

Pesticides

Introduction

Pesticides are, by definition, poisons. Designed to kill living organisms, they are one of the few substances that are both toxic and deliberately released into the environment. These twin properties make pesticides unique as environmental contaminants.¹ Pesticides are present in almost every environmental media that has been monitored – including surface water, ground water, ambient air, household dust, soil, fog, rain, and snow.² A recent national survey by the U.S. Geological Survey found pesticide residues in every stream monitored.³ Of common foods sampled by the U.S. Department of Agriculture's (USDA) Pesticide Data Program, pesticide residues were found in more than 70 percent of fruits and vegetables, more than 60 percent of wheat samples, and 99 percent of milk samples.^{1,4} They are also found in the bodies of nearly all U.S. adults and children.^{1,5}

California leads the nation in pesticide use.⁶ Indeed, California is responsible for one-quarter of all pesticides used in the U.S.⁷ Along with New York, Massachusetts, and Oregon, California is also one of few states that maintains a comprehensive pesticide registry. All agricultural pesticide use in the state must be reported monthly to the California Department of Pesticide Regulation (CDRR). However, individual consumers and institutions are not required to report their pesticide applications.⁸

Concerns about a possible link between pesticides and breast cancer are longstanding in both the research community and the cancer activist

community. Ten common pesticides have been associated with increases in mammary gland tumors in at least one animal study.⁹ The endocrine-disrupting abilities of many other pesticides, especially those that act as estrogens, have raised questions about possible contributory roles for these chemicals in breast cancer etiology.¹⁰ Recently, concern has been expressed over the widespread use of organophosphates (e.g. malathion) and pyrethroids (e.g. permethrin) in residential areas for public health programs, such as vector control to contain West Nile Virus. There is also concern, but more limited information, about synergists, surfactants, and other “inert” ingredients.

Of particular concern among many researchers and activists are the triazine herbicides. These include the weed killer atrazine, the most common pesticide used in the U.S. and the most common pesticide contaminant of drinking water. Restricted for use in the European Union, atrazine increases estrogen production in vitro and induces mammary gland tumors in one strain of laboratory rat.¹¹ Recent animal studies also suggest that early-life exposures to atrazine can alter mammary gland development in ways that may predispose the breast to cancer.^{12, 13}

In this chapter, we review the evidence for a pesticide-breast cancer link, with an emphasis on pesticides in current use. Widely-studied organochlorine pesticides are also considered here. This particular class of insecticides is further explored in the subchapter on persistent organic pollutants (POPs) that immediately follows. This redundancy reflects that fact that some studies have considered chlorinated pesticides in the

larger context of POPs exposure – which includes non-agricultural chemicals such as dioxins and PCBs – while other studies have considered chlorinated pesticides along with agricultural chemical exposures of other kinds. While most organochlorine pesticides have been phased out of use and body burden residues are falling,⁵ a few still remain in common use. Notable among these are methoxychlor and endosulfan.

Regulatory History of Pesticides

Before World War II, the agricultural industry was small and depended on a handful of chemical compounds, including petroleum products (such as diesel fuel) and arsenicals (such as Paris green). Between 1917 and 1942, lead arsenate and calcium arsenate were the most common pesticides in use.¹⁴ Lead arsenate was commonly used in apple orchards during this time period. In the 1930s, fluoride-based pesticides, such as cryolite and barium fluorosilicate, were introduced by western fruit growers. The chronic effects of exposure to petroleum-, heavy metal-, and fluoride-based pesticides were never systematically evaluated by the U.S. government.¹⁴ However, soil and household dust samples collected in and around homes constructed on land previously used as orchards frequently show ongoing contamination by heavy metals, including arsenic and lead.^{15, 16}

Synthetic organic pesticides were introduced into agriculture at the end of World War II. Within ten years, carbon-based pesticides captured 90 percent of the agricultural pest-control market and had almost completely routed the pest-control techniques of the prewar years.^{17, 18} Hence the baby boom generation is the first to experience

lifelong exposures to synthetic organic pesticides. This cohort is just beginning to reach the age of maximum risk for breast cancer.

Many pesticides were developed under the secrecy of wartime and with military purposes in mind. For example, DDT was first deployed in wartime Naples to halt a typhus epidemic. The phenoxy herbicides (2,4D and 2,4,5T) were developed with the goal of destroying the Japanese rice crop. Organophosphates were developed by a German company as nerve gasses. The first generation of organophosphate poisons were tested on prisoners in the concentration camps of Auschwitz.¹⁹⁻²¹ The peculiar origins of chemical pesticides as weapons of warfare have meaning for our current toxicological understanding of these chemicals, which is notably incomplete. Little advance testing was conducted for chronic, low-level exposures prior to their reinvention as a civilian tool of pest control.

Since 1972, pesticides have been regulated under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), which subjects them to more scrutiny than other toxic chemicals.¹ For example, FIFRA requires registration for all pesticides, which includes mandatory data collection on potential health risks. Regulatory decision-making under FIFRA is based on risk-benefit standards, with weight given to the economic benefit of controlling the pest, rather than a strictly health-based standard. In 1988, FIFRA was amended to bring data collection up to date for older pesticides that went on the market before such testing was required. This process is still ongoing.²²

The U.S. Environmental Protection Agency (EPA)

Identifying Gaps in Breast Cancer Research

sets standards called tolerances for allowable levels of pesticides on food. The U.S. Food and Drug Administration (FDA), charged with enforcement, monitors the food supply for pesticide residues, with the exception of meat and poultry, which is monitored by the USDA. From 1958 to 1996, the Delaney Clause prohibited the presence of cancer-causing pesticides in processed foods. However, this law was openly flouted. In 1993, a report from the National Research Council found that federal regulations were inadequate to protect children, due both to their increased susceptibility to harm and their unique food consumption patterns.¹⁸ As a result, the Delaney Clause was replaced in 1996 by the Food Quality Protection Act. This law lifted the strict prohibition on pesticides in processed foods in order to allow detectable levels, but required the EPA to provide an additional margin of safety for tolerance limits when the risks for children are uncertain. It also required that the EPA consider the cumulative impact of pesticides that have a common mechanism of toxicity and gave the agency until 2006 to review the safety of the estimated 800 pesticides in use in the U.S.²³

Additionally, the Food Quality Protection Act directed the EPA to develop a battery of screening tests for hormonally-active pesticides and gave it a 1999 deadline. However, the Endocrine Disruptor Screening Program has been crippled by funding problems and the repeated disbanding of its advisory panel. The deadline for validating test screening points has been pushed back to the end of 2007 and commencement of testing pushed back until 2008.

In May 2007, the EPA released a draft list of 73

pesticides that will be tested under the program. This testing will take place in two phases: tier 1 tests will be in vitro screening assays to identify potential endocrine disruptors; tier 2 tests will be rodent assays. The Natural Resources Defense Council, an advocacy group, along with some leading researchers, have questioned the protocols on the grounds that (1) they favor rodent strains known to be unresponsive to endocrine disruptors in the tier 2 tests,²⁴ (2) they fail to consider prenatal exposures,²⁵ (3) they allow test animals to eat chow that may mask the effects of endocrine disruption,²⁵ and (4) they do not sufficiently test for very low-dose exposures.²⁶ In other words, according to these critics, the choice of lab animal and their diet, as well as the chemical dose range and the timing of exposure, are biased toward missing, rather than finding, effects.²⁵

Another recent regulatory action on pesticides undertaken by the EPA involves an organophosphate insecticide. In May 2006, the EPA proposed the continued sale of dichlorvos, although the agency had been poised to ban this pesticide two decades earlier.²³ In February 2007, the Natural Resources Defense Council filed a lawsuit against the EPA for failing, for 20 years, to finish an expedited review of dichlorvos, an organophosphate insecticide that is currently in used in pest strips, aerosol sprays, “bug bombs,” and pet collars.²⁷ Dichlorvos is one of ten pesticides identified by Rudel⁹ as a mammary carcinogen in lab animals.

For regulatory purposes, pesticide ingredients are divided into two categories: active and inert. This is an arbitrary distinction with little toxicological meaning, as more than 500 inert ingredients are

also used, or have been previously used, as active ingredients in other pesticide formulations. In the parlance of regulation, “inert” does not mean biologically inactive or non-toxic, but instead refers only to its function in the formulated product. Inerts can work as solvents, surfactants, potentiators, or preservatives, for example. On average, common household pesticides contain 86 percent inert ingredients. These are rarely identified on the product label, nor are they subject to chemical testing under FIFRA.¹

Pesticides in drinking water are regulated in much the same way as those in food. Just as food has tolerances, drinking water has maximum contaminant levels. These represent the highest limits allowable by law of particular toxic substances, including pesticides. Maximum contaminant levels are not health-based standards. Instead, they take into consideration costs and available technology to reduce contaminants to particular levels, which then become the legal benchmark. In 1974, the Safe Drinking Water Act brought all community water systems under federal and state regulation and required the EPA to set legal limits for contaminants. Individual states are in charge of enforcement. The promulgation of maximum contaminant limits for pesticides was established with the amendments of 1986. Routine monitoring of agricultural chemicals in drinking water began in the state of Illinois in 1992 and now includes all fifty states. Thus, an historical chronicle of pesticide contamination of drinking water does not exist for women old enough to be at risk for breast cancer. Since 1996, amendments to the Safe Drinking Water Act have compelled water utilities to make information about pollutants in drinking water

available to the public in their water bills at least once per year. The law also mandated the creation of a national database of contaminants found in drinking water.²⁸

Pesticides that drift in the air are regulated under the federal Clean Air Act. In California they are also regulated under the Toxic Air Contaminant Act of 1983.⁶ The California Department of Pesticide Regulation has been taken to task for failure to enforce the Toxic Air Contaminant Act through the creation of enforceable drift laws.⁶

In 1990, responding to demands for more realistic and comprehensive pesticide use data, California became the first state to require full reporting of agricultural pesticide use. Under the program, all agricultural pesticide use must be reported monthly to the county agricultural commissioner, who in turn, reports the data to Department of Pesticide Regulation. California has a broad legal definition of agricultural use, so the reporting requirements include pesticide applications to parks, golf courses, cemeteries, rangeland, pastures, and along roadside and railroad rights-of-way. In addition, all post-harvest pesticide treatments of agricultural commodities must be reported, along with all pesticide treatments in poultry and fish production, as well as some livestock applications. The primary exceptions to the reporting requirements are home and garden use and most industrial and institutional uses.⁸

Routes of Exposure

Pesticides have many routes of exposure, and the relative importance of each depends on at least three factors: the type of pesticide, the pest control practices of the community, and the age of the

exposed individual. In general, food is the main route of exposure to organochlorine pesticides, which are persistent and tend to biomagnify in the food chain. Food also appears to be an important route of exposure to organophosphate pesticides. Studies of preschool children in the Seattle area found significantly lower organophosphate pesticide metabolites in the urine of children fed organic diets, compared to those on conventional diets. When children fed conventional diets were shifted to organic diets, through one-to-one substitutions of food items, median concentrations of organophosphate pesticide metabolites in urine fell dramatically, indicating that food was the source of exposure to these pesticides.^{29, 30}

Drinking water is the main route of exposure to triazine herbicides such as atrazine, which is highly mobile in soil and not subject to biomagnification.

Air can be an important route of exposure to many types of pesticides. More than 90 percent of the pesticides used in California are prone to drift. "Second hand pesticides," like second hand tobacco smoke, create involuntary exposures through inhalation. A 2003 analysis of pesticide air monitoring data showed widespread pesticide drift. Farmers and farmworkers were the most highly exposed. However, building fumigations can also be important as airborne routes of exposure for urban and suburban residents.⁶

For children of farmers and farmworkers, exposure can occur through the so-called take-home pathway, when adults track pesticides into their homes. Children of pesticide applicators have higher levels of pesticide metabolites in their urine than the children of non-agricultural

workers, and these levels correlate with metabolite levels in the urine of adults living in the same household, as well as with pesticide levels in vehicle and household dust, as was demonstrated in a recent study of apple and pear workers in Washington state.³¹ Similar results have been reported in California's Salinas Valley by the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS). Eighty-five percent Hispanic, this intensely agricultural region is home to an estimated 38,000 farmworkers. A 2002 quantitative exposure analysis study revealed elevated levels of recently-applied pesticides in the household dust where farm worker families live, and on the clothes and in the urine of farm worker children, particularly toddlers.^{32, 33}

The CHAMACOS cohort study has also found an inverse relationship between pesticide exposure during pregnancy and length of gestation: higher levels of the organochlorine hexachlorobenzene were associated with shorter gestations.³⁴ Similarly, higher levels of organophosphate pesticides in maternal urine during pregnancies were associated with shorter gestations. Markers of organophosphate exposure in umbilical cord blood were also correlated with shorter gestations.³⁵ These results may have relevance for breast cancer research, because preterm birth is a risk factor for early puberty, which itself raises the risk for breast cancer in adulthood.³⁶ In other words, pesticide exposure in prenatal life may alter fetal programming in ways that indirectly increase susceptibility to breast cancer as, for example, by accelerating the pace of sexual maturation. This potential pathway toward breast cancer requires further investigation.

Critical Review of the Literature

In Vitro Studies

In the human breast epithelial cell line MCF10F, the organophosphate pesticide parathion was able to alter gene expression, induce malignant transformation, and appeared to act as an initiator of breast cancer. Interestingly, atropine, which is used as an antidote to parathion in pesticide poisonings, significantly inhibited the genetic alterations triggered by parathion exposure.³⁷

The weed killer atrazine increases aromatase expression in some human cancer cell lines and thereby increases estrogen production. According to one recent study, it does so by binding to and inhibiting phosphodiesterase, which results in elevated cAMP, which, in turn, stimulates transcription of the aromatase gene.¹¹ However, the precise molecular mechanism is incompletely understood and appears to vary between cell types.¹¹

Several pesticides have been shown to exhibit estrogenicity in the ESCREEN assay developed by Soto and others.³⁸ Notable among these is the chlorinated pesticide endosulfan, which is still in current use and is a common contaminant in California's Alamo River (Imperial County). A 2000 survey of pesticides in California surface water found endosulfan in 64 percent of all samples collected from the Alamo.³⁹

The ESCREEN assay also revealed that estrogenic chemicals may act cumulatively: when mixed together, they induce estrogenic responses in human breast cell lines at concentrations lower than those required when each compound is

administered alone.⁴⁰ These results have particular significance for pesticides, which are, more often than not, found together in environmental media. California's Alamo River, for example, contains not only endosulfan but also diazinon and chlorpyrifos.³⁹

Phenol derivatives generally contribute to estrogenic activity. One of these, 2,4-dichlorophenol (2,4-DCP), is the primary metabolite of the widely used phenoxy herbicide 2,4-D, which is classified by the International Agency for Research on Cancer as a class 2B, possible carcinogen. Gene-expression profiling in some, but not all assays, has shown that the activity of genes related to proliferation was altered after treatment with 2,4-DCP.⁴¹ Very little is known about human exposure to 2,4-DCP, and health effects in animal models and humans are poorly understood.⁴²

In Vivo Studies

Animal studies reveal that atrazine can affect mammary gland development. Early-life exposure to atrazine delays mammary gland differentiation in ways that prolong the presence of terminal end buds in the gland.^{13, 43} The lingering presence of terminal end buds in the breast has been demonstrated to raise the susceptibility of the breast to carcinogenic damage.^{13, 43} Moreover, among Long-Evans rats, very low levels of atrazine metabolite mixtures administered during late pregnancy were able to perturb mammary gland development of female offspring in ways that persisted into adulthood and that were unrelated to pubertal timing.¹²

Atrazine does not induce mammary gland tumors in female F344 rats, but it does induce tumors in Sprague Dawley rats. These tumors are generally presumed not to be relevant to humans, based on the observation that atrazine also induces premature reproductive aging in Sprague Dawley rats, which is thought to be associated with elevated estrogen levels. By contrast, in humans, reproductive aging is associated with lower estrogen levels. However, data do not exist to support this presumption.⁹

In addition to atrazine, the pesticides demonstrated to cause mammary gland tumors in animal studies are 1,2-dibromo-3-chloropropane (DBCP), captifol, chlordane, clonitralid, dichlorvos, fenvalerate, nifurthiazole, simazine, and sulfalate.⁹ Of these ten, seven are banned or restricted. DBCP is a fumigant that was heavily used on grapes, tomatoes, and pineapples until its ban in 1985.⁴⁴ Captifol is a phthalate fungicide for which registration was cancelled in 1986.⁴⁵ Chlordane, a chlorinated insecticide once used in fire ant control, is now also restricted.⁴⁵ Fenvalerate, once widely used as a flea and tick repellent and a termiticide, is a pyrethroid insecticide that has been cancelled for use.⁴⁵ Sulfalate is a carbamate herbicide that was phased out of use in the early 1990s. Clonitralid is restricted and is used primarily to kill sea lampreys and snails. However, there is widespread potential for human exposure in the Great Lakes area.⁴⁶ Nifurthiazole is an antibacterial agent no longer produced in the U.S.⁴⁷

The remaining three – dichlorvos, simazine, and atrazine – are both legal and common. Dichlorvos is an organophosphate insecticide. As described

above, it is used in no-pest strips, flea collars, bug bombs, and ant and roach sprays for the home. It is also used in barns.⁴⁵ Simazine is a triazine herbicide that remains in wide use as a soil sterilant and weed killer, although its use as an algacide in swimming pools and hot tubs has been prohibited.⁴⁸ Indeed, it is the 20th most common agricultural herbicide in the U.S.. California receives the highest use of simazine in the U.S.⁴⁹ Simazine has been detected in California well water⁵⁰ as well as in the San Joaquin River and its tributaries. According to a 2000 analysis, simazine was among the five most frequently detected pesticides in California surface water.³⁹ Atrazine, the number-one pesticide used in the U.S., is also present in California ground water in the northern third of the state and throughout the Central Valley.⁵⁰

Human Studies

Studies that examine breast cancer risk among women with occupational exposures

Some, but not all, epidemiological studies of women farmers report increased risks for breast cancer.^{7, 10, 51} Breast cancer risk doubled among North Carolina women farmers who did not wear protective gear while spraying pesticides or who worked in the fields during or shortly after spraying.⁵² Most epidemiologic studies of breast cancer among women farmers and farmworkers have relied on estimations of past exposure, which can be subject to exposure misclassification. They have often presented results for all pesticides or multiple classes of pesticides, which makes it difficult to evaluate the role of an individual

compound, but accounts for the fact that exposure generally does not occur to individual pesticides.¹⁰

The ongoing Agricultural Health Study has examined pesticide use and breast cancer among farmers' wives in a large prospective cohort study in Iowa and North Carolina. So far, overall pesticide use is not associated with increased risk of breast cancer, but follow-up time is still relatively short, and it may be too early to observe statistically significant associations. Nevertheless, risk was elevated modestly among wives whose homes were closest to areas of pesticide application. Moreover, breast cancer risk was related to the use of several specific pesticides, with the strongest link to husbands' use of 2,4,5-TP (2,4,5-trichlorophenoxypropionic acid). Also known as silvex, this phenoxy herbicide is known to be contaminated with dioxin. As of 1985, it is no longer available for use in the U.S.⁴⁵ Weaker links were found with the chlorinated insecticide dieldrin (outlawed in 1971) and the phthalate fungicide captan (outlawed in 1989). This cohort will be followed further.¹⁰

In California, 81 percent of women farmworkers are Hispanic.⁷ These women typically begin their work in the fields as children and teenagers and are thus potentially exposed to multiple pesticides from a young age onward.⁷ A nested case-control study of 128 newly-diagnosed breast cancer cases within a cohort of Hispanic women farm workers found increased breast cancer risk among younger women and those with early-onset breast cancer. Those women in the highest quartile of pesticide use had odds ratios that were 40 percent higher than those in the lowest quartile. Risk of breast cancer was not associated with any particular

single crop except mushrooms, where exposed women were at six-fold increased risk, compared to non-exposed women. All women in this study were members of the United Farm Workers (UFW) union.⁷

Studies that examine breast cancer risk among women living in agricultural areas

For adults, living in a crop-production area where pesticides are used increases the risk of several cancers, including lymphomas, leukemias, ovarian cancer, and brain cancer; Kelsey provides a review.⁶ Results for breast cancer have been mixed. This possible association between breast cancer and living in areas where pesticides have been heavily used outdoors has been difficult to study, because several important breast cancer risk factors, including reproductive history, physical activity level, and body weight, are likely to vary geographically and be associated with rural/urban living. So, for example, hypothetically, an increase in risk due to pesticides could be offset by decreased risk due to earlier childbearing, higher physical activity, or lower obesity rates. In fact, one ecological study that looked at pesticide-use data and cancer-incidence data in California deliberately excluded breast cancer from its correlation analysis because other factors, such as reproductive histories, also varied between counties.⁵³

Three studies aimed at evaluating whether breast cancer rates in California are related to recent pesticide use have reached different conclusions. Using data from both the state cancer registry and from the pesticide use registry, a 2005 study found no evidence that California women living in areas of recent, high agricultural pesticide use

experience higher rates of breast cancer.⁵⁴ Proximity to pesticide-intense farm fields during childhood or puberty, however, was not investigated.

Similarly, a 2004 study found no association between residential proximity to recent agricultural pesticide use and invasive breast cancer incidence among members of the California Teachers Study cohort, which has been followed for cancer incidence since 1995.⁵⁵ It should be noted, however, that exposure classification was based on the current address of participants and no comprehensive residential history was available for these analyses. Conversely, a third study that focused solely on Hispanic women in California observed an association between pesticide use and breast cancer incidence. Specifically, risk of breast cancer was positively associated with pounds of two organochlorine pesticides, methoxychlor and toxaphene. No association was found for the triazine herbicides atrazine and simazine. In this study, no distinction was made between Hispanic women who worked in agricultural operations and those who simply lived near the fields.⁵⁶ It is possible that there is less variation in other breast cancer risk factors, such as reproductive history, in an analysis that is limited to Hispanic women. There may also be better differentiation between highly-exposed (farm worker) women and low-exposed women.

Some studies have demonstrated associations between residential proximity to areas of past pesticide use and increased risk of breast cancer. In Long Island, a more than six-fold increase in risk of breast cancer was seen in long-time

residents who lived on land previously used for agriculture and who also had never given birth or were older than 26 years old at the time of first childbirth (OR 6.4 (2.2–18.2)). In other words, there was an interaction between agricultural history and reproductive history. This study also found an increased breast cancer risk among women residing within one mile of a hazardous waste site containing organochlorine pesticides.⁵⁷

The Cape Cod Breast Cancer and Environment Study, a case-control study of 2,100 women, reconstructed in detail historical exposure to pesticides used in insect control and agriculture, and on roadside rights of way, and estimated women's annual exposure at each Cape Cod address where they lived since 1948. Results from this study did not demonstrate consistent associations between breast cancer and living in areas where banned or currently-used pesticides were applied.⁵⁸ However, this and another study conducted on Cape Cod⁵⁹ did find weak, statistically non-significant associations between breast cancer and living near cranberry bogs.

One ecologic cohort study in Kentucky found an association between breast cancer and atrazine-contaminated well water.⁶⁰

Studies that examine links between breast cancer and residential pesticide use

In a recent report from the Long Island Breast Cancer Study, self-reported use of lawn and garden pesticides was associated with a 40 percent increased risk of developing breast cancer, but there was no dose-response relationship. In this study, which is the first to investigate self-reported pesticide use in a residential setting, 1,508 women

with newly-diagnosed breast cancer and 1,556 women without breast cancer were questioned about their pesticide practices.⁶¹

Studies that examine links between breast cancer and organochlorine pesticides

Because pesticides have so many possible routes by which they may enter the body, assessing real-life exposures is challenging – Especially for highly polar, water-soluble chemicals that have short half-lives. For persistent chemicals that are stored in body fat, such as organochlorine pesticides, exposures can be measured in blood or fat samples, often many years after exposure. By the early 1990s, several descriptive studies had suggested that blood levels or adipose levels of DDT and its DDE metabolites, as well as that of other organochlorine pesticides, might predict breast cancer risk.⁶² A causal link between organochlorine exposure and breast cancer seemed to make biological sense. Many organochlorines act as weak estrogens, and pesticides such as DDT, chlordane, and dieldrin were known to cause other types of cancer.⁶² And indeed, a prospective, nested, case-control study from Denmark did report positive results with dieldrin exposure: women with the highest blood levels of dieldrin had double the risk of breast cancer.⁶³

However, the results of most recent case-control studies – which have focused on white, Western adult women – have been largely negative (reviewed by Brody et al.,⁴³ Clapp et al.,⁶⁴ Engel et al.,¹⁰ Khanjani et al.,⁶⁵ and Mills et al.⁷). It is still unclear if particular subpopulations of women – of different racial or ethnic backgrounds, for example – may have higher breast cancer risks from past or current organochlorine pesticide exposure.⁶² At

least one small study found that black women with breast cancer, as a group, had higher blood levels of DDE than black women without breast cancer.⁶⁶ Not yet investigated is the question of whether exposure to organochlorine pesticides during breast development in early life plays a contributory role. Also unknown is the effect of organochlorine pesticide exposure on age at diagnosis, breast tumor progression, metastatic potential, or morbidity. Emerging research on gene-environment interactions highlights the need for future analyses that focus on genetically-susceptible subpopulations.⁴³ According to a review by Brody, certain genetic polymorphisms appear to play a role in modulating the carcinogenicity of another group of organochlorine compounds, the PCBs,⁴³ and could play a role in dampening or magnifying the effects of organochlorine pesticides as well. These effects may be masked in exposure studies of the general population.

For further discussion of DDT and other organochlorine pesticides, see Section I, Chapter B.2, Persistent Organic Pollutants.

Studies of breast cancer and currently-used pesticides

Other than the organochlorine insecticides, which are now mostly outlawed, few pesticides have been investigated in relation to breast cancer risk. There is a particular dearth of information about currently-used pesticides and breast cancer risk. Among currently-used pesticides, researchers have established connections in some studies, but not all, to breast cancer and atrazine, 2,4D, and malathion.^{7, 10, 64}

Conclusions and Future Directions

There are many reasons to explore further the possible link between pesticides and breast cancer risk in California: Human pesticide exposure is ubiquitous. California leads the nation in pesticide use. Many pesticides are known endocrine disruptors, and several pesticides in common use are known to cause mammary tumors in laboratory animals. The epidemiological data are inconsistent and difficult to evaluate because of limitations in the methods and data available to estimate exposures across a lifetime. In light of recent animal studies that reveal effects of early-life exposure on mammary gland development, further epidemiologic study should take timing of exposure into account. The following are suggested avenues for further inquiry:

1) Environmental epidemiology needs to be integrated with disparities research. Hispanic women in California experience a 42 percent lower risk of breast cancer than do non-Hispanic white women. Reproductive patterns probably explain part of this difference. Among Hispanic farmworkers, the intense physical activity required by farm labor may also have a protective effect.⁷ Accordingly, Hispanic women living in intensely agricultural areas and/or working as farmworkers need to be compared to Hispanic women without such exposures. Simply comparing rates of breast cancer among women of all races among counties with varying pesticide use patterns may blur important associations within and among subpopulations. That is, pesticides in agricultural counties may be significantly contributing to the burden of breast cancer among Hispanic farmworkers, but comparing their rates to

populations of predominantly white women in non-agricultural areas will not reveal this association.

2) The biologic impact of combined exposures remains unknown.¹⁰ New methods in epidemiology, analytical chemistry, and toxicology need to be developed to explore real-life mixtures. Evidence from in vitro studies indicates that effects of pesticides can be cumulative and additive.⁶⁷

3) The biological impact of pesticide exposures at early developmental stages remains unknown.¹⁰ Animal studies, particularly of atrazine, indicate the importance of cellular events taking place many years before breast cancer develops.¹³ Pesticide use patterns at the time of diagnosis do not reflect conditions at the time that these cellular changes take place. This is especially problematic for many currently-used pesticides, which are not persistent. Future studies should focus on pesticide exposures at biologically relevant time points (i.e. *in utero*, puberty, before childbirth).

4) Known mammary carcinogens in common use, such as atrazine, simazine and dichlorvos, deserve closer scrutiny. The commonly-used herbicide 2,4D and its phenolic metabolite, 2,4DCP, also deserve further investigation. California's pesticide reporting program can pinpoint areas of intense use of these pesticides.

5) Studies should focus on commercial formulations, including the inert ingredients, and not just the active ingredients.

6) Interactions between reproductive history and pesticide exposure deserve further investigation.

7) Future studies should also consider interactions between pesticide exposure and genes relevant in the biological pathways by which these chemicals influence breast cancer risk.

References

1. Cox C, Surgan M. Unidentified inert ingredients in pesticides: implications for human and environmental health. *Environ Health Perspect.* 2006, 114(12):1803-6.
2. Majewski MS, Chapel PD. *Pesticides in the Atmosphere: Distribution, Trends and Governing Factors.* Chelsea, MI, USA: Ann Arbor Press, 1993.
3. Gilliom RJ, Barbash JE, Crawford CG, Hamilton PA, Martin JD, Nakagaki N, Nowell LH, Scott JC, Stackelberg PE, Thelin GP, Wolock DM. *The Quality of our Nation's Waters: Pesticides in the Nation's Streams and Ground Water, 1992-2001.* Reston, VA, USA: United States Geological Survey (USGS), National Water-Quality Assessment Program, 2007. Report ID: USGS Circular 1291. Available at <http://pubs.usgs.gov/circ/2005/1291/pdf/circ1291.pdf>. (ISBN: 1411309553)
4. United States Department of Agriculture (USDA), Agricultural Marketing Service, Science and Technology Programs. *Pesticide Data Program: Annual Summary Calendar Year 2004.* Washington, DC, USA: United States Department of Agriculture (USDA), 2006. Available at <http://www.ams.usda.gov/science/pdp/summary2004.pdf>.
5. United States Centers for Disease Control and Prevention (CDC). *Third National Report on Human Exposure to Environmental Chemicals.* Atlanta, GA, USA: National Center for Environmental Health, Division of Laboratory Sciences, 2005. Report ID: NCEH Pub. No. 05-0570. Available at <http://www.cdc.gov/exposurereport/3rd/pdf/thirdreport.pdf>.
6. Kegley SE, Katten A, Moses M, Pesticide Action Network, Californians for Pesticide Reform. *Secondhand Pesticides: Airborne Pesticide Drift in California.* San Francisco, CA, USA: Pesticide Action Network, 2003.
7. Mills PK, Yang R. Breast cancer risk in Hispanic agricultural workers in California. *Int J Occup Environ Health.* 2005, 11(2):123-31.
8. California Department of Pesticide Regulation (CDPR). *Pesticide Use Reporting: An Overview of California's Unique Full Reporting System, May 2000* [web page]. Sacramento, CA, USA: California Department of Pesticide Regulation (CDPR), 2000. Available at <http://www.cdpr.ca.gov/docs/pur/purovrw/tabofcon.htm>. Accessed 28 Aug 2007.
9. Rudel RA, Attfield KR, Schifano JN, Brody JG. Chemicals causing mammary gland tumors in animals signal new directions for epidemiology, chemicals testing, and risk assessment for breast cancer prevention. *Cancer.* 2007, 109(S12):2635-66.

California Breast Cancer Research Program

10. Engel LS, Hill DA, Hoppin JA, Lubin JH, Lynch CF, Pierce J, Samanic C, Sandler DP, Blair A, Alavanja MC. Pesticide use and breast cancer risk among farmers' wives in the agricultural health study. *Am J Epidemiol.* 2005, 161(2):121-35.
11. Fan W, Yanase T, Morinaga H, Gondo S, Okabe T, Nomura M, Komatsu T, Morohashi K, Hayes TB, Takayanagi R, Nawata H. Atrazine-induced aromatase expression is SF-1 dependent: implications for endocrine disruption in wildlife and reproductive cancers in humans. *Environ Health Perspect.* 2007, 115(5):720-7.
12. Enoch RR, Stanko JP, Greiner SN, Youngblood GL, Rayner JL, Fenton SE. Mammary gland development as a sensitive end point after acute prenatal exposure to an atrazine metabolite mixture in female Long-Evans rats. *Environ Health Perspect.* 2007, 115(4):541-7.
13. Fenton SE. Early life exposures to environmental compounds: lessons learned from animal models. *The Ribbon - A Newsletter of the Cornell University Program on Breast Cancer and Environmental Risk Factors (BCERF).* 2007, 12(1):1-4.
14. Wargo J. *Our Children's Toxic Legacy: How Science and Law Fail to Protect Us from Pesticides.* New Haven, CT, USA: Yale University Press, 1998. (ISBN: 9780300074468)
15. Robinson GRJr., Larkins P, Boughtonb CJ, Reeda BW, Sibrellb PL. Assessment of contamination from arsenical pesticide use on orchards in the Great Valley region, Virginia and West Virginia, USA. *J Environ Qual.* 2007, 36:654-63.
16. Wolz S, Fenske RA, Simcox NJ, Palcisko G, Kissel JC. Residential arsenic and lead levels in an agricultural community with a history of lead arsenate use. *Environ Res.* 2003, 93(3):293-300.
17. Hayes WJ, Laws ER. *Handbook of Pesticide Toxicology.* San Diego, CA, USA: Academic Press, 1991. (ISBN: 9780123341617)
18. National Research Council (NRC), Committee on Pesticides in the Diets of Infants and Children. *Pesticides in the Diets of Infants and Children.* Washington, DC, USA: National Academy Press, 1993. (ISBN: 9780309048750)
19. Chambers JE, Levi PE. *Organophosphates: chemistry, fate and effects.* San Diego, CA, USA: Academic Press, 1992. (ISBN: 9780121673451)
20. Lilienfeld DE, Gallo MA. 2,4-D, 2,4,5-T, and 2,3,7,8-TCDD: an overview. *Epidemiol Rev.* 1989, 11:28-58.

Identifying Gaps in Breast Cancer Research

21. Russell EPIII. Speaking of annihilation: mobilizing for the war against human and insect enemies, 1914-1945. *J Am History*. 1996, 82:1505-29.
22. United States Environmental Protection Agency (US EPA). Federal Insecticide, Fungicide and Rodenticide Act. United States Code, Title 7-Agriculture; Chapter 6-Insecticides and Environmental Pesticide Control; SubChapter II-Environmental Pesticide Control, Sections 136 et seq. 1996. Available at http://www.access.gpo.gov/uscode/title7/chapter6_subchapterii_.html.
23. Raeburn P. Slow Acting: After 25 years, EPA still won't ban a risky pesticide [magazine article]. In: *Scientific American Magazine*. p. 14. New York, NY, USA: Munn & Co., 2006 Aug.
24. Hileman B. Latest News: EPA unveils testing list: Critics say EPA's endocrine disrupter screening program will miss dangerous chemical [article]. In: *Chemical & Engineering News*. 85(25):p. 13. Washington, DC, USA: American Chemical Society, 2007 Jun 18.
25. Goetinck-Ambrose S. Scientists criticize EPA chemical screening program: Experts worry agency's program will miss harmful effects on hormones; agency counters program developed in an open manner [newspaper article]. In: *The Dallas Morning News*. Dallas, TX, USA: The Dallas Morning News, 2007 May 27. Section Science/Medicine. Available at <http://www.dallasnews.com/sharedcontent/dws/news/healthscience/stories/052707dnentendocrine.3a08215.html>.
26. Risk Policy Report. Activists say endocrine screening list ignores high-risk substances [article]. In: *Environmental NewsStand: Risk Policy Report*. 14(25). Washington, DC, USA: Inside Washington Publishers, 2007 Jun 19.
27. Natural Resources Defense Council (NRCD) v. Stephen L. Johnson, Administrator, United States Environmental Protection Agency (US EPA). Case No. CV 06-4843 PSG(JTLx) Order granting in part and denying in part plaintiff's motion for partial summary judgement on the pleadings. United States District Court, Central District of California, Western Division; 2007 Mar 21.
28. United States Environmental Protection Agency (US EPA). Safe Drinking Water Act. United States Code; Title 42-The Public Health and Welfare; Chapter 6A-Public Health Services; Subchapter XII-Safety of Public Water Systems, Sections 300f et seq. 1974. Available at http://www.access.gpo.gov/uscode/title42/chapter6a_subchapterxii_.html.
29. Curl CL, Fenske RA, Elgethun K. Organophosphorus pesticide exposure of urban and suburban preschool children with organic and conventional diets. *Environ Health Perspect*. 2003, 111(3):377-82.

30. Lu C, Toepel K, Irish R, Fenske RA, Barr DB, Bravo R. Organic diets significantly lower children's dietary exposure to organophosphorus pesticides. *Environ Health Perspect.* 2006, 114(2):260-3.
31. Coronado GD, Vigoren EM, Thompson B, Griffith WC, Faustman EM. Organophosphate pesticide exposure and work in pome fruit: evidence for the take-home pesticide pathway. *Environ Health Perspect.* 2006, 114(7):999-1006.
32. Bradman A, Whitaker D, Quiros L, Castorina R, Henn BC, Nishioka M , Morgan J, Barr DB, Harnly M, Brisbin JA, Sheldon LS, McKone TE, Eskenazi B. Pesticides and their metabolites in the homes and urine of farmworker children living in the Salinas Valley, CA. *J Expo Sci Environ Epidemiol.* 2006, doi: 10.1038/sj.jes.7500507 (available at <http://dx.doi.org/>).
33. Eskenazi B, Bradman A, Castorina R. Exposures of children to organophosphate pesticides and their potential adverse health effects. *Environ Health Perspect.* 1999, 107 Suppl 3:409-19.
34. Fenster L, Eskenazi B, Anderson M, Bradman A, Harley K, Hernandez H, Hubbard A, Barr DB. Association of in utero organochlorine pesticide exposure and fetal growth and length of gestation in an agricultural population. *Environ Health Perspect.* 2006, 114(4):597-602.
35. Eskenazi B, Harley K, Bradman A, Weltzien E, Jewell NP, Barr DB, Furlong CE, Holland NT. Association of in utero organophosphate pesticide exposure and fetal growth and length of gestation in an agricultural population. *Environ Health Perspect.* 2004, 112(10):1116-24.
36. Parent AS, Teilmann G, Juul A, Skakkebaek NE, Toppari J, Bourguignon JP. The timing of normal puberty and the age limits of sexual precocity: variations around the world, secular trends, and changes after migration. *Endocr Rev.* 2003, 24(5):668-93.
37. Calaf GM, Roy D. Gene expression signature of parathion-transformed human breast epithelial cells. *Int J Mol Med.* 2007, 19(5):741-50.
38. Soto AM, Sonnenschein C, Chung KL, Fernandez MF, Olea N, Serrano FO. The E-SCREEN assay as a tool to identify estrogens: an update on estrogenic environmental pollutants. *Environ Health Perspect.* 1995, 103 Suppl 7:113-22.
39. Olle TM, Orme S, Heavner B. *Water Woes: An Analysis of Pesticide Concentrations in California Surface Water.* San Francisco, CA, USA: California Public Interest Research Group (CALPRIG) Charitable Trust and the Pesticide Action Network Regional Center, 2000. Available at http://www.environmentalcalifornia.org/uploads/c7/eU/c7eUM6AACnrdMNJBcv7tHw/Water_Woes.pdf.

Identifying Gaps in Breast Cancer Research

40. Soto AM, Chung KL, Sonnenschein C. The pesticides endosulfan, toxaphene, and dieldrin have estrogenic effects on human estrogen-sensitive cells. *Environ Health Perspect.* 1994, 102(4):380-3.
41. Terasaka S, Inoue A, Tanji M, Kiyama R. Expression profiling of estrogen-responsive genes in breast cancer cells treated with alkylphenols, chlorinated phenols, parabens, or bis- and benzoylphenols for evaluation of estrogenic activity. *Toxicol Lett.* 2006, 163(2):130-41.
42. Fenton SE. Personal communication to Catherine Thomsen. 2007 Aug 31.
43. Brody JG, Moysich KB, Humblet O, Attfield KR, Beehler GP, Rudel RA. Environmental pollutants and breast cancer: epidemiologic studies. *Cancer.* 2007, 109(12 Suppl):2667-711.
44. United States Environmental Protection Agency (US EPA), Office of Ground Water and Drinking Water (OGWDW). Consumer Factsheet on Dibromochloropropane. On. National Primary Drinking Water Regulations: Drinking Water and Health. Atlanta, GA, USA: United States Environmental Protection Agency (US EPA), 2006. Available at http://www.epa.gov/safewater/contaminants/dw_contamfs/dibromoc.html.
45. Briggs SA, Rachel Carson Council. Basic Guide to Pesticides: Their Characteristics and Hazards. Washington, DC, USA: Hemisphere Pub. Corp., 1992. (ISBN: 9781560322535)
46. National Cancer Institute (NCI). Bioassay of Clonitralid for Possible Carcinogenicity (CAS No. 1420-04-8) (NCI-CG-TR-91). In: National Cancer Institute (NCI). Carcinogenesis: Technical Report Series. Bethesda, MD, USA: United States Department of Health, Education and Welfare (DHEW), Public Health Service (PHS), National Institutes of Health (NIH), 1978. Report ID: DHEW Publication No. (NIH) 78-1341. Available at http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/tr091.pdf.
47. Brody JG, Rudel RA, Michels KB, Moysich KB, Bernstein L, Attfield KR, Gray S. Environmental pollutants, diet, physical activity, body size, and breast cancer: where do we stand in research to identify opportunities for prevention? *Cancer.* 2007, 109(S12):2627-34.
48. Snedeker, S.M. Pesticides and Breast Cancer Risk: Simazine. Ithica, NY, USA: Cornell University, College of Veterinary Medicine, Program on Breast Cancer and Environmental Risk Factors, 1998. Report ID: Fact Sheet # 16. Available at <http://envirocancer.cornell.edu/FactSheet/Pesticide/fs16.simazine.cfm>.
49. United States Environmental Protection Agency (US EPA). Triazine Cumulative Risk Assessment and Atrazine, Simazine, and Propazine Decisions; June 22, 2006. On. Pesticides: Health and Safety. Washington, DC, USA: United States Environmental Protection Agency (US EPA), 2006. Report ID: 2007 Aug 28. Available at http://epa.gov/oppsrrd1/cumulative/triazine_fs.htm.

California Breast Cancer Research Program

50. Domagalski JL, Knifong DL, Dileanis PD, Brown LR, May JT, Connor V, Alpers CN. Water Quality in the Sacramento River Basin, California, 1994-98. Reston, VA, USA: United States Geological Survey (USGS), National Water-Quality Assessment Program (NAWQA), 2000. Report ID: Circular 1215. Available at <http://pubs.usgs.gov/circ/circ1215/pdf/circ1215.pdf>.
51. Brody JG, Rudel RA. Environmental pollutants and breast cancer. *Environ Health Perspect.* 2003, 111(8):1007-19.
52. Duell EJ, Millikan RC, Savitz DA, Newman B, Smith JC, Schell MJ, Sandler DP. A population-based case-control study of farming and breast cancer in North Carolina. *Epidemiology.* 2000, 11(5):523-31.
53. Mills PK. Correlation analysis of pesticide use data and cancer incidence rates in California counties. *Arch Environ Health.* 1998, 53(6):410-3.
54. Reynolds P, Hurley SE, Gunier RB, Yerabati S, Quach T, Hertz A. Residential proximity to agricultural pesticide use and incidence of breast cancer in California, 1988-1997. *Environ Health Perspect.* 2005, 113(8):993-1000.
55. Reynolds P, Hurley SE, Goldberg DE, Yerabati S, Gunier RB, Hertz A, Anton-Culver H, Bernstein L, Deapen D, Horn-Ross PL, Peel D, Pinder R, Ross RK, West D, Wright WE, Ziogas A. Residential proximity to agricultural pesticide use and incidence of breast cancer in the California Teachers Study cohort. *Environ Res.* 2004 , 96(2):206-18.
56. Mills PK, Yang R. Regression analysis of pesticide use and breast cancer incidence in California Latinas. *J Environ Health.* 2006, 68(6):15-22; quiz 43-4.
57. O'Leary ES, Vena JE, Freudenheim JL, Brasure J. Pesticide exposure and risk of breast cancer: a nested case-control study of residentially stable women living on Long Island. *Environ Res.* 2004, 94(2):134-44.
58. Brody JG, Aschengrau A, McKelvey W, Rudel RA, Swartz CH, Kennedy T. Breast cancer risk and historical exposure to pesticides from wide-area applications assessed with GIS. *Environ Health Perspect.* 2004, 112(8):889-97.
59. Aschengrau A, Ozonoff D, Coogan P, Vezina R, Heeren T, Zhang Y. Cancer risk and residential proximity to cranberry cultivation in Massachusetts. *Am J Public Health.* 1996, 86(9):1289-96.
60. Kettles MK, Browning SR, Prince TS, Horstman SW. Triazine herbicide exposure and breast cancer incidence: an ecologic study of Kentucky counties. *Environ Health Perspect.* 1997, 105(11):1222-7.

Identifying Gaps in Breast Cancer Research

61. Teitelbaum SL, Gammon MD, Britton JA, Neugut AI, Levin B, Stellman SD. Reported residential pesticide use and breast cancer risk on Long Island, New York. *Am J Epidemiol.* 2007, 165(6):643-51.
62. Snedeker SM. Pesticides and breast cancer risk: a review of DDT, DDE, and dieldrin. *Environ Health Perspect.* 2001, 109 Suppl 1:35-47.
63. Hoyer AP, Grandjean P, Jorgensen T, Brock JW, Hartvig HB. Organochlorine exposure and risk of breast cancer. *Lancet.* 1998, 352(9143):1816-20.
64. Clapp RW, Howe GK, Jacobs MM. *Environmental and Occupational Causes of Cancer: A Review of Recent Scientific Literature.* Lowell, MA, USA: Lowell Center for Sustainable Production, University of Massachusetts Lowell, 2005. Available at http://www.sustainableproduction.org/downloads/StateoftheScienceFinalDownloadable_000.pdf.
65. Khanjani N, Hoving JL, Forbes AB, Sim MR. Systematic Review and Meta-analysis of Cyclodiene Insecticides and Breast Cancer. *J Environ Sci Health C Environ Carcinog Ecotoxicol Rev.* 2007, 25(1):23-52.
66. Krieger N, Wolff MS, Hiatt RA, Rivera M, Vogelman J, Orentreich N. Breast cancer and serum organochlorines: a prospective study among white, black, and Asian women. *J Natl Cancer Inst.* 1994, 86(8):589-99.
67. Porter WP, Jaeger JW, Carlson IH. Endocrine, immune, and behavioral effects of aldicarb (carbamate), atrazine (triazine) and nitrate (fertilizer) mixtures at groundwater concentrations. *Toxicol Ind Health.* 1999, 15(1-2):133-50.