associated with earlier age at puberty, including outcomes such as thelarche and precocious puberty, as well as earlier age at menarche.

Menstrual and Ovarian Function

Longer cycles, missed periods and abnormal bleeding have been observed in an agricultural health study of hormonally active pesticides (lindane, atrazine, mancozeb, maneb).

Fertility and Fecundity

Working with or applying pesticides, primarily in agricultural and horticultural settings, appears to consistently reduce fertility and/or fecundity in women.

Menopause

Age at natural menopause is younger for women exposed to DDT, DDE, and other pesticides.

Breast Cancer

Case studies that measure exposure to a single agent at the time of breast cancer diagnosis have produced inconsistent results.(76) However, a prospective study measuring exposure several years prior to a breast cancer diagnosis revealed a positive link between exposure to the pesticides DDT and toxaphene and breast cancer.(77) Specifically, exposure to DDT prior to age 14 increased the risk of eventual breast cancer diagnosis.



MECHANISMS OF TOXICITY

The following section describes three inter-related concepts that are important to understanding how pesticides can exert toxic effects with particular relevance to the field of reproductive and developmental health, including: [1] the influence of timing or life stage during which exposure occurs; [2] the disruption of hormonal function; and [3] the epigenetic processes that alter gene activity without changing the DNA sequence.

Developmental Origins of Health and Disease

The embryo, fetus and developing human are highly vulnerable to exposure to even small amounts of toxicants.(76, 79-81) A critical window of susceptibility is a unique time period during development when exposures to environmental contaminants can disrupt or interfere with the physiology of a cell, tissue, or organ.(79) Exposures during this window may result in adverse, permanent effects that can have lifelong and even intergenerational impacts on health. In contrast, during a sensitive window of susceptibility, exposures may still affect development or eventually result in adult disease, but with reduced magnitude compared to the effect of exposure during other time periods.(82) Given that development continues after birth, critical and sensitive windows are seen periconceptually, during pregnancy, infancy, lactation, childhood, and puberty.

The body of evidence linking environmental exposure or other stimuli or insults during a critical period of growth and development to disease or dysfunction later in life evolved independently in the fields of nutrition and environmental health.(83, 84) In the field of nutrition, the hypothesis of “developmental origins of adult disease” stemmed from epidemiologic studies beginning in the mid-1980s in the United Kingdom by Barker and colleagues that identified strong relationships between maternal under nutrition, low birth weight and long-term risk of metabolic syndrome.(85-88) A large body of experimental and epidemiologic data have since substantiated and further refined scientific understanding of these linkages.(83, 84)

In the field of environmental health, the adverse health impacts documented among the children of women who took the drug diethylstilbestrol (DES) during pregnancy are the “proof of principle” of developmental origins of adult disease.(83) DES resulted in cancer and other adverse reproductive health outcomes in the daughters and sons of women who took the drug while pregnant, and these health impacts emerged only decades after the in utero exposure occurred.

Recent animal research into the mechanisms of toxicity of the organophosphate pesticide chlorpyrifos further elucidates the importance of “timing” of exposure. The conventional view of neurotoxicity from chlorpyrifos involves its metabolism by the liver to chlorpyrifos oxon, the postulated more toxic breakdown product, which causes an irreversible inhibition of acetylcholinesterase. However, animal studies by Slotkin and colleagues demonstrated that exposures occurring at times of critical brain development can produce more subtle adverse effects. In addition, effects can occur below the threshold for signs of exposure, and in the absence of detectable cholinesterase inhibition.(89,90) Moreover, these studies have shown that chlorpyrifos disrupts rat brain development through a variety of cellular and molecular mechanisms, with both the mechanism and the outcome changing with the progression of cell differentiation.

The importance of exposure timing is also evidenced by the stage-specific effects demonstrated by exposure to ethylene oxide, a fumigant. Ethylene oxide can induce skeletal effects when administered to mice at the zygote stage of development before initiation of skeletogenesis.(67, 91) The spectrum of skeletal effects observed after exposure at the zygote stage differs from those observed after exposure during organogenesis.

In accordance with the developmental basis of adult disease hypothesis, perinatal and prenatal exposure to pesticides have been implicated via neuropathologic and animal models in the etiology of idiopathic Parkinson’s Disease.(92-95) While human studies have shown pesticides such as paraquat to be linked to Parkinson’s Disease, epidemiologic data that address the relationship between in utero exposure to pesticides and late onset neurologic diseases such as Parkinson’s are lacking.

The USEPA has not yet incorporated implications of the critical timing of exposure into pesticide toxicity testing protocols, and data collected by USEPA from pesticide manufacturers often overlook developmental, morphologic, and functional damage of fetal origin.(96)

Endocrine Disruption

The USEPA defines endocrine disruptors as compounds that “interfere with the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body that are responsible for the maintenance of homeostasis (normal cell metabolism), reproduction, development, and/or behavior.” Endocrine disrupting compounds (EDCs) can have effects on male and female reproduction, breast development and cancer, prostate cancer, neuroendocrinology, the thyroid, metabolism and obesity, and cardiovascular endocrinology.(76)

Laboratory and cell culture studies have demonstrated that pesticides can disrupt estrogen, androgens, thyroid, and the pituitary/hypothalamic axis.(78) For example, epidemiologic studies published in 2007 and 2008 found a statistically significant inverse relationship between levels of thyroid hormones and pesticides in pregnant women and in cord blood,(97, 98) suggesting that background levels of exposure to pesticides can affect thyroid function during pregnancy. These findings have important implications because thyroid hormones of maternal origin play an essential role in fetal neurodevelopment.(97)

Pesticides can have several mechanisms by which they interfere with the endocrine system. Pesticides that have hormonal, mutagenic or other toxicities that act at extremely low doses (parts per trillion) are of particular concern when considered in the context of critical and sensitive windows of development. For example, there is recent evidence that when even a very low dose EDC exposure coincides with a critical or sensitive window of susceptibility, it may be more potent than a higher dose exposure, or the low dose

exposure may otherwise exert a nontraditional dose-response curve.(76) The consequences of exposure to endocrine disrupting chemicals may also be delayed with additive or synergistic effects from myriad chemical exposures.(76) The paramount concern raised by the emerging scientific evidence is that very small exposures to some endocrine disrupting chemicals, especially at critical stages of fetal development, may result in adverse reproductive and other outcomes.(99) Data primarily from laboratory animal and cell culture studies have shown over 50 pesticides to have known or suspected endocrine disrupting properties in the female reproductive system.(78)

Findings from wildlife studies are an important early warning system of potential human harm. A variety of environmental contaminants, including pesticides, have the potential to act as endocrine disruptors in wildlife. For example, after a 1980 pesticide spill (dicofol and DDT) polluted Lake Apopka, Florida, there was a dramatic decline of the American alligator population compared to a nearby uncontaminated lake. Subsequent studies of the hatchlings showed significantly reduced hatchability and offspring survival, demasculinization of males, and superfeminization of females.(100) Furthermore, a 2010 study found that African clawed frogs born and raised in water contaminated with 2.5 ppb of atrazine exhibited depressed testosterone, decreased breeding gland size, demasculinized/feminized laryngeal development, suppressed mating behavior, reduced spermatogenesis, and decreased fertility.(101) The study also found that ten percent of the exposed males developed into functional females that copulated with unexposed males and produced viable eggs.

MECHANISMS OF TOXICITY *continued*

Epigenetics

The term “epigenetics” includes any process that alters gene activity without mutating the DNA sequence, and leads to modifications that can be transmitted to daughter cells.(102) These epigenetic modifications may regulate gene expression via DNA methylation and histone acetylation.(76) In 2005, studies on laboratory animals began to establish epigenetics as a mechanism of action for how pesticides and other toxic environmental chemicals may act on a gestating mother to influence her grandchildren and potentially subsequent generations.(103) Studies of male rats exposed to the fungicide vinclozolin reported that epigenetic damage may be passed on to future generations.(103) In 2008, scientists found that female rats exposed to vinclozolin during a specific period of pregnancy exhibit a transgenerational increase in pregnancy abnormalities and female adult onset disease states.(104) It should be noted, however, that the administered doses were much higher than the expected average occupational exposure to this pesticide, and the observed effects await independent experimental confirmation.

PREVENTING THE REPRODUCTIVE HEALTH IMPACTS OF PESTICIDE EXPOSURE

Take Action in Clinical and Policy Arenas

Obstetricians, gynecologists, nurses and other reproductive health care professionals can be extremely effective in reducing the use of harmful pesticides in their patients’ environments. Clinicians do not need to become pesticide experts in order to fulfill this crucial role. Individuals hoping to bear children are intensely and justifiably interested in the impact of the environment on their pregnancies and the health of their future children, and look to their clinician for guidance on how to avoid potentially harmful exposures. In addition to the current standard queries about a patient’s alcohol and smoking history, clinicians need to be prepared to provide anticipatory guidance and respond to patient inquiries about hazardous environmental exposures encountered at home, at work and in the community.(50) Interventions have been shown to be effective in reducing the body burden of pesticides. Researchers documented an immediate decrease in urinary metabolites of the organophosphorous pesticides, malathion and chlorpyrifos, in 23 elementary age children after substituting conventional diets with organic food items.(105)

Beyond the clinic, active participation of well-informed health professionals is critical to translating existing and emerging scientific findings into policies to improve birth outcomes at a larger scale.(106) Table 1 provides examples of policy statements by the California Medical Association (CMA) related to pesticide exposure. The practice of pediatrics offers a valuable model of successful efforts to involve health care professionals in prevention strategies within clinical and policy settings.(107, 108) Similarly, the involvement of reproductive health professionals can greatly improve periconceptual, fetal and neonatal health.

Recognize, Diagnose and Report

Have ready access to the recommended referral list of resources and contacts. The list includes expansive information on each of the topics below and can be found at: <http://www.prhe.ucsf.edu/prhe/pmlinks.html>

- Ask patients about their household and workplace pesticide exposure.
- Take an occupational and environmental history.(109)
- Consider pesticide exposure in the differential diagnosis.
- Report exposure incidents to the proper health authorities. Visit the resources list online for detailed information on how to report pesticide illness.
- Do not prescribe or recommend to patients the use of over-the-counter lice shampoo containing pesticides. According to the USEPA, combing is the most important aspect of head lice control.
- Call upon appropriate specialists or experts for assistance in challenging cases. For more information, physicians can contact the Association of Occupational and Environmental Clinics at: www.aoec.org or (888)347-2632.

Advise Patients to Avoid Pesticides Whenever Possible

Clinicians should intervene as early as possible (e.g. at preconceptual counseling) to prevent exposures by alerting patients to potential hazards and providing guidance on how to address the problems of pests in the least toxic manner. By the first prenatal care visit, disruptions of organogenesis may have already occurred.

Anticipatory guidance can include information about how to avoid exposure at home and at work. Clinicians can incorporate information and resources about environmental hazards into childbirth class course curriculum to help women and men make optimal choices for themselves and their children.(110) A patient brochure with tips for preventing exposure accompanies this white paper and can be found online at: http://prhe.ucsf.edu/sites/prhe.ucsf.edu/files/Pesticides_En2016.pdf

Table 1. California Medical Association Pesticide Exposure Prevention Policies

	IMPROVING HEALTH THROUGH SUSTAINABLE FOOD PURCHASING (2007) Encourage hospitals to adopt policies and implement practices that increase the purchasing and serving of food ... grown according to organic or other methods that emphasize renewable resources, ecological diversity, and fair labor practices.
	PESTICIDES AND SCHOOLS (2004) Strengthen health protection of students, teachers, and other school employees ... through adequately funded and implemented least-toxic school pest management programs, that strictly prohibit the school use of highly toxic pesticides.
	AGRICULTURAL PESTICIDE DRIFT (2000) Strengthen efforts to protect schools and residential areas from pesticide drift and off-site pesticide movement.
	FARMWORKER PROTECTION FROM PESTICIDES (2000) Support efforts to reduce farmworker exposure to pesticides; strengthen enforcement of existing laws by increasing fine levels; encourage physician awareness of pesticide illness and reporting.
	HEALTHY SCHOOLS (1999) Protect indoor air at California schools; recommend statewide implementation of least-toxic school pest management programs; include parents in pest management decision-making.

PREVENTING THE REPRODUCTIVE HEALTH IMPACTS OF PESTICIDE EXPOSURE

Bring the Clinician Perspective to Policy Arenas

continued

In the policy arena, reproductive health professionals can advocate for improved institutional and public policy that will help reduce exposures for the whole population.(111) **For example:**

- Encourage pest control policies in your institutions, schools and daycares that “do no harm.” The clinical voice is an essential component in collaborative efforts to promote integrated pest management (IPM) (Box 2). Identify how pesticide use decisions are made in your institution and advocate for IPM. For example, in the IPM in Health Care Facilities Project, over a dozen environmental leaders in the health care facility sector in Maryland have taken up the challenge of toxics reduction and elimination in their buildings and grounds through institutionalization of pest management programs that focus on non-chemical pest prevention strategies to avert pest problems.(112)
- Establish a reproductive environmental health committee in your local, state and/or national professional organizations. For example, for more than half a century, the American Academy of Pediatrics has had a Council on Environmental Health (COEH) studying environmental issues of concern to children, and recommending actions and guidelines for pediatric practice and policy.(113) The American Academy of Pediatrics COEH publishes a clinicians’ desk reference, Pediatric Environmental Health, which contains tools for identifying, treating, and preventing pediatric environmental health hazards such as pesticides. (114) Reproductive health care professionals can establish similar committees to make recommendations and develop educational materials for clinicians within a reproductive health framework that promotes prevention.
- Work to obtain the endorsement of professional associations, decision-making bodies, academic institutions, and health care institutions for the Health Professionals and Environmental Health Education Position Statement. See: <http://www.neefusa.org/health/about/short-ps.htm>
- Schedule Grand Rounds presentations on the issue of pesticides and reproductive health at your institution. Organizations such as Physicians for Social Responsibility have presentations available on the subject and, in many regions of the country, have member-clinicians who can provide educational presentations.
- Become a champion for reproductive environmental health in your institution. Train-the-trainer health faculty initiatives have been highly successful in building environmental health capacity among pediatric healthcare professionals.(107)
- Advocate for your institution to join the Health Care Without Harm campaign, a global coalition of 473 organizations in more than 50 countries working to protect health by reducing pollution in the health care sector.

Box 2. What is integrated Pest Management (IPM)?

The USEPA defines Integrated Pest Management (IPM) as an “effective and environmentally sensitive approach to pest management that relies on a combination of common-sense practices. IPM programs use current, comprehensive information on the life cycles of pests and their interaction with the environment. This information, in combination with available pest control methods, is used to manage pest damage by the most economical means and with the least possible hazard to people, property, and the environment.” IPM strategies have been shown to be effective in reducing pest infestation levels and the internal dose of insecticides during pregnancy.(16, 38)

- Work for and support improved reproductive environmental health public policy through your local, state and national professional organizations. Professional organizations of physicians have consistently called for regulatory and other efforts to address the environmental threats to human health. **For example:**

- The American Society for Reproductive Medicine has an Environment and Reproduction Special Interest Group which specifically “seeks to enhance understanding of the effect of environmental factors on reproductive health through excellence in education, research and clinical practice.”(115)
- The CMA has adopted five policies geared at diminishing the reproductive and other health risks of pesticide exposure (Table 1).
- The American Medical Association (AMA) has adopted policies promoting the incorporation of environmental health into medical education.(116) In 2009, AMA also adopted a policy to promote the engagement of clinicians and policy makers in creating a healthy and sustainable food system (Box 3).(117)
- In 2009, the Endocrine Society published a scientific statement on endocrine disrupting chemicals (EDCs) such as organochlorine pesticides and industrial chemicals, plastics and plasticizers, fuels, and other chemicals present in the environment or in widespread use.(76) The Endocrine Society Statement makes recommendations to increase understanding of the effects of EDCs, including enhancing increased basic and clinical research, invoking the precautionary principle², and advocating involvement of individual and scientific society stakeholders in communicating and implementing changes in public policy and awareness.

The CMA, AMA and Endocrine Society policy statements can be used to model policy in other states and professional organizations. A database of additional relevant professional statements can be found at:

<http://prhe.ucsf.edu/sites/prhe.ucsf.edu/files/ProfessionalStatementsDatabase.pdf>

Box 3. Why Should Health Professionals Promote Local Organic Food?

According to the American Medical Association: “Locally produced and organic foods are considered part of a healthy sustainable food system for many reasons. They reduce the use of fuel, decrease the need for packaging and resultant waste disposal, preserve farmland, and/or support a greater diversity of crops. The related reduced fuel emissions contribute to cleaner air and in turn lower the incidence of asthma attacks and other respiratory problems. Organic meat production helps reduce the development of antibiotic resistance, as well as air and water pollution. Organic and local foods can have improved nutrient profiles: ripe produce, and some organic produce, contain peak amounts of micronutrients and phytochemicals, and pasture-raised, grass-fed animals produce leaner beef, and meat and milk with higher levels of beneficial essential fatty acids such as omega-3s. Some people also believe local and organic foods taste better, which may encourage increased consumption of fruits, vegetables, and lean meat, while also decreasing exposure to pesticides and hormones. Shorter supply chains in local food systems also lessen their vulnerability to food contamination.”(118)

2. The precautionary principle states that “when an activity raises threats of harm to human health or the environment, precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically. In this context the proponent of an activity, rather than the public, should bear the burden of proof.” See: <http://www.sehn.org/precaution.html>

Table 2. The Strength of Epidemiologic Evidence¹ of Relationships Between Reproductive Health Outcomes and Pesticide Exposure (Adapted from Wigle et al, 2008)⁶⁰

Health Outcome	2,4,5 T, chlorophenate wood preservatives	Other chlorophenoxy herbicides	Other or unspecified herbicides	DDT/DDE	
Childhood Cancer					
<i>Leukemia</i>	paternal		prenatal		
<i>Lymphoma</i>					
<i>Brain</i>	paternal		prenatal		
<i>Neuroblastoma</i>					
<i>Wilm's tumor</i>			prenatal		
<i>Other Cancers</i>			prenatal (germ cell)		
Delayed Conception²		prenatal	prenatal	prenatal, paternal	
Spontaneous abortion³	paternal	prenatal paternal	prenatal, paternal	prenatal, paternal	
Stillbirth⁴	paternal		prenatal	prenatal	
Preterm Birth⁵	paternal	prenatal	paternal	prenatal	
Fetal Growth Deficit⁶	paternal	prenatal	prenatal	prenatal	
Birth Defects					
<i>Neural Tubes</i>	paternal	prenatal	prenatal		
<i>Cardiac</i>	paternal	prenatal	prenatal		
<i>Orofacial</i>	paternal	prenatal			
<i>Musculo-skeletal</i>	paternal	prenatal	prenatal		
<i>Urinary Tract</i>	paternal	prenatal			
<i>Male Genital</i>	paternal	prenatal, paternal	prenatal	prenatal	
Adult Cancer - Testicular					
Developmental Milestones					
Cognitive Function age 0-2 yr				prenatal, lactational	
Cognitive Function age >=3 yr				prenatal, lactational	
Problem Behaviors			paternal		
Motor Function age 0-2 yr				prenatal, lactational	
New-Onset Childhood Asthma					
Childhood Lung Infections				prenatal	
Childhood Middle Ear Infections					
Allergies					
Child Growth and Pubertal Development - Postnatal growth in height				prenatal, lactational or childhood	

¹ Exposure periods in bold indicate relationships for which several epidemiologic studies, including at least one case control or cohort study, found fairly consistent associations and evidence of exposure-risk relationships after control for potential confounders. Exposure periods not in bold indicate relationships for which epidemiologic studies were limited in number and quality (e.g., small studies, ecological studies, limited control of potential confounders), had inconsistent results, or found little to no evidence of exposure-risk relationships.

² For delayed conception, prenatal or paternal exposure, respectively, refer to preconception female or male partner exposure.

CONCLUSION

The widespread presence of pesticides in the environment can expose humans to compounds that can increase the risk of a diverse range of adverse human reproductive health outcomes throughout one's life. Reproductive health professionals can be instrumental in advising patients how to avoid pesticide exposures and thus help ensure the healthiest reproductive outcome. In addition, optimal intervention rests on public policies that call for preventing harmful exposures before they occur, and reproductive health professionals can effectively bring this message to the public and policy makers. Complete definitions of reproductive health should embrace everyone's right to environments that prevent exposure to potential reproductive toxicants and provide the nutritive and social sustenance necessary for healthy pregnancies, children, adults, and future generations.



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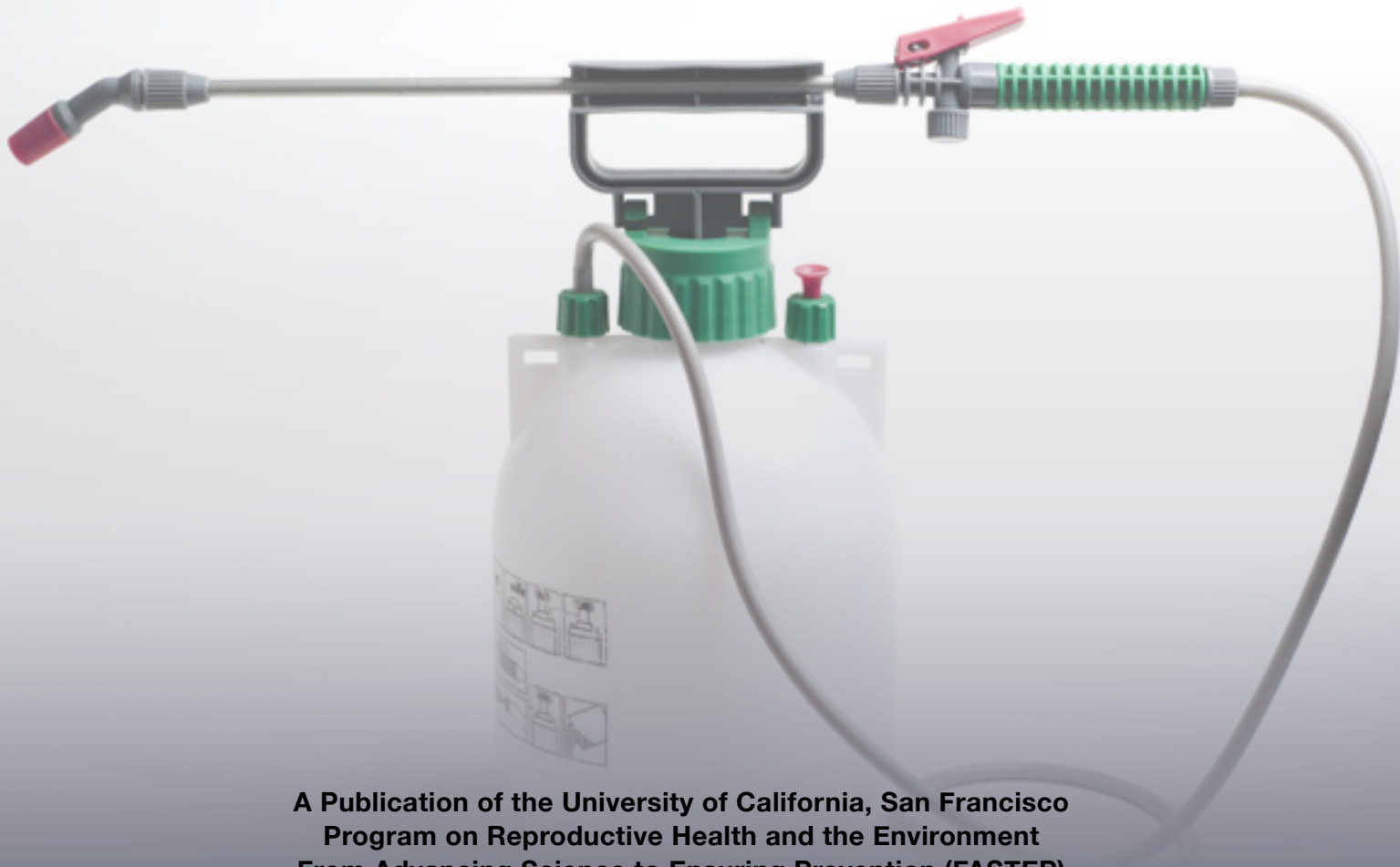
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FASTEP is an alliance of academic, government and non-governmental partners spanning the fields of reproductive, environmental, occupational and pediatric health and toxicology. Our goal is to secure each and everyone's right to optimal reproductive health by fostering environments that prevent exposure to toxic substances and support healthy pregnancies, children, adults and future generations.



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