Reproductive Health And Pesticides

What Do We Know,
What Can Clinicians Do?

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http://www.prhe.ucsf.edu/prhe/about/index.html

Faculty disclosure

- Dr. Woodruff has no financial affiliations to disclose

Note: Additional disclosure information is located within the program

Objectives

At the conclusion of the session, participants will be able to:

- Summarize the scientific literature on the impacts of environmental contaminants on reproductive health in adolescents, men, and women.

Objectives (cont)

At the conclusion of the session, participants will be able to:

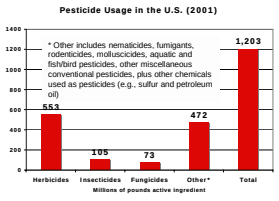
- Identify and implement use of tools that can assist patients in making informed decisions about avoiding common environmental contaminants.

Objectives (cont)

At the conclusion of the session, participants will be able to:

- Propose clinical care recommendations related to environmental contaminants that have the potential to improve reproductive health.

Background



- Pesticides are chemicals intended to be toxic to living organisms
- Classified by "target" organism and chemical class --- i.e., insecticide and organophosphate
- Over 1.2 billion pounds of pesticides used in U.S. in 2001

Source: Pesticides Industry Sales and Usage 2000 and 2001 Market Estimates By Timothy Kiely David Donaldson Arthur Grube, Ph.D. USEPA (2004). http://www.epa.gov/oppbead1/pestsales/

Background


Research | Article

Differential Effects of Glyphosate and Roundup on Human Placental Cells and Aromatase

Sophie Richard, Safa Moslemi, Herbert Sipahutar, Nora Benachour, and Gilles-Eric Seralini

The dilution of glyphosate (the active ingredient) in Roundup (with inerts) may multiply glyphosate's endocrine effect

- Pesticides are formulated from mixtures of **"active"** and **"inert"** ingredients
- Over **1300** active ingredients with dissimilar structures and diverse toxicities that may act through different mechanisms
- "Inert" is a functional designation, NOT a measure of health risk.
  - Inerts can increase the ability of pesticide formulations to affect significant toxicologic end points, including developmental neurotoxicity, genotoxicity, and disruption of hormone function

Sources: Cox C, and Surgan M. Unidentified Inert Ingredients in Pesticides: Implications for Human and Environmental HealthEnviron Health Perspect. 2006 December; 114(12): 1803–1806. Richard S, Moslemi S, Sipahutar H, Benachour N, Seralini G-E. Differential effects of glyphosate and Roundup on human placental cells and aromatase. Environ Health Perspect. 2005;113:716–720. Pesticide Action Network, North America. PAN Pesticide Database. List of US Registered Active Ingredients. From Pesticide Product Information Systems. U.S. EPA, June 26, 2006, and California Registered active ingredients. California Department of Pesticide Regulation, January 28, 2005. http://www.pesticideinfo.org/Detail_Country.jsp?Country=United%20States&offset=1200

Exposure

- **Ubiquitous**
  - In nearly every home, business, farm, school, hospital and park in the U.S.
  - The USEPA estimates almost three of four U.S. households use pesticides
  - Every child conceived today in the Northern hemisphere is exposed to pesticides from conception throughout gestation and lactation regardless of where it is born
- **Disparities**
  - Most vulnerable populations are fetus, infants, children and exposed workers

Sources: Kiely T, Donaldson D, Grube A. Pesticide Industry Sales and Usage. 2000 and 2001 Market Usage. USEPA May 2004. Colborn T. A Case for Revisiting the Safety of Pesticides: A Closer Look at Neurodevelopment. Environmental Health Perspectives Vol. 114, No. 1. January 2006. USEPA http://www.epa.gov/pesticides/factsheets/registration.htm

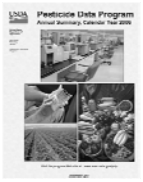
Pesticide Exposure: Disparities

- Women in a largely agricultural cohort in the Salinas Valley of California had median postpartum urinary DAP metabolite levels that were 2.5 times higher than those for NHANES women.


Research | Children's Health

Organophosphate Urinary Metabolite Levels during Pregnancy and after Delivery in Women Living in an Agricultural Community

Pesticides in Food



Pesticide residue data on commodities most frequently consumed by infants and children

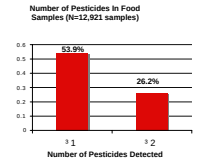
Samples collected close to the point of consumption and prepared emulating consumer practices - washed, peeled, etc.

Pesticide Residues in Samples of:

62.1 % Fruits & Vegetables (N= 6101/9818)

30% Peanut Butter (N= 223/739)

19% Bottled Water (N=70/367)



Source: USDA Pesticide Data Program
http://www.ams.usda.gov/AMSv1.0/ams.fetchTemplateData.do?template=TemplateC&navID=PesticideDataProgram&rightNavI=PesticideDataProgram&topNav=&leftNav=Science&page=PesticideDataProgram&resultType=

Pesticides in Food

Average food ingestion exposures for the U.S. population exceeds "benchmark" concentrations for arsenic, chlordane, DDT, dieldrin and dioxins

A benchmark concentration represents a daily concentration below which there is a high probability of no adverse health effect


Dietary Exposures to Food Contaminants across the United States

Source: Dietary Exposures to Food Contaminants across the United States Dougherty CP, Henricks Holtz, S, Reinert JC, Panyacosit L, Axelrad DA, Woodruff TJ. Environmental Research Section A 84, 170 - 185 (2000)

Pesticides in Water

Environmental Effects of Pesticide Runoff

- Millions of birds, fish and smaller aquatic animals that fish depend on for food die every year from exposure to pesticides
- Major contamination of waterways
- Population declines in animals and plants by destroying habitats and reducing food supplies
- Impairment of normal reproduction
- Destruction of both pest and beneficial organisms

Pesticides at Home

- **Lawn application of 2,4-D Pre-application exposure 1.94 mcg/d**
- **Post-Application – 8.87 mcg/d**
  Two Weeks After Application
- **2,4-D pesticide <u>tracked in</u> by family dog and home owner (applicator)**

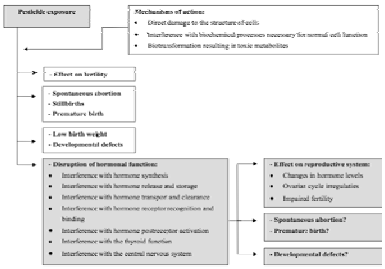
Source: Nishioka MG, Lewis RG, Brinkman MC, Burkholder HM, Hines CE, Menkedick JR, 2001. Distribution of 2,4-D in air and on surfaces inside residences after lawn applications: comparing exposure estimates from various media for young children. Environ Health Perspect. 2001 Nov;109(11):1185-91.

Reproductive Health Outcomes

Every chemical class of pesticides has at least one agent capable of affecting a reproductive or developmental endpoint in laboratory animals or people

Frazier LM. Reproductive disorders associated with pesticide exposure. J Agromedicine. 2007;12(1):27-37.

Potential effects of pesticides on female reproduction



Source: Bretveld RW. et al. Pesticide exposure: the hormonal function of the female reproductive system disrupted? Reprod Biol Endocrinol. 2006 May 31;4:30.

Preconception and Prenatal Exposures (Male and Female)

Preconception, prenatal, and/or pesticide exposure via lactation has been linked to:

- Delayed conception
- Spontaneous abortion
- Stillbirth
- Preterm birth
- Fetal growth deficit
- Birth defects
- Childhood and adult cancer
- Delayed developmental milestones
- New-onset childhood asthma
- Childhood lung and middle ear infections, allergies, and impacts on postnatal growth in height

Source: Wigle DT, Arbuckle TE, Turner MC et al. Epidemiologic Evidence of Relationships Between Reproductive and Child Health Outcomes and Environmental Chemical Contaminants. *Journal of Toxicology and Environmental Health, Part B*, 11:3731517, 2008.

Preconception and Prenatal Exposures (Male and Female)

Strongest available human evidence*

- Adverse impacts to **fetal growth and survival** and prenatal exposure to DDT/DDE;
- **Spontaneous abortion** and prenatal exposure to ethylene oxide; and
- **Childhood cancers** (leukemia, lymphoma, brain and bone) and prenatal and paternal exposure to a variety of pesticides

* Based on 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

Source: Wigle DT, Arbuckle TE, Turner MC et al. Epidemiologic Evidence of Relationships Between Reproductive and Child Health Outcomes and Environmental Chemical Contaminants. *Journal of Toxicology and Environmental Health, Part B*, 11:3731517, 2008.

Pesticides Known to Cause Reproductive Toxicity

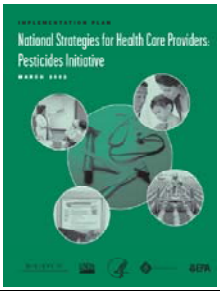
Cal-EPA's list of chemicals known to have reproductive toxicity includes 42 pesticides

Pesticides Known to the State of California to Cause Reproductive or Developmental effects	Type
1080	Rodenticide
Aldicarb	Insecticide
Arsenic acid	Herbicide
Arsenic pentoxide	Multiple uses, insecticide, wood treatment
Arsenic trioxide	Rodenticide
Benomyl	Fungicide
Bromacil, lithium salt	Herbicide
Bromacil-5-chloride	Herbicide
Chlorsulfuron	Herbicide
Cyanazine	Herbicide
Cycloate	Herbicide
Diclofop-methyl	Herbicide
Disodium cyanodithioimido carbonate	Microbiocide
Diuron	Herbicide
Ethylene oxide	Fumigant
Fenoxaprop ethyl	Herbicide
Fluazifop-butyl	Herbicide
Hydramethylnon	Insecticide
Maneb	Fungicide
Metam-sodium	Fumigant
Methyl bromide	Fumigant
Metiram	Fungicide
Myclobutanil	Fungicide
Nabam	Fungicide
Nicotine	Insecticide
Norflurazon	Herbicide
Oxadiazon	Herbicide
Oxydemeton-methyl	Insecticide
Oxythioquinox	Insecticide, fungicide, fumigant
Potassium dimethyl dithio carbamate	Microbiocide
Propargite	Insecticide
Resmethrin	Insecticide
Sodium dimethyl dithio carbamate	Microbiocide
Streptomycin sulfate	Fungicide
Tau-fluvalinate	Insecticide
Thiophanate-methyl	Fungicide
Triadimefon	Fungicide
Tributyltin methacrylate	Antifoulant, microbiocide
Triforine	Fungicide
Triphenyltin Hydroxide	**Fungicide**
Vinclozolin	Fungicide
Warfarin	Rodenticide

Sources: Solomon G. Pesticides and Health. A Resource for Health Care Professionals (2000). Physicians for Social Responsibility and Californians for Pesticide Reform; California Environmental Protection Agency

Prevention - What Can Clinicians Do?

- **Prevent Harm** - Health care providers can be extremely effective in addressing pesticide exposures in the lives of their patients and in their communities. The do not need to become experts in order to fill an important and crucial role (NEETF, 2002).
- **Intervene Early** - By the first prenatal care visit, disruptions of organogenesis may have already occurred (Frazier, 2007)



Sources: The National Environmental Education & Training Foundation. National Strategies for Health Care Providers: Pesticides Initiative. March 2002 http://www.neefusa.org/pdf/ImplementationPfdf
Frazier LM. Reproductive disorders associated with pesticide exposure. J Agromedicine. 2007;12(1):27-37.

Clinical Setting

Recognize, Diagnose and Report

- Take an environmental and occupational history
- Consider pesticide exposure in differential diagnosis
- Call upon an appropriate specialist or expert for assistance in challenging cases
- Have ready access to a recommended referral list of resources and contacts
- Report exposure incidents to the proper health authorities - California health care providers are required to report pesticide-related illness

Source: The National Environmental Education & Training Foundation National Strategies for Health Care Providers: Pesticides Initiative. March 2002 http://www.neefusa.org/pdf/ImplementationPfdf

Clinical Setting

Provide Anticipatory Guidance to Patients

Prevent Exposure At Work

- Do not enter treated areas until it is safe
- Do not bring food into a treated areas
- Keep pesticides off your skin
- Use respiratory protection when required
- Wash hands before eating

Don't Take The Workplace Home

- Do not use water in drainage ditches for drinking, bathing, swimming or fishing
- Change clothes and shower if possible before entering house and or/playing with your children
- Never take pesticide containers home
- Keep pesticides out of your home
- Store and wash clothes separately

Know Your Rights

Workers in agriculture and structural pest control are at risk

Clinical Setting

Provide Anticipatory Guidance to Patients

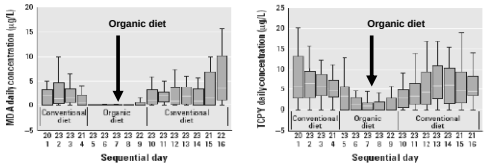
Prevent Exposure At Home

- **Prevent a pest problem before it happens**
  - Fix leaks
  - Put food in tightly sealed containers
  - Seal cracks and holes in walls, floors and baseboards
  - Keep floors and surfaces clean at all times
- **Use alternatives**
  http://www.pesticide.org/factsheets.html#alternatives

Clinical Setting

Provide Anticipatory Guidance to Patients

Prevent Exposure From Food



- 23 children monitored for metabolites before/after organic diet
- Levels of urinary metabolites for chlorpyrifos and malathion reduced to non-detectable
- Again elevated on re-introduction of conventional diet

Source: Lu C et al. 2006. Organic diets significantly lower children's dietary exposure to organophosphorus pesticides. Environ Health Perspect. 2006 Feb;114(2):260-3.

Clinical Setting

Provide Anticipatory Guidance to Patients

Prevent Exposure From Food

- Grow your own organic vegetables (test the soil for lead first!)
- Buy organic food
- Your patients can lower their pesticide exposure by almost 90 percent by avoiding the top twelve most contaminated fruits and vegetables and eating the least contaminated instead

Source: Environmental Work Group http://www.

Policy Arena

Advocate for Healthy Food Systems

Farmers Market

Kaiser Hospital, Richmond, CA

- **Global Health and Safety Initiative**

  A sector-wide collaboration to transform the way that healthcare designs, builds and operates its facilities as well as the products healthcare uses within those facilities

Source: The Global Health and Safety Initiative http://www.globalhealthsafety.org/about/index.php?flash=about_us

Policy Arena

Advocate for Improved Public Policy

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.

Complete text of California Medical Association resolutions at: http://www.sfbaypsr.org/work_cma.html

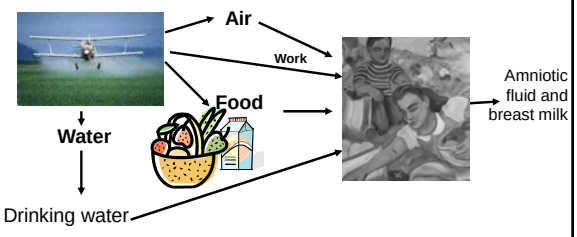
Conclusions

- The body of scientific evidence continues to build regarding the impact of pesticides on reproductive health
- A precautionary approach that emphasizes prevention provides for good patient and public health
- Guidance on preventing patient exposures to pesticides should be incorporated into preconception and prenatal visits
- Clinicians can contribute greatly to "upstream" prevention issues beyond the clinical setting

Additional Resources

- USEPA Recognition and Management of Pesticide Poisonings by the U.S. EPA (Available in Spanish)
  http://www.epa.gov/oppfead1/safety/healthcare/handbook/handbook.htm
- U.S. Environmental Protection Agency www.epa.gov/pesticides
- California Environmental Protection Agency Office of Environmental Health Hazard Assessment http://www.oehha.ca.gov/pesticides/programs/services.htm
  On-line free training - https://www.mededpesticide.org/
- Association of Occupational and Environmental Clinics http://www.aoec.org
- National Pesticide Information Center http://npic.orst.edu/

One person, one pesticide, multiple routes



"The Timing Makes the Poison"

- **Stage specific effects of pesticide exposure**
  - Ethylene oxide can ***induce skeletal effects*** when administered to mice at the zygote stage of development … ***long before skeletogenesis begins***
  - Spectrum of skeletal effects observed after exposure at the zygote stage differs from those observed after exposure during organogenesis

Generoso WM, Rutledge JC, Cain KT, Hughes LA, Braden PW. Exposure of female mice to ethylene oxide within hours after mating leads to fetal malformation and death. Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis Volume 176, Issue 2, February 1987, Pages 269-274. National Research Council. Scientific Frontiers in Developmental Toxicology and Risk Assessment. National Academy of Sciences (2000). P.62.

Characteristics of pesticide exposure that influence health outcome

- Nature of the chemical
- Individual susceptibility
- Amount
- Duration
- Timing

Preconception & Prenatal Exposure

	2,4,5 T, chlorophe wood preservat	Other chlorop herbicides	Other or unsp herbicides	DDT/DDE	Organo-phos insecticide	Other or unsp insecticides, r	Fungicides (Ethy	lene oxide	Unspecified pes
Delayed Concept		Prenatal	Prenatal	Prenatal, Paternal	Prenatal	Paternal	Paternal		Prenatal, Paten
Spontan abortion	Paternal	Prenatal	Prenatal, Paternal	Prenatal, Paternal	Prenatal, Paterna	Prenatal, Paterna	Prenatal, Prena	Prenatal Paterna	Prenatal, Paten
Stillbirth	Paternal		Prenatal	Prenatal	Prenatal	Prenatal	Prenatal		Prenatal, Paten
Preterm Birth	Paternal	Prenatal	Paternal	Prenatal	Prenatal	Prenatal	Prenatal		Prenatal, Paten
Fetal Gr Deficit	Paternal	Prenatal	Prenatal	Prenatal	Prenatal	Prenatal	Prenatal		Prenatal, Paten

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.

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.

Source: Wigle DT, Arbuckle TE, Turner MC et al. Epidemiologic Evidence of Relationships Between Reproductive and Child Health Outcomes and Environmental Chemical Contaminants. *Journal of Toxicology and Environmental Health, Part B*, 11:3732517, 2008.

Preconception & Prenatal Exposure

	2,4,5 T, chlorophenate wood preservatives	Other or unspecified herbicides	Other or unspecified insecticides, repellants	Fungicides (any)	Unspecified pesticides	Soil fumigants
Childhood Cancer						
Leukemia	Paternal	Prenatal	Prenatal, Paterna	Paternal	Prenatal, Paterna	
Lymphoma			Occupational		Prenatal, Paternal	
Brain	Paternal	Prenatal	Prenatal, Paternal	Prenatal, Paternal	Prenatal, Paternal	Prenatal
Neuroblastoma			Prenatal, Paternal		Prenatal, Paternal	
Wilm's tumor		Prenatal	Prenatal		Prenatal, Paternal	
Other Cancers		Prenatal (germ cell)	Prenatal, Paternal (Germ cell)		Prenatal, Paternal (Germ cell, bone , soft tissue sarcoma, eye tumors)	

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.

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Adult Exposures (Women and Girls)

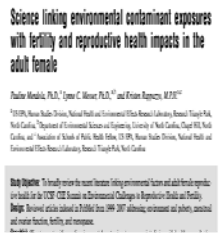
Limited data "[do] not provide consistent evidence for the presence or absence of risk for particular contaminants. … Compounds that can influence the normal balance of hormones, including many pesticides … appear related to risk for many adverse reproductive outcomes." Examples:

Puberty
DDT/ DDE 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 observed in a study of hormonally active pesticides

Fertility and Fecundity
Working with or applying pesticides, primarily in agricultural and horticultural settings, appears to consistently reduce fertility and/or fecundability

Menopause
Age at natural menopause was younger for women exposed to DDT, DDE, and other pesticides


Science linking environmental contaminant exposures with fertility and reproductive health impacts in the adult female

Pauline Mendola, Ph.D.,[1] Lynne C. Messer, Ph.D.,[2,3] and Kristen Rappazzo, M.P.H.[2,3]

Mendola P, Messer LC, Rappazzo K. Science linking environmental contaminant exposures with fertility and reproductive health impacts in the adult female. Fertil Steril. 2008 Feb;89(2 Suppl):e81-94.

Adult Exposure (Males)

Sterility

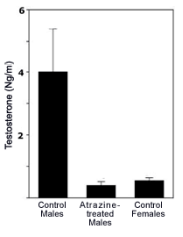
- Occupational exposure to dibromochloropropane (DBCP) caused profound and in many cases permanent effects on spermatogenesis (Whorton et al., 1977)
- Human data on the relationship of semen quality with pesticide exposure are limited and do not currently allow for a definitive conclusion on whether adult exposure, **at background environmental levels**, alters semen quality (Hauser, 2006)

QuickTime™ and a TIFF (LZW) decompressor are needed to see this picture.

Whorton D, Foliart D. DBCP: eleven years later. Reprod Toxicol. 1988;2(3-4):155-61; Whorton D, Krauss RM, Marshall S, Milby TH. Infertility in male pesticide workers. Lancet. 1977 Dec 17;2(8051):1259-61; Hauser R. The environment and male fertility: recent research on emerging chemicals and semen quality. Semin Reprod Med. 2006 Jul;24(3):156-67.

Hormonally Active Pesticides

- Signals from wildlife and animal studies



Atrazine is the most commonly used herbicide in US --- found regularly in rain and drinking water in the US.

Exposure to atrazine induced testosterone failure in frogs (Hayes et al., 2003)

Hundreds of animal studies demonstrate developmental effects of hormone-like compounds present in the environment are biologically plausible--- cause and effect relationships in human populations have not been established (Foster, 2000)

Hayes T, Haston K, Tsui M, Hoang A, Haeffele C, Vonk Foster, AW. Atrazine-Induced Hermaphroditism at 0.1 ppb in American Leopard Frogs (Rana pipiens): Laboratory and Field Evidence Environmental Health Perspectives Volume 111, Number 4, April 2003; Chan S, Platt L, Hughes C. Detection of endocrine disrupting chemicals in samples of second trimester human amniotic fluid. Journal of Clinical Endocrinology and Metabolism. Vol. 85 No. 8. 2000

Human Evidence
Pesticides and Reproductive and Developmental Health

Scope of human evidence

- **257 studies and reports as of 2002**
- Few human studies of reproductive and developmental outcomes for most currently used pesticides
- Most human data are for banned or restricted pesticides
- 5 pesticides accounted for over one-third of all studies (87/257) and almost two-thirds of all studies that specified a pesticide (N=87/137)
  - DDT
  - Agent Orange
  - DBCP
  - Lindane
  - Pentachlorophenol
- DDT and its metabolite DDE had greatest number of studies (27/257)

Source: Laessig S, Tabacova SA, Kimmel CA. A review of reproductive and developmental effects of pesticide exposure in humans. Journal of Children's Health. Vol. 1. No. 4, pp.405-447 (2003)