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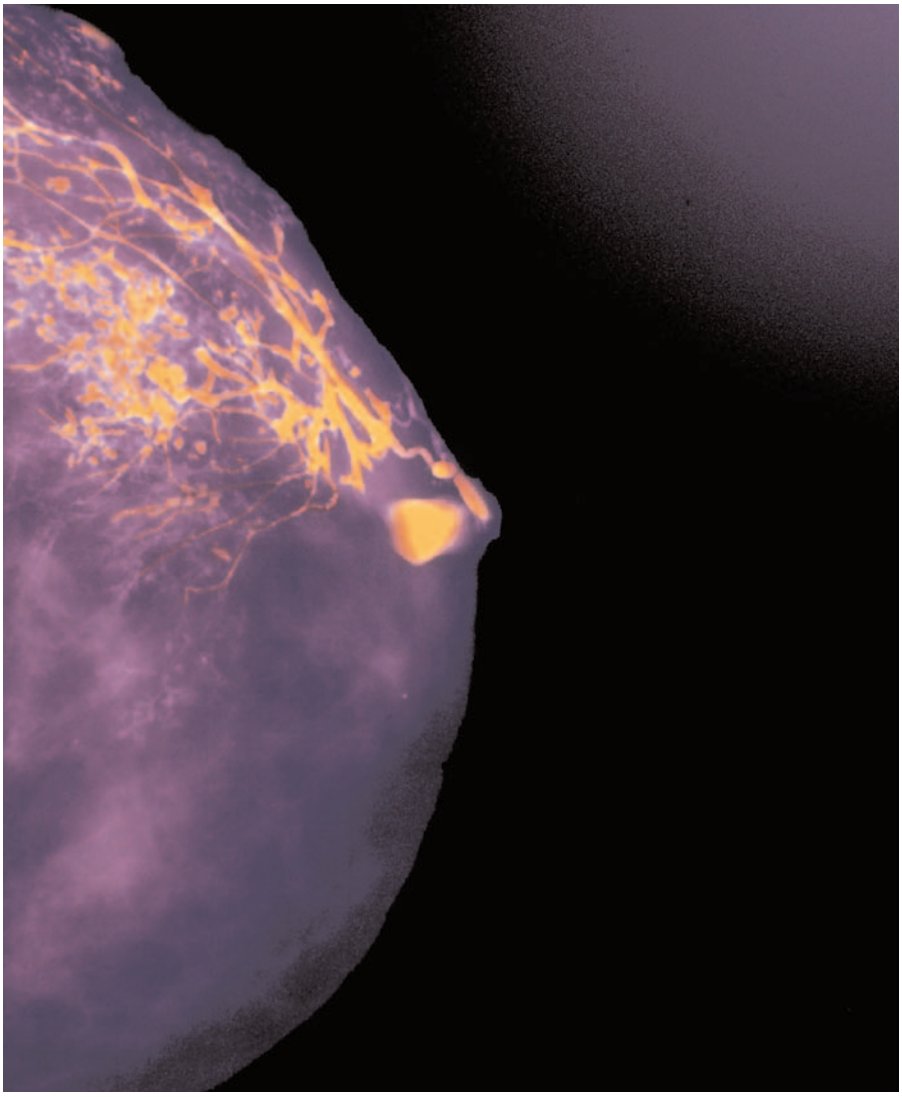

State of the Evidence

What Is the Connection Between the Environment and Breast Cancer?

Edited by Nancy Evans, Health Science Consultant, Breast Cancer Fund

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Executive Summary

Breast cancer rates have been climbing steadily in the United States and other industrialized countries since the 1940s, amounting to more than one million cases per year worldwide.[1] In the United States, a woman's lifetime risk of breast cancer has nearly tripled during the past four decades. In 2005, an estimated 211,240 U.S. women were diagnosed with invasive breast cancer and more than 58,000 women were expected to be diagnosed with one type of in situ breast cancer, meaning the tumor is confined to its original location in the breast. In 2005, breast cancer was expected to kill more than 40,000 American women[2] and more than 410,000 women worldwide.[3] The rate of new cases per year continues to inch upward in the United States even though billions of dollars have been spent on breast cancer research.

Less than one out of every 10 cases occurs in women born with a genetic predisposition for the disease.

Less than one out of every 10 cases occurs in women born with a genetic predisposition for the disease, and as many as half of all breast cancers occur in women who have no known risk factors for the disease. Recent research has made it more and more clear that breast cancer arises from a complicated mix of multiple factors, which may include inherited or acquired genetic mutations, altered gene expression and/or exposures to external agents that affect genes or the production of estrogen or other hormones. More than one exposure or event is usually required before cancer will develop, but the same set of genetic and environmental circumstances will not produce cancer in every individual.

Two decades of research on laboratory animals, wildlife and cell behavior[4] have shown the inadequacy of the long-held belief that "the dose makes the poison." Scientists now know that the timing, duration and pattern of exposure are at least as important as the dose. Low-dose exposure to chemicals in the environment—parts per billion or even per trillion—during a critical window of an organism's development can cause permanent damage to organs and systems.

We are all exposed to radiation and to hundreds, if not thousands, of chemicals every day of our lives, yet we know very little about the likely synergistic effects of these multiple exposures.[5] Testing one exposure at a time for its effects ignores this reality.

An estimated 100,000 synthetic chemicals are believed to be in use today in the United States. Another 1,000 or more are added each year.[6] More than 90 percent have never been tested for their effects on human health.[7] Many of these chemicals persist in the environment, accumulate in body fat and remain in breast tissue for decades. Studies by the U.S. Centers for Disease Control and Prevention (CDC) show that Americans of all ages carry a body burden of at least 148 chemicals that have been measured, some of them banned for more than two decades because of toxicity.[8] These studies alone cannot establish cause but can reveal the internal contamination of our bodies by chemicals with known carcinogenic activity.

Patterns of breast cancer incidence indicate the importance of environmental exposures. Women who move from countries with low breast cancer rates to industrialized countries soon acquire the higher risk of their new country. The largest study ever conducted among twins found that environmental exposures unique to those with breast cancer made the most significant contribution to the development of the disease.

This State of the Evidence report demonstrates that a significant body of scientific evidence links exposure to radiation and synthetic chemicals to an increased risk of breast cancer. It summarizes the findings of more than 350 experimental, epidemiologic and ecological studies and describes some of the ongoing controversies in breast cancer research. The report recommends new directions for future research and includes a 10-point plan to act on the evidence and reduce human exposure to radiation and synthetic chemicals. This plan is based primarily on the precautionary principle, which in part states that indication of harm, not just proof of harm, is grounds for action.[9]

Evidence That Environmental Factors *Cause* Breast Cancer

Ionizing radiation is the longest-established environmental cause of human breast cancer. In 2005, the National Toxicology Program classified X-radiation and gamma radiation as known human carcinogens.[10] Radiation is a mutagen as well as a carcinogen; the same is true of some chemicals. Radiation may even enhance the ability of hormones or other chemicals to cause cancer.[11,12]

Compelling scientific evidence points to some of the 100,000 **synthetic chemicals**[13] in use today as contributing to the development of breast cancer, either by altering hormone function or gene expression.

- There is broad agreement that exposure over time to natural estrogens in the body increases the risk of breast cancer. Hormone replacement therapy (HRT)[14] and hormones in oral contraceptives[15,16,17,18,19] and some other pharmaceuticals also increase this risk. The National Toxicology Program now lists steroidal estrogens (the natural chemical form of estrogen) as known human carcinogens.[20] The International Agency for Research on Cancer (IARC) has listed both steroidal and nonsteroidal estrogens as known human carcinogens since 1987.
- Synthetic agents that mimic the actions of estrogens are known as **xenoestrogens** and are one type of endocrine-(hormone-) disrupting compound. They are present in many pesticides, fuels, plastics, detergents and prescription drugs.[21] Chronic exposure to widespread and persistent xenoestrogens may help explain the increase in breast cancer in industrialized countries around the world. Xenoestrogens known to increase the risk of breast cancer include:
  - Bisphenol-A (BPA), one of the most pervasive chemicals in modern life, used to make polycarbonate plastic;

  - **Diethylstilbestrol** (DES), prescribed for three decades to millions of women to prevent miscarriage, the drug was banned in 1971 because it caused cancer in their daughters;
  - **Polyvinyl chloride** (PVC), used extensively in plastics including food packaging, medical products, appliances, cars, toys, credit cards and rainwear;
  - **Dieldrin**, a pesticide banned from all uses in 1987; and
  - Ingredients in many **household products**, especially cleaning agents, solvents and pesticides.
- Elevated rates of breast cancer have been found among workers exposed to a variety of **solvents** in the electronics, fabricated metal, lumber, furniture, printing, chemical, textile and clothing industries.
- **Aromatic amines** are a class of chemicals found in the plastic and chemical industries, in air and water pollution, diesel exhaust, tobacco smoke and in grilled meats and fish.[22] One type of aromatic amine, o-toluidine, is known to cause mammary tumors in rodents.[23, 24]
- The Environmental Protection Agency determined that **1,3-butadiene** is carcinogenic to humans by inhalation and the National Toxicology Program classifies 1,3-butadiene as a known human carcinogen.[25] 1,3-butadiene is an air pollutant created by internal combustion engines and petroleum refineries. It is also used in some manufacturing processes and is found in tobacco smoke.

Evidence Indicating *Probable* Environmental Links To Breast Cancer

- Various studies have shown that **polycyclic aromatic hydrocarbons** (**PAHs**) appear to play a role in the development of breast cancer. PAHs are compounds found in soot and fumes from combustion of diesel and other fuels, and from grilling meat.
- Two types of chemicals known to disrupt hormone function are the organochlorine pesticide **DDT** and **PCBs** (polychlorinated biphenyls), which were used to manufacture electrical equipment and numerous other industrial and consumer products. Both DDT and PCBs have been banned in the United States for three decades, yet both are still found in the body fat of humans and animals, as well as in human breast milk.[26, 27]
- Of all toxic chemicals, **dioxin** may be the most ubiquitous—and the most toxic. Dioxin is formed by the incineration or combustion of products containing chlorinated compounds, including PVC (polyvinyl chloride) and PCBs. The body fat of every human being, including every newborn, contains dioxin.
- **Ethylene oxide** is a known human carcinogen; the National Toxicology Program identifies it as a mammary carcinogen in animals. Ethylene oxide is a fumigant used to sterilize surgical instruments and is also used in some cosmetics products.[28]

Evidence Indicating *Possible* Environmental Links To Breast Cancer

- The insecticide **heptachlor** was used widely in the United States throughout the 1980s, especially for termite control. It still contaminates both soil and humans. Heptachlor's breakdown product (heptachlor epoxide) is known to accumulate in body fat, including breast tissue. It affects the way the liver processes estrogen, thus allowing levels of circulating estrogens to rise. Heptachlor epoxide may also increase breast cancer risk by disrupting cell growth regulation.[29]
- **Triazine herbicides** are the most heavily used agricultural chemicals in the United States. Triazines include atrazine, simazine and cyanazine. All three have been shown to cause mammary cancer in animals.
- Growing concern about exposure to ultraviolet (UV) radiation from the sun and the risk of skin cancer has led to widespread use of **sunscreens**. Research has found that some sunscreens contain chemicals (also used in other cosmetics) that are not only estrogenic but also lipophilic (fat-seeking).
- **Phthalates** are a group of endocrine-disrupting compounds commonly used to render plastics soft and flexible. They are found in soft plastic "chew toys" marketed for infants and also in some varieties of nail polish, perfumes, skin moisturizers, flavorings and solvents. Disruption of hormonal processes can increase breast cancer risk.
- Modern food production methods have created avenues for exposure to environmental carcinogens and endocrine-disrupting compounds in **food and food additives**. These exposures include pesticides sprayed on crops, antibiotics used on poultry and hormones injected into cattle, sheep and hogs. Consumption of animal products may present inherent risks because pesticides and other environmental toxicants can accumulate in fatty tissue of animals, just as they do in humans. Two examples of agricultural practices that may increase breast cancer risk include:
  - Monsanto's genetically engineered hormone product, recombinant bovine growth hormone (**rBGH**), which increases milk production in dairy cows and which was subsequently renamed recombinant bovine somatotrophin (**rBST**).
  - **Zeranol** (**Ralgro**), a nonsteroidal growth promoter with estrogenic activity and one of the most widely-used hormones in U.S. beef cattle.
- A growing body of evidence implicates **non-ionizing radiation** (electromagnetic fields and radio-frequency radiation [EMF]) as possible contributors to the development of breast cancer. The International Agency for Research on Cancer (IARC) has classified EMF as a possible human carcinogen. Microwaves, radio waves, radar and lights are examples of non-ionizing radiation. Everyone in the industrialized world is exposed to electromagnetic fields every day.

New Research Included In This 2006 Edition

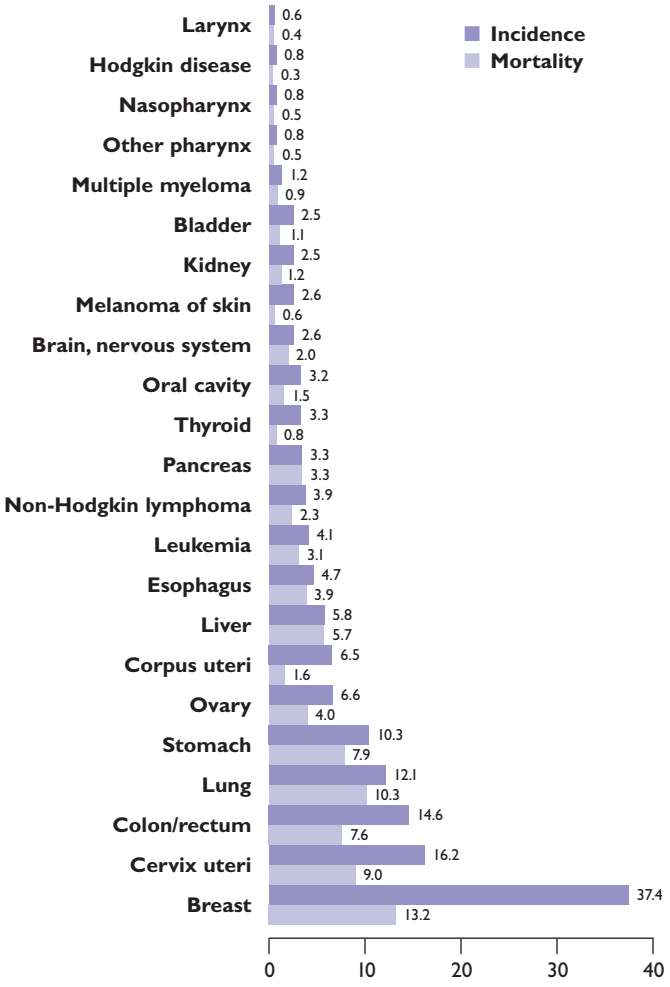
- A major study by Tufts University scientists demonstrated the critical importance of early life exposure to chemicals and the profound effects that can occur from very low doses. The scientists found that exposing pregnant mice to extremely low levels of bisphenol-A altered the development of the mammary gland in their offspring at puberty.[30]
- Re-analysis of a large study of Nordic twins published in 2000[31] concluded that "genetic susceptibility makes only a small to moderate contribution" to the incidence of breast cancer.[32]
- The U.S. Centers for Disease Control and Prevention Third National Report on Human Exposure to Environmental Chemicals revealed that the bodies of Americans of all ages contain 148 synthetic chemicals, some of which are known or suspected carcinogens.[33] Many of these chemicals were also found in the umbilical cord blood of newborn babies.[34]
- Two new articles that reviewed evidence linking breast cancer with environmental factors found that environmental exposures, in combination with genetic predisposition, age at exposure and hormonal factors, have a cumulative impact on breast cancer risk.[35,36]
- A new report from the National Research Council confirms there is no safe dose of ionizing radiation—even the smallest dose has the potential to cause an increased cancer risk in humans.[37]
- A number of new studies implicate exposure to ionizing radiation, particularly before age 20 or during pregnancy, as increasing breast cancer risk.[38,39,40,41,42,43] Additional studies implicate radiotherapy for breast cancer in increasing the risk of additional breast and other cancers.[44,45]
- Research on the structure of genes shows that exposure to ionizing radiation can induce genomic instability and other neoplastic heritable changes, not only in directly-irradiated cells but also in cells not directly exposed to radiation.[46,47,48,49]
- An interdisciplinary analysis of the history of hormone replacement therapy (HRT) revealed that scientists were aware of the cancer risk of HRT in the 1930s. The team of experts asked the question: Why, for four decades, since the mid-1960s, were millions of women prescribed powerful pharmacological agents already demonstrated, three decades earlier, to be carcinogenic? In answering this question, the experts identified five missing elements in the process: the invisible industrialist, regulatory agencies and public interest compared with private interests, beliefs regarding individual risk compared with collective risk, the growth of individualized "preventive medicine" and the gendering of hormones and regulation of women's sexuality. They stated that understanding HRT use in the 20th century demands engaging "with core issues of accountability, complexity, fear of mortality and the conduct of socially responsible science."[50]
- Progestin was linked to increased risk of breast cancer recurrence in two large trials: the Hormone Replacement Therapy After Breast Cancer—Is It Safe? (HABITS)[51] and the Stockholm trial.[52]
- Polychlorinated biphenyls (PCBs) were associated with increased breast cancer risk in a study from Belgium.[53]
- Researchers found an increased breast cancer risk among Long Island, NY, women residing within one mile of hazardous waste sites containing organochlorine pesticides.[54] A separate study measured levels of organochlorine

pesticides and PCBs in the adipose tissue of 224 Long Island women with non-metastatic breast cancer and found that those with the highest level of PCBs had an increased risk of recurrence.[55]

- Pesticide use and breast cancer risk among farmers' wives was examined in a large prospective cohort study in Iowa and North Carolina. Researchers found an increased risk of breast cancer among the wives of farmers using certain chlorinated pesticides and among those living closest to areas of pesticide application.[56]
- An ecological study in 82 Mississippi counties showed a significant association between breast cancer incidence and maximum emissions of environmental chemicals.[57]
- Longer residence on Cape Cod, Mass., is associated with elevated breast cancer risk.[58] Suspected environmental exposures include pesticides and drinking water contaminated by industrial, agricultural and residential land use.
- Researchers in Spain studied the combined effects of environmental estrogens, measured as the total effective xenoestrogen (estrogen-mimicking) burden, and found increased risk among postmenopausal women with the highest levels. The pesticides aldrin and lindane were also individually associated with elevated risk.[59]
- Clustering patterns of breast cancer cases among premenopausal women in western New York state were found to be more related to residence at birth and menarche than residence in any time period of adult life.[60]
- Prenatal and early life exposure to genistein (a phytoestrogen—found in plants) and a mixture of organochlorine chemicals induced marked changes in mammary glands of adult female rats, indicating that phytoestrogens influence the toxicologic effects of mixtures.[61]
- Early life exposure to high levels of polycyclic aromatic hydrocarbons (PAHs), present in tobacco smoke and other air pollution, increased the risk of premenopausal breast cancer in a case-control study of more than 3,200 women.[62]
- A study of 21,000 Japanese women concluded that smoking, both active and passive, increases the risk of developing breast cancer in premenopausal women.[63]
- Methyl mercury can significantly alter growth-related signaling in human breast cancer cells and, therefore, should be considered a potential endocrine-disrupting compound.[64]
- Phthalates, which are ingredients ubiquitous in cosmetics and personal care products, were shown to significantly increase cell proliferation in human breast cancer cells. Scientists also found that certain phthalates inhibited the cell-killing capacity of tamoxifen (a drug with anti-estrogen activity) in MCF-7 breast cancer cells.[65]
- German scientists reported that Eusolex 6300, a sunscreen, showed estrogenic effects similar to 17-beta-estradiol (the most common form of natural estrogen) on mammalian and amphibian cells.[66]

Phthalates, which are ingredients ubiquitous in cosmetics and personal care products, were shown to significantly increase cell proliferation in human breast cancer cells.

Cancer Rates Among Women By Cancer Site Worldwide, 2002.



Incidence and mortality rates per 100,000 for cancers among women, age standardized to the world standard population. Source: Parkin DM, Bray F, Ferlay J, Pisani P (2002). Global Cancer Statistics, 2002. CA A Cancer Journal for Clinicians 55(2): 74-108.

- Studies showed that zeranol, the nonsteroidal growth promoter used in beef cattle, and 17-beta-estradiol have a similar potential to induce neoplastic changes in human breast epithelial cells.[67]
- Three new studies link insulin-like growth factors with increased breast cancer risk. This suggests that rBST, the genetically engineered hormone product found in many dairy products, which stimulates production of IGF-1, may be associated with increased risk of breast cancer.[68,69,70]
- Three pesticides—chlordane, malathion and 2,4-D—were associated with increased risk of breast cancer in Latina agricultural workers in California.[71]
- A study of female autoworkers linked exposure to metalworking fluids with increased risk of breast cancer, particularly when the exposure occurred within 10 years of diagnosis.[72]
- Occupational exposure to extremely low-frequency electromagnetic fields was shown to increase breast cancer risk among postmenopausal women, especially when exposure occurred before age 35.[73]
- A cluster of male breast cancers was reported among a small group of men occupationally exposed to high electromagnetic fields.[74]
- An Italian study found that truck driving was the most frequent occupation of male breast cancer patients with BRCA1/BRCA2 mutations, possibly implicating exposure to PAHs.[75] A review of the epidemiologic literature on male breast cancer also identifies exposure to EMFs and PAHs as risk factors.[76]

Advance The Research Agenda

To reduce the burden of breast cancer in our society, public officials and the scientific and corporate communities must act based on what is already known about agents that increase the risk of this disease. At the same time, major gaps exist in our current knowledge and we need more studies asking tough questions about the underlying causes of breast cancer. While we need further research on screening, diagnosis and treatment, decades of paying little attention to true prevention of breast cancer have resulted in needless sickness and death. Research efforts should seek information that will compel public policies aimed to prevent breast cancer. The types of research most likely to support such policies are those examining:

- The interplay between timing of exposures, multiple exposures, low-dose exposures, chronic exposures (including occupational exposures) and cumulative exposures;
- Exposures of women at home and in the paid workplace;
- Disparities in health outcomes and environmental exposures; and
- Development of less invasive, more effective breast cancer screening methods.

Implement Policy Changes

While research proceeds, fundamental changes are needed in both the public and private sectors regarding exposure to radiation and the production, use and disposal of chemicals found to increase the risk of breast cancer or suspected of doing so. Considerable resources continue to be spent to encourage women to make changes in their personal lives that might reduce their risk of breast cancer. But many factors that contribute to the disease lie far beyond an individual's personal control and can only be addressed by government policy and private sector changes. Breast cancer is not just a personal tragedy; it is a public health crisis that requires political will to change the status quo.

This crisis must be addressed by adopting the precautionary principle as a public policy. Under this principle, indication of harm, rather than definitive proof of harm, triggers policy actions. In addition, the precautionary principle obligates producers of chemicals and radiological products to assess the health, safety and environmental impacts of their products before introducing or releasing them. It also requires industry to make the results of their assessments publicly available. Industry is further obliged to examine a full range of alternatives to toxic ingredients and to select the alternative with the least potential impact on human health and the environment, including the possibility of not introducing a questionable product at all. The precautionary principle rests on the democratic principle that government officials are obligated to serve the public interest by protecting human health and the environment. Decision-making under the precautionary principle must be transparent, participatory and informed by the best available data.

We ignore at our peril evidence that radiation and chemicals are contributing to the growing human and economic cost of breast cancer. Halting the scourge of this disease requires that we take action based on existing evidence to protect the health of people and the planet. Waiting for absolute proof brings more needless suffering and loss of lives. It is in our power to change the course we are on. It is time to act on the evidence.

A 10-Point Plan For Reducing The Risk Of Breast Cancer And Ultimately Ending The Epidemic:

1. Establish environmental health tracking (EHT) programs at state and federal levels.
2. Practice "healthy purchasing" by adopting precautionary purchasing laws at the local, state and federal levels.
3. Protect workers from hazardous exposures.
4. Educate the public about the health effects of radiation and how to reduce exposure to both ionizing and non-ionizing radiation.
5. Hold corporations accountable for hazardous practices.
6. Offer local, state and federal incentives for clean, green practices.
7. Strengthen right-to-know legislation and public participation in decisions about toxic exposures.
8. Enforce existing environmental protection laws.
9. Require greater transparency in funding of scientific and medical training, research and publications.
10. Create a comprehensive chemicals policy based on the precautionary principle.

Framework Of This Report

Breast cancer now strikes more women in the world than any other type of cancer except skin cancer. Globally, more than 1.1 million people were diagnosed with breast cancer in 2002 and 1.5 million cases are anticipated in the year 2010.[77] In the United States, a woman's lifetime risk of breast cancer nearly tripled during the past four decades. In 1964, a woman's lifetime risk of breast cancer was one in 20. By 2005, it was one in seven and incidence rates continue to rise.[78] In 2005, an estimated 211,240 women in the United States were diagnosed with invasive breast cancer and more than 58,000 women were diagnosed with ductal carcinoma in situ. Breast cancer was expected to kill more than 40,000 American women and more than 410,000 worldwide in 2005.[79] Breast cancer is the second leading cause of death (after heart disease) in American women ages 25 to 54.[80,81,82] Although breast cancer in men accounts for less than one percent of cases, in the United States the incidence has increased by 25 percent in the past 25 years.[83] An estimated 1,690 men could expect to be diagnosed with breast cancer in 2005.[84]

Even when all known risk factors and characteristics, including family history and genetics, are taken into account, as many as 50 percent of breast cancer cases remain unexplained.

Once a disease almost exclusively of postmenopausal women, breast cancer now strikes women in their 20s and 30s, especially African American women.[85] Of the estimated 211,000 women in the United States diagnosed with breast cancer in 2005, approximately 9,500 were women under 40.[86 *]

More American women have died of breast cancer in the last 20 years than the number of Americans killed in World War I, World War II, the Korean War and the Vietnam War combined.

Scientists have demonstrated a link between several social and lifestyle factors and increased breast cancer risk. These factors include personal characteristics such as early puberty, late menopause, a woman's age at her first full-term pregnancy, alcohol consumption[87,88] and social factors such as income. However, even when all known risk factors and characteristics, including family history and genetics, are taken into account, as many as 50 percent of breast cancer cases remain unexplained.[89,90]

Despite the widely varying incidence across the globe, high rates of breast cancer are unmistakably related to widespread use of man-made chemicals.[91] Industrialized nations of North America and northern Europe have the highest rates, while Asia and Central Africa have the lowest rates. In northern Africa, as in many countries either developing or in transition,[92,93,94,95,96,97] breast cancer rates are escalating sharply.[98]

*Note: all data figures refer to invasive breast cancer and do not include in situ cases unless otherwise noted.

Environmental carcinogenesis is the newest and one of the most ominous of the end-products of our industrial environment. Though its full scope and extent are still unknown, because it is so new and because the facts are so extremely difficult to obtain, enough is known to make it obvious that extrinsic carcinogens present a very immediate and pressing problem in public and individual health. It should become one of the most urgent tasks of all medical men, public health officials, labor and management leaders and members of legislatures, to become familiar with the problems of environmental cancer. They must all work together to combat its causes at the source, before the dread disease spreads to more and more of our people.

— Wilhelm C. Heuper, M.D.,
National Cancer Institute, 1948

The increasing incidence of breast cancer and other cancers has paralleled the proliferation of synthetic chemicals since World War II. An estimated 100,000 synthetic chemicals are in use today in the United States. Another 1,000 or more are added each year.[99] Complete toxicological screening data is available for just 7 percent of these chemicals. More than 90 percent have never been tested for their effects on human health.[100] Many of these chemicals persist in the environment, accumulate in body fat and remain in breast tissue for decades. Studies of women's chemical body burden show that all of us carry contaminants in our bodies. Some of these contaminants, including chemicals used in common fuels, solvents and other industrial practices, have been linked to mammary tumors in animals.[101,102] (See Appendix 1 for a complete listing of chemicals shown to induce mammary tumors in animals.)

Women who move from countries with low breast cancer rates to industrialized countries soon acquire the higher risk of their new country. For example, women who emigrate to the United States from Asian countries, where the rates are four to seven times lower, experience an 80 percent increase in risk after living in the United States a decade or more.[103] A generation later, the risk for their daughters approaches that of U.S.-born women.

Emigration to industrialized countries may alter any aspect of an individual's environmental exposures. Immigrants' breast cancer risk—and that of their daughters—may increase if they adopt a Western lifestyle. If diet plays a role, the increased risk could be because of nutritional content, contaminants or food additives. Emigration may also affect reproductive behavior, such as the use of oral contraceptives.[104]

A person's age at the time of emigration also affects cancer risk. A Swedish study of people with many different cancers showed that age at emigration determined whether the individual acquired the cancer risk of the country of origin or the country of destination. Researchers concluded that "birth in Sweden sets the Swedish pattern for cancer incidence, irrespective of the nationality of descent, while entering Sweden in the 20s is already too late to influence the environmentally imprinted program for the cancer destiny."[105]

Inherited genetic mutations have received much attention recently but they account for only a small fraction—no more than 10 percent—of the breast cancer epidemic.[106] Women with an inherited mutation on the BRCA1 or BRCA2 genes have a 60 to 82 percent probability of getting breast cancer in their lifetimes.[107] While breast cancer devastates families with these mutations, all families share more than genetic make-up. They also share a common environment. A study in 1988

found that adopted children whose adoptive parents died of cancer were five times as likely as the general population to get the same cancer,[108] revealing a connection to common exposures and lifestyles independent of inherited genes.

In the largest study of twins ever conducted , researchers found that among twins in which at least one twin developed breast cancer, environmental exposures unique to the twins with breast cancer made the most significant contribution to the development of the cancer. Inherited genes contributed 27 percent of breast cancer risk, shared environmental factors 6 percent and non-shared environmental factors 67 percent of the risk.[109] In other words, most breast cancer is not inherited. A recent re-analysis of this study concluded that "genetic susceptibility makes only a small to moderate contribution" to the incidence of breast cancer.[110]

The epidemiologic research on chemicals and breast cancer does not demonstrate cause and effect relationships. Indeed, a multifactorial disease such as breast cancer involves webs of causation, not a single cause. What we need to know is how chemicals alter breast cancer risk in the context of multiple contributing causes. Nonetheless, a considerable and growing body of evidence presents powerful—even alarming—cause for concern. Epidemiologic studies are limited in their ability to identify specific links between breast cancer and cancer-causing chemicals, but numerous laboratory studies have been more revealing of such links. To date, tests performed on laboratory animals (a standard for public health research) implicate 47 chemical compounds in breast cancer formation.[111]

Scientists and activists alike recognize that testing one chemical at a time ignores the reality that we are all exposed to hundreds, if not thousands, of chemicals every day of our lives. Potential synergistic effects of exposures are usually unknown to us and often occur over long periods of time, thus making cause and effect relationships very difficult to establish.[112] While scientists have yet to develop sound methods for studying the effects of mixtures on human health, they recognize that establishing such methods is critical to understanding the impacts of real life exposures.[113] Future research designs must incorporate the realities of multiple exposures. Unless and until research mirrors the realities of actual exposures, evidence regarding environmental causes of breast cancer will remain incomplete.

Purpose Of This Report

A significant body of scientific evidence indicates that exposure to radiation and synthetic chemicals contributes to the increased incidence of breast cancer. However, research efforts to explain the major reasons for today's high incidence of breast cancer have resulted in differing findings and ongoing controversy.

This report summarizes the findings of more than 350 experimental, epidemiologic and ecological research studies on environmental links to breast cancer and recommends new directions for future research and policies. It provides a 10-point plan to act on the evidence and reduce the burden of synthetic chemicals in our environment and in our bodies and reduce our exposure to radiation. This plan is based primarily on the precautionary principle,[114] which states that indication of harm, not just proof of harm, should be grounds for action. This report documents both proof of harm and indications of harm from involuntary environmental exposures.

What Does "Environment" Mean?

The authors of this report recognize that "environment" encompasses the totality of living and working conditions as well as physical, biological, social and cultural responses to these conditions. For the purposes of this report, however, we are concerned with people's exposures to environmental agents beyond their control, such as pesticides, dioxin, secondhand tobacco smoke and other chemicals. On a daily basis, we are all exposed to one or more of these agents in air, food, water, soil, medications, common household products or the workplace.

Radiation (both ionizing and non-ionizing) is also discussed as an environmental exposure, even though some exposure to radiation is voluntary, as in the case of X-rays and other radiological procedures. Patients may choose whether to undergo these procedures; however, these are often uninformed choices since little or no specific information about radiation dose or potential risk usually is provided by health professionals. Exposure to non-ionizing radiation is largely involuntary and ubiquitous.

Many of the environmental exposures discussed in this report may interact with each other to increase the risk of breast cancer. Their effects may be additive (the sum of their individual effects) or synergistic (greater than the sum of their individual effects).

Factors sometimes considered environmental but not involuntary, including nutrition, alcohol or tobacco use, exercise, exposure to natural estrogens and body weight, are not discussed in this report.

Involuntary environmental exposures can occur in many ways and in many settings:

- Environmental exposures can occur daily at home, at school, in the workplace, in health care facilities and in other settings.
- Environmental exposures can occur in the womb, when carcinogens in the mother's body cross the placenta to the fetus, and at any time during one's lifetime.
- Social, economic and cultural factors such as employment, income, housing and diet often determine the nature and extent of one's environmental exposures.
- Exposures may be chronic (in one's workplace or residence, for example) or acute (from an industrial accident, such as a release of radioactive materials or other hazardous substances).

Evidence That Timing Of Exposure Matters

Two decades of research on laboratory animals, wildlife and cell behavior (in vitro)[115] have shown the inadequacy of the long-held belief that "the dose makes the poison." Scientists now know that the timing, duration and pattern of exposure are at least as important as the dose. Low-dose exposure to environmental chemicals—parts per billion or even per trillion—during a critical window of an organism's development can cause permanent damage to organs and systems.

The tragic legacy of diethylstilbestrol (DES), a drug once prescribed to prevent miscarriages, shows that cancer can begin in the womb.[116] Prenatal development of any organism is an exquisitely sensitive process regulated by an intricate system of hormonal signals. When those signals are disrupted by exposure to radiation, chemicals or metals such as lead or mercury, the developmental damage can be devastating and

permanent. A woman's body is the first environment for the developing infant, but unfortunately, that once-safe environment has become a toxic site. Studies by the U.S. Centers for Disease Control and Prevention show that women have higher levels of many chemicals in their bodies than men do.[117] Umbilical cord blood of newborn infants[118] offers further evidence of prenatal contamination.

A case-control study of 3,200 women (ages 35 to 79 years) in western New York showed that exposure to high levels of polycyclic aromatic hydrocarbons (PAHs) at birth was associated with increased risk of postmenopausal breast cancer. Scientists used air monitoring records from 1959 to 1997 to establish PAH levels in residential areas for cases and controls. PAHs are products of incineration found in air pollution, vehicle exhaust (particularly diesel), tobacco smoke and grilled foods.[119]

The same group of scientists found that clustering patterns of breast cancer cases among premenopausal women in western New York were more closely related to place of residence at birth and at menarche than at any other period of adult life. These findings offer further evidence that early environmental exposures may be related to breast cancer risk, especially for premenopausal women.[120]

Fetal exposure of mice to low-dose bisphenol-A changed the timing of DNA synthesis in the epithelium and stroma of their mammary glands, increased the number of terminal ducts and terminal end buds (i.e., the structures where cancer arises), and increased the sensitivity of the mammary gland to estrogens during postnatal life.[121,122] According to Markey et al., these findings "strengthen the hypothesis that in utero exposure to environmental estrogens may predispose the developing fetus to mammary gland carcinogenesis in adulthood."[123]

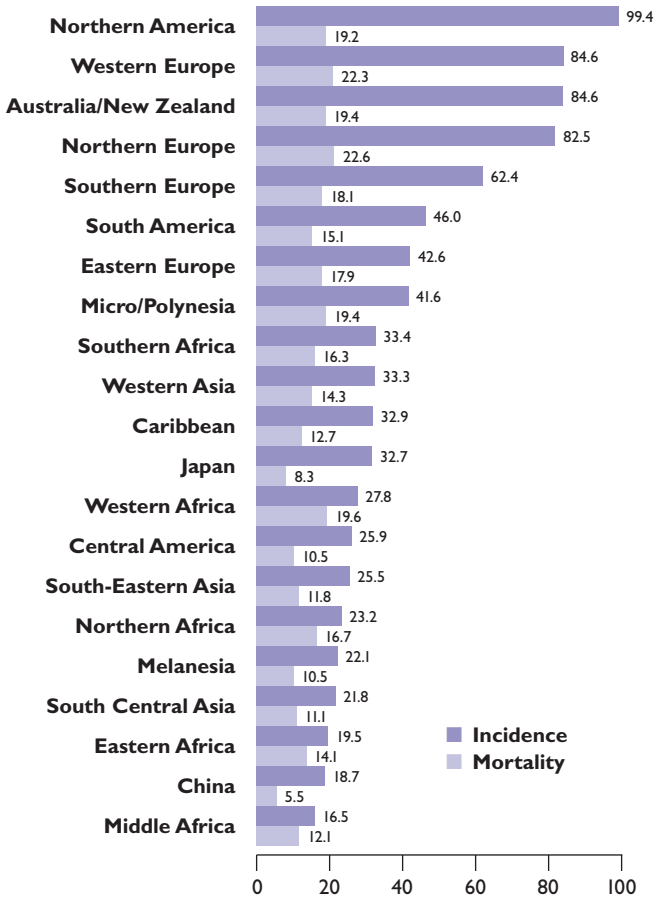
Canadian scientists found that prenatal exposure to a mixture of organochlorine chemicals followed by early life exposure to genistein (a phytoestrogen in soy products) induced marked changes in the mammary glands of female rats when they reached adulthood. These changes included pronounced ductal hyperplasia, lactational changes and fibrosis, whereas the mammary glands in the control group (not treated with genistein) were histologically normal.[124]

Recent studies on the importance of timing also suggest that cancer may result from altered development in breast tissue rather than from genetic mutation. Namely, researchers exposed rodent mammary epithelial cells to a known carcinogen, N-nitrosomethylurea (NMU), and implanted these cells into mammary gland stroma of four groups of rodents, some of whose stroma were exposed to NMU and some without NMU exposure. Only the rodents whose stroma was exposed to NMU developed epithelial cell tumors.[125]

These and other recent studies add credence to the Tissue Organization Field Theory (TOFT), which proposes that carcinogens alter the interaction between cells in the stroma and those in the epithelium of the breast, thereby disrupting normal development and predisposing the organism to cancer.[126,127,128,129,130]

The younger the organism, the more vulnerable the developing cells and tissues are to environmental exposures. The most critical windows of vulnerability for the developing breast are the prenatal, prepubertal and adolescent periods, through to a woman's first full-term pregnancy.

2002 Breast Cancer Rates, Per 100,000 Population



Incidence and mortality rates for female breast cancer, age standardized to the world standard population.

Source: Parkin DM, Bray F, Ferlay J, Pisani P (2002). Global Cancer Statistics, 2002. CA A Cancer Journal for Clinicians 55 (2): 74-108.

Types Of Research

Three types of research are used to study possible connections between breast cancer and environmental factors. Each type has advantages and limitations.

It has now been scientifically demonstrated that there is indeed a link between chemical products and the appearances of diseases, such as cancers, infertility, degenerative diseases of the central nervous system and allergies.

Standing Committee of European Doctors[177]

No research has proven that exposure to synthetic chemicals or radiation is responsible for the fact that breast cancer risk in the United States has nearly tripled over the past 40 years. Yet, taken together, these different types of research provide compelling evidence that exposure to certain agents contributes to an increased risk of breast cancer.

1. Experimental (Laboratory) Research

In experimental research, investigators expose human breast cells or animals to particular agents. In vitro studies (in petri dishes) permit researchers to observe closely the way in which normal cells become abnormal cells and to investigate cell proliferation and other phenomena that are part of the progression toward cancer. In vivo studies (in animals) examine windows of susceptibility and tissue interactions during carcinogenesis. Proving specific causes of human disease can be difficult in a laboratory because experiments cannot replicate the behavior of cells within a living organism and because humans are constantly exposed to a complex array of agents in uncontrolled conditions.

2. Ecological Research

Ecological studies examine environmental and socioeconomic characteristics in geographic areas with high incidence of a disease and compare these characteristics to areas with low incidence of the disease. Ecological studies alone do not provide strong evidence of disease causation, but they can generate hypotheses about exposures and health outcomes and justify the need for epidemiologic research.

3. Epidemiologic Research

Epidemiology is the study of the distribution and determinants of disease in human populations. Epidemiologic studies can be either descriptive or analytical. Descriptive studies examine the distribution of disease in a population and the basic characteristics of that disease in terms of time, place and who is affected. Analytical studies test a hypothesis about the relationship between a disease and a suspected cause. Epidemiologic research can demonstrate associations between particular exposures and diseases; however, it cannot examine the biological mechanisms involved.

Evidence That Environmental Factors Cause Breast Cancer

Ionizing Radiation

Exposure to ionizing radiation is the best- and longest-established environmental cause of human breast cancer in both women and men. In 2005, the National Toxicology Program classified X-radiation and gamma radiation as known human carcinogens.[132] Radiation is a mutagen as well as a carcinogen. Radiation may even enhance the ability of hormones or other chemicals to cause cancer.[133,134] However, not everyone exposed to radiation develops cancer.

Ionizing radiation is a form of radiant energy with enough power to break off electrons from atoms (to ionize the atoms) and energize the electrons, which then travel at high speed through body tissue, damaging genetic material.[135] X-rays and gamma rays are the only forms of radiant energy with sufficient power to penetrate and damage body tissue below the surface.

More is known about the relationship between radiation dose and cancer risk than any other human carcinogen, and female breast cancer is the best quantified radiation-related cancer.

— Charles E. Land[131]

Ionizing radiation can also induce genomic instability, an increased rate of changes in chromosomes. According to one Harvard scientist, "Genomic instability is a hallmark of cancer cells, and is thought to be involved in the process of carcinogenesis."[136] Genomic science shows that ionizing radiation affects not only the DNA in cells that are directly exposed but also the DNA in cells not directly exposed to radiation. These effects are called "bystander effects," and include cell death, genetic mutations, enhanced cell growth, genomic instability and neoplastic (tumor-forming) changes. Radiation-induced genomic instability has been shown in both in vitro and animal studies.[137,138,139]

The link between radiation exposure and breast cancer has been confirmed in atomic bomb survivors.[140,141,142] Rates of breast cancer were highest among women who were under 20 when the United States dropped atomic bombs on Hiroshima and Nagasaki.[143] In addition, scientists from the National Cancer Institute reported a significant association between ionizing radiation exposure and the incidence of male breast cancer in Japanese atomic bomb survivors.[144]

There is no such thing as a safe dose of radiation.[145,146,147,148] A 2005 National Research Council report confirms this finding in stating that "the risk of cancer proceeds in a linear fashion at lower doses [of ionizing radiation] without a threshold and that the smallest dose has the potential to cause a small increase in risk to humans."[149] Radiation damage to genes is cumulative over a lifetime.[150] Repeated low-dose exposures over time may have the same harmful effects as a single high-dose exposure.

Patients who ask about the radiation dose involved in any medical procedure are often dismissed with the answer that it is similar to the exposure one would get in a cross-country plane flight. This is seldom true, however. An average radiation dose of one rad (or centigray) to the breast is equivalent to the breast irradiation received during about 3,300 hours of flying.[151] Thus, a typical mammogram of 0.2 rads would equal the radiation dose received by the breast in 660 hours of flying, not a single trip.

There is no such thing as a safe dose of radiation.

The many sources of ionizing radiation include X-rays, computed tomography (CT) scans, fluoroscopy and other medical radiological procedures. Sources of gamma rays include emissions from nuclear power plants, scientific research involving radionuclides, military weapons testing and nuclear medicine procedures such as bone, thyroid and lung scans.[152] Increased radiation exposure from multiple sources may have contributed to the 90 percent increase in breast cancer incidence in the United States between 1950 and 2001.[153]

There is credible evidence that medical X-rays (including fluoroscopy and CT scans) are an important and controllable cause of breast cancer.[154,155] Although X-rays have been a valuable diagnostic tool for more than a century, the radiation dose has not always been carefully controlled and sometimes has been higher than needed to obtain high quality images, particularly in the case of fluoroscopy and CT scans. Dose reduction can be achieved without sacrificing image quality. In mammography, for example, efforts to reduce the radiation dose to as low as reasonably achievable (ALARA) levels have reduced the radiation dose from an estimated two rads in 1976 to 0.2 rads today.[156]

CT scans, introduced in the 1970s, greatly increased the radiation dose per examination compared with ordinary X-rays.[157] According to the National Cancer Institute, CT scans "comprise about 10 percent of diagnostic radiological procedures in large U.S. hospitals," but contribute an estimated 65 percent of the effective radiation dose to the public from all medical X-ray examinations.[158]

Decades of research have confirmed the link between radiation and breast cancer in women who were irradiated for many different conditions, including tuberculosis,[159] benign breast disease,[160] acute postpartum mastitis,[161] enlarged thymus,[162] skin hemangiomas[163] and Hodgkin's disease.[164,165,166,167,168,169,170,171]

The type of cancer that can result from radiation exposure depends on the area most directly exposed and the age at which an individual is exposed. Radiological examination of the spine, heart, lungs, ribs, shoulders and esophagus also exposes parts of the breast to radiation. X-rays and fluoroscopy of infants irradiate the whole body.[172]

Some studies suggest that doctors and patients should carefully evaluate the risks and benefits of radiotherapy for survivors of early breast cancer, particularly older women. Women over age 55 derive less benefit from radiotherapy in terms of reduced rate of local recurrence[173] and may face increased risks of radiation-induced cardiovascular complications,[174] as well as secondary cancers such as leukemias and cancers of the lung, breast and esophagus.[175] Recent SEER data showed a 16-fold increased relative risk of angiosarcoma of the breast and chest wall following irradiation to a primary breast cancer.[176]

Although the benefits of medical procedures involving radiation exposure often outweigh the risks, it is essential that physicians and the public recognize the dangers of radiation exposure and, where feasible and practical, seek alternative diagnostic and therapeutic methods such as MRI and ultrasound.

Chemicals

The following sections summarize the science that has established links between synthetic chemicals and breast cancer incidence and mortality.

1. Estrogens And Progestins

The female body produces two major hormones: estrogen and progesterone. These two hormones have both complementary and opposing effects which together control the menstrual cycle. There are three types of estrogen: estradiol, estriol and estrone, the most potent of which is estradiol. Progestins are synthetic substitutes for natural progesterone. In the 1950s, research showed that estrogen replacement alone increased the risk of uterine cancer. This caused pharmaceutical companies to add a progestin to estrogen, creating the first combination hormone replacement therapy (HRT).

In 2002, the National Toxicology Program added HRT and steroidal estrogens (used in oral contraceptives) to the list of known human carcinogens.[178] The International Agency for Research on Cancer (IARC) has listed steroidal estrogens as known human carcinogens since 1987. However, these classifications only confirm scientific evidence from the 1930s, which linked steroidal estrogens with increased cancer risk.[179] (See sidebar.)

Although women need estrogens for childbearing, strong bones and healthy hearts, research has established that longer exposure to estrogens leads to a higher risk of breast cancer. Longer exposure can occur in women who begin to menstruate before age 12, do not reach menopause until after age 55, have children late in life or not at all, do not breast-feed or use HRT after menopause. When a woman's natural estrogens are supplemented by oral contraceptives and/or HRT, her risk of breast cancer increases.[180,181,182] Women who previously used oral contraceptives and later received HRT face an even greater breast cancer risk than those who have not used either or have used only one.[183]

In 2003, Swedish researchers halted a study of HRT in women with a history of breast cancer. Originally planned as a five-year study, the Swedish trial was stopped after two years because women taking HRT had three times the rate of recurrence or new tumors compared to women who received other treatments for menopausal symptoms.[184]

In 2003, researchers in the Million Women Study (MWS) in the United Kingdom reported that the use of all types of postmenopausal HRT[185] significantly increased the risk of breast cancer and that the risk was greatest among users of estrogen-progestin combination therapy. The study enrolled more than 1 million women ages

50 to 64. Researchers estimated that women who used estrogen-progestin HRT for 10 years were almost four times more likely to develop breast cancer than women who used estrogen-only HRT (19 additional breast cancers per 1,000 women compared to five per 1,000). Researchers concluded, "Use of HRT by women ages 50 to 64 in the U.K. over the past decade has resulted in an estimated 20,000 extra breast cancers, 15,000 of them associated with estrogen-progestin combination; the extra deaths cannot yet be reliably estimated."[186]

The MWS study further confirms the link between HRT and breast cancer reported by the Women's Health Initiative (WHI) study in 2002. The WHI study enrolled more than 16,000 women ages 50 to 79 years of age. Half the women took Prempro, a combination of estrogen plus progestin. The other half took a placebo. Researchers halted the WHI study after five years because they saw a 26 percent increase in the relative risk of breast cancer (38 women with breast cancer versus 30 women per 10,000 person-years), in addition to significant increases in the risk of heart disease, stroke and blood clots.[187] However, during the course of the WHI study, 42 percent of the participants withdrew. When the researchers reanalyzed the data based on the number of women actually treated with HRT, the relative risk of breast cancer increased from 26 percent to 49 percent (43 women with breast cancer versus 30 women per 10,000 person-years). Other health risks also increased in the women taking HRT.

These two large studies confirmed decades of research indicating that HRT increases the risk of breast cancer and other life-threatening conditions. Furthermore, these studies indicated that both endogenous hormones and exogenous substances that act like hormones increase the risk of hormone-related cancers, including breast cancer.

Short Chronology Of The History Of Sex Hormones, Cancer And The Production And Use Of Estrogen For Menopause

1930s
The commercial production and sale of hormones as drugs is accompanied by debates on the potential danger of induction of malignancies.

1940s-1950s
Doubts arise regarding the safety of menopausal hormones. Premarin is nevertheless a commercial success, as women increasingly begin to use menopausal hormones.

1960s
Changes in women's status and life expectancy encourage menopausal therapy: Feminine Forever published (1966). HRT is presented as a therapy that allows women to free themselves from the malediction of estrogen loss, and to conserve femininity.

1970s
The rise of women's movement and women's health movement. Rise of feminist criticism of the pill and of HRT, in context of broader concerns about dangers of "hormone therapy" (including DES). The description of increase in the incidence of endometrial cancer in women who used menopausal estrogen (1975) leads to the halving of the U.S. number of HRT prescriptions.

1980s
Widespread introduction of progestin-estrogen treatment for women with an intact uterus. HRT is increasingly presented as a preventive drug; emphasis shifts from "young and sexy forever" to "healthy forever". From early 1980s on, a steady increase in use of HRT (as measured in number of prescriptions and sale of drugs), despite the persistence of critical voices. At the end of 1980s, HRT consumption exceeded the pre-1975 volume.

1990s
The steady increase in HRT uptake continues. This treatment is strongly promoted by most doctors, and sustained, especially in the United States, by the ethos of individualized preventative medicine. It continues, nevertheless, to be questioned by scientists, feminist scholars and advocates in their overlapping permutations. WHI—the first large-scale randomized prospective clinical trial of menopausal hormones—starts, partly as an answer to feminist criticism of HRT.

2000s
HERS study results on cardiovascular disease are surprising. Early interruption of WHI, after the finding of an excess of cancers and cardiovascular incidents in the experimental branch. In 2002 and 2003, a sharp decrease in HRT prescriptions in English-speaking countries.

Adapted from Krieger et al (2005). Hormone replacement therapy, cancer, controversies, and women's health. Journal of Epidemiology and Community Health 59:740-748.

Numerous studies have shown an increased risk of breast cancer in women using oral contraceptives.[188,189,190,191] The risk is greatest among current and recent users, particularly those who have used them for more than five years, premenopausal women, those with a family history of breast cancer[192] and women with the BRCA1 and BRCA2 mutations.[193]

Higher body fat levels in postmenopausal women may increase breast cancer risk because fat is a reservoir for many synthetic lipophilic (fat-seeking) chemicals, such as organochlorines. Some of these lipophilic chemicals mimic the effects of natural estrogens. Breasts are composed primarily of fat and are repositories for these contaminants. Studies of postmenopausal women have found a correlation among a higher proportion of body fat, higher amounts of free circulating estrogens and an increased risk of the disease.[194] An international analysis of data from eight prospective studies confirmed this link.[195]

Breast cancer in men also implicates estrogen as a contributing factor. Although breast cancer is rare in men, those who develop the disease have higher than normal levels of estrogen.[196]

2. Synthetic Estrogens (Xenoestrogens)

In 1991, researchers at Tufts University discovered that a chemical leaching from polystyrene laboratory tubes was causing breast cancer cells to grow, even though no estrogens had been added to the culture. Subsequent investigation showed that the substance leached was p-nonyl-phenol, an additive commonly used in plastics, and that it behaved like a natural estrogen.[197] This landmark discovery by Tufts researchers generated widespread interest in xenoestrogens—synthetic agents that mimic the actions of estrogens. Xenoestrogens are one type of endocrine disrupting compound (EDC) and are present in many pesticides, fuels, plastics, detergents and prescription drugs.[198]

In 1993, a team of researchers developed the hypothesis that xenoestrogens play a role in a significant proportion of breast cancer cases.[199] Because xenoestrogens mimic naturally occurring estrogens, they may also cause breast cells to proliferate, increasing the risk of breast cancer. Chronic exposure to widespread and persistent xenoestrogens may help explain the increase in breast cancer in industrialized countries around the world.

In brief, the argument for the indirect role of pesticides in cancer is based on their proven ability to damage the liver and reduce the supply of B vitamins, thus leading to an increase in the 'endogenous' estrogens, or those produced by the body itself. Added to these are the wide variety of synthetic estrogens to which we are increasingly exposed – those in cosmetics, drugs, foods and occupational exposures. The combined effect is a matter that warrants the most serious concern.

— Rachel Carson, "Silent Spring," 1962

The research on xenoestrogens intensified in 1994 when the Tufts University researchers identified certain pesticides as xenoestrogens because they caused breast cancer cells to proliferate in tissue cultures.[200] By 1997, a number of studies from other laboratories had reported on compounds that acted like estrogens when put in contact with breast cancer cells—indicating that these compounds may, therefore, act like estrogens in

humans.[201,202,203] Additional studies have found a broad array of chemicals in the environment that interfere with hormonal metabolism.[204]

Also in 2005, researchers from the University of Texas and Clemson University published a study showing that mice exposed to 4-nonylphenol (4-NP) had an increased risk of breast cancer compared to mice exposed to equivalent doses of estradiol. They found that 4-NP stimulated the production of estriol (a natural estrogen) in the liver.[205] Nonylphenols are found in some plastics, pesticides, liquid laundry detergents and spermicides.

Recently, researchers in Spain studied the combined effects of environmental estrogens, measured as the total effective xenoestrogen burden (TEXB-alpha) and found an increased risk of breast cancer among postmenopausal women with the highest levels of TEXB-alpha. In the same study, the pesticides aldrin and lindane also were associated individually with elevated risk.[206]

Laboratory studies have shown that a number of metals including copper, cobalt, nickel, lead, mercury, tin and chromium have estrogenic effects on breast cancer cells.[207] A new study from Australia reports that methyl mercury can significantly alter growth-related signaling in MCF-7 breast cancer cells—indicating that it, too, can disrupt the endocrine system.[208]

Meanwhile, on Cape Cod, where nine of 15 towns have breast cancer rates 20 percent above the average rates for Massachusetts, researchers from the Silent Spring Institute are engaged in a study that has raised suspicions about exposure to synthetic estrogens in the environment and increased risk of breast cancer.[209] The vast sandy beaches of the Cape create a fragile ecosystem that allows contaminants to seep quickly through porous soil into underground aquifers. Pesticides used on forests, cranberry bogs, golf courses and lawns make their way into the water supply.

In the first stage of the study, researchers found synthetic estrogens in septic tank contents, groundwater contaminated by waste water and in some private wells.[210] In the second stage of the study, Silent Spring researchers tested for hormonally active agents and mammary carcinogens in indoor air and household dust samples from 120 homes on Cape Cod. They tested for 89 compounds and found a total of 52 different compounds in air and 66 in dust, including phthalates, parabens, alkylphenols, flame retardants, PAHs, polychlorinated biphenyls (PCBs), bisphenol-A and banned and currently used pesticides.[211]

Concerned about xenoestrogenic compounds in pesticides, researchers at Silent Spring Institute used Geographic Information Systems (GIS) tech-

Common Chemicals Linked To Breast Cancer And Their Sources

Chemical Class	Potential Sources	Example Chemical
Phthalates	Plastic, nail polish and other cosmetics	dibutyl phthalate
Alkylphenols	Detergents, plastic, pesticide formulations	nonylphenol
Flame retardants	Furniture foam and stuffing, carpets and drapes, electronic equipment (TVs, computers)	polybrominated diphenyl ether (PBDE 47)
Polycyclic aromatic hydrocarbon (PAHs)	Stoves and heaters, cigarette smoke, outdoor air pollution, auto exhaust, combustion sources such as fireplaces;	benzo(a)pyrene
Polychlorinated biphenyls (PCBs)	Older electrical equipment	PCB 52
Banned pesticides	Historical pesticide use in/near the home	DDT, dieldrin, chlordane
Currently used pesticides	Recent pesticide use in/near the home	chlopyrifos, permethrin
Other phenols and miscellaneous	Disinfectants, polycarbonate plastics, cosmetics	o-phenyl phenol, bisphenol-A, parabens

Source: Adapted from Krieger at al (2005). Hormone replacement therapy, cancer, controversies, and women's health. Journal of Epidemiology and Community Health 59:740-748. Adapted and reproduced with permission from the BMJ Publishing Group.

nology to examine breast cancer risk and historical exposures to pesticides on Cape Cod. To date, they have found modest increases in risk associated with aerial application of persistent pesticides on cranberry bogs and less persistent pesticides applied for tree or agricultural pests.[212]

Silent Spring recently published a study showing that longer residence on Cape Cod is associated with increased risk of breast cancer. Women who lived just five or more years on the Cape experienced an increased risk. The highest risk occurred among women who had lived on the Cape for 25 to 29 years. Suspected environmental exposures include pesticides and drinking water contaminated by industrial, agricultural and residential land use.[213]

Chronic exposure to widespread and persistent xenoestrogens may help explain the increase in breast cancer in industrialized countries.

The following sections address some of the most common xenoestrogens and the evidence linking them to breast cancer.

a. Diethylstilbestrol (DES)

The most convincing evidence that synthetic chemicals can act like hormones and produce delayed detrimental effects is the tragic experience with diethylstilbestrol (DES). Between 1941 and 1971, doctors prescribed DES for millions of pregnant women to prevent miscarriages. The drug was banned when daughters of women who took the drug were found to have higher rates of an extremely rare vaginal cancer than those who were not exposed to DES in the womb.[214,215,216] Research indicates that DES may also have increased the risk of breast cancer in some of the women who took it during the 1950s.[217]

A study of daughters, now age 40 or older, of women who took DES during pregnancy found more than twice the risk of breast cancer in the daughters compared to other women their age.[218] This study adds to the body of evidence that intrauterine exposures can have life-long effects on cancer development.

b. Bisphenol-A (BPA)

Bisphenol-A (BPA) is one of the most pervasive chemicals in modern life. More than 2 billion pounds of BPA are produced in the United States each year. BPA is the building block of polycarbonate plastic and is also used in the manufacture of epoxy resins and other plastics including polyester and styrene. It is commonly found in the lining of metal food cans and in some types of plastic food containers, including some baby bottles, microwave ovenware and eating utensils. Because BPA is an unstable polymer and is also lipophilic (fat-seeking), it can leach into infant formula and other food products, especially when heated.[219] Once in food, BPA can move quickly into people—a particular concern for women of childbearing age and young children. BPA has been found in umbilical cord blood at birth and in placental tissue.[220] CDC researchers also found BPA in 95 percent of more than 300 urine samples.[221]

A growing body of evidence links intrauterine exposure to BPA with drastic changes in the development of the reproductive system and mammary glands. Researchers at Tufts University exposed mice in utero to low doses of BPA. When researchers examined the mammary glands of the female animals at 10 days, one month and six months after birth, they found the development of the animals' mammary glands had been altered

in ways associated with the development of breast cancer in rodents and in humans.[222] This evidence suggests that fetuses and embryos, whose growth and development are regulated by the endocrine system, are the most vulnerable to and may have the most lasting effects from exposure to synthetic estrogens or other chemicals that disrupt endocrine function.

In 2005, Tufts University scientists found that exposing pregnant mice to extremely low levels of BPA altered the development of the mammary gland in the female offspring at puberty. If the changes observed (increased sensitivity to estrogens, decreased cell death and increases in the number and size of terminal end buds) were to occur in humans, they would increase the risk of breast cancer. The animals were exposed to levels of BPA 2,000 times less than the level the Environmental Protection Agency designates as safe.[223]

A laboratory study from Spain suggests that BPA acts through all the same response pathways as natural estrogen (17-beta estradiol).[224] Although this study involved high doses, two recent studies showed that low-dose BPA increased breast cell proliferation in vitro via the membrane estrogen receptor.[225,226]

Extensive scientific literature implicates BPA in a wide array of health effects, including breast cancer as described above. Disagreements with this literature have come almost exclusively from plastics industry scientists, who claim they are unable to replicate studies showing that BPA can cause harm. An analysis by two leading experts reveals a clear pattern of bias in reporting of research findings. These experts have called for the EPA to conduct a new risk assessment of BPA.[227] As of December 2004, a total of 115 studies on the health effects of BPA had been published. None of the 11 studies funded by industry reported adverse effects at low-level exposure, whereas 94 of 104 government-funded studies conducted in academic laboratories in Japan, Europe and the United States did find adverse effects from low BPA levels.

c. Polyvinyl Chloride (PVC)

Manufacturers use polyvinyl chloride (PVC) extensively to produce food packaging, medical products, appliances, cars, toys, credit cards and rainwear. When PVC is made, vinyl chloride may be released into the air or wastewater. Vinyl chloride has also been found in the air near hazardous waste sites and landfills and in tobacco smoke. Animal studies of long-term exposure to low levels of airborne vinyl chloride show an increased risk of mammary tumors.[228] Vinyl chloride has also been linked to increased mortality from breast and liver cancer among workers involved in its manufacture.[229,230]

d. Pesticides

From the 1950s until 1970, the pesticides aldrin and dieldrin were widely used for crops including corn and cotton. Because of concerns about damage to the environment and, potentially, to human health, the EPA banned all uses of aldrin and dieldrin, except in termite control, in 1975. In 1987, the EPA banned these pesticides altogether.[231] Thus, most of the human body burden of this chemical comes either from past exposures or lingering environmental residues.

One body burden study showed a clear relationship between breast cancer incidence and dieldrin. Conducted by the Copenhagen Center for Prospective Studies in collaboration with the CDC, the study examined a rare bank of blood samples taken prior to the development of breast cancer.[232] During the late 1970s and early 1980s, approximately 7,500 Danish women, ranging from 30 to 75 years of age, had blood samples taken.

Researchers detected organochlorine compounds in most of the 240 women who were diagnosed with breast cancer prior to the study's publication in 2000. They found dieldrin, which has exhibited estrogenic activity during in vitro assays, in 78 percent of the women who were later diagnosed with breast cancer. Women who had the highest levels of dieldrin long before cancer developed had more than double the risk of breast cancer compared to women with the lowest levels. This study also showed that exposure to dieldrin correlated with the aggressiveness of breast cancer: higher levels of dieldrin were associated with higher breast cancer mortality.[233]

Investigation continues into potential links between pesticides and other chemicals and breast cancer risk on Long Island. One recent study found a higher risk of breast cancer among women residing within one mile of hazardous waste sites containing organochlorine pesticides compared with women living farther away from such sites.[234] A second study measured levels of organochlorine pesticides and polychlorinated biphenyls (PCBs) in surgical specimens of adipose tissue (fatty tissue) from 224 women with nonmetastatic breast cancer. Within 3.6 years, 30 women had been diagnosed with recurrence of breast cancer. The highest tertile of total PCB concentration was associated with an increased risk of recurrence versus the lowest tertile. However, pesticide levels were not associated with increased risk of recurrence.[235]

A case-control study of 128 Latina agricultural workers newly diagnosed with breast cancer in California identified three pesticides—chlordane, malathion and 2,4-D—associated with an increased risk of breast cancer. Scientists found that the risks associated with use of these chemicals were higher in young women and in those with early-onset breast cancer than in unexposed women.[236]

We have put poisonous and biologically potent chemicals indiscriminately into the hands of persons largely or wholly ignorant of their potentials for harm. We have subjected enormous numbers of people to contact with these poisons, without their consent and often without their knowledge. I contend, furthermore, that we have allowed these chemicals to be used with little or no advance investigation of their effect on soil, water, wildlife and man himself. Future generations are unlikely to condone our lack of prudent concern for the integrity of the natural world that supports all life.

— Rachel Carson, "Silent Spring," 1962

Researchers from the National Cancer Institute studied the association between pesticide use and breast cancer risk in farmers' wives in the Agricultural Health Study. This large prospective cohort study enrolled more than 30,000 women in Iowa and North Carolina. Researchers found evidence of increased risk of breast cancer in women using 2,4,5-trichlorophenoxypropionic acid (2,4,5-TP) and possibly in women using dieldrin and captan, although the small number of cases among those who had personally used pesticides precluded firm conclusions. Risk was also modestly elevated in women whose homes were closest to areas of pesticide application.[237]

e. Household Products

Chemicals that either mimic estrogen or are otherwise hormonally active (i.e., they interfere with normal hormone metabolism) can be found in many household products, particularly cleaning agents and pesticides. Insecticides in current use include estrogenic compounds such as methoxychlor, endosulfan and lindane.[238]

f. Cosmetics And Personal Care Products

Nearly 90 percent of ingredients used in cosmetics and personal care products have not been safety tested for human health effects. However, some ubiquitous ingredients such as parabens have been shown to be estrogenic in vitro[239,240,241] and in vivo.[242,243]

Parabens are a group of compounds widely used as anti-microbial preservatives in food, pharmaceutical and cosmetics products, including underarm deodorants. Parabens are absorbed through intact skin and from the gastrointestinal tract and blood. U.K. researchers found measurable concentrations of six different parabens in 20 human breast tumors.[244]

Placental extract (from human, equine or porcine sources) and other estrogenic chemicals are also used in cosmetics and hair care products, particularly products marketed to women of color. Placental extract is believed to promote growth and thickness of hair. However, research indicates that use of these products in infants and children may be linked to precocious puberty or early sexual maturation, which may increase risk of breast cancer.[245,246,247]

3. The Phytoestrogens (Plant Estrogens) Hypothesis

The prevailing evidence against synthetic estrogens must also be understood alongside evidence about the effects of plant estrogens (phytoestrogens). Such foods as whole grains, dried beans, peas, fruits, broccoli, cauliflower and, especially, soy products are rich in phytoestrogens. Although scientific evidence suggests that plant-based estrogens offer nutritional benefits, it also suggests that these substances are not completely benign.

Some research indicates that phytoestrogens may counteract the effects of synthetic xenoestrogens. Adding soy products to women's diets has led to lower levels of harmful estrogens in their bodies.[248] Some human and laboratory studies suggest that plant-based estrogens may help reduce a woman's risk of breast cancer.[249]

On the other hand, Japanese researchers reported that genistein, a type of phytoestrogen found in most soy products, and daidzein, another phytoestrogen, and their metabolites cause oxidative DNA damage, which is thought to play a role in tumor initiation.[250] There is evidence that genistein can interfere with the anti-tumor activity of tamoxifen at low levels. It may be unwise for women with estrogen receptor-positive tumors to increase their phytoestrogen intake. Overall, the evidence on whether dietary phytoestrogens increase or decrease breast cancer risk in adult women remains incomplete and inconclusive.

4. Solvents

Industrial use of organic solvents has increased over the last several decades, particularly in the manufacture of computer components. Some solvents used in this industry (such as benzene, toluene and trichloroethylene) have been shown to cause mammary tumors in laboratory animals.[251] Such solvents are also used in other industries, including cosmetics manufacturing.[252]

Until recently, there were no studies of cancer rates among workers in the semiconductor industry.[253] A 2003 Taiwanese study, however, showed an increased risk of breast cancer among electronics workers exposed to chlorinated organic solvents.[254] A government study of cancer rates in a Scottish semiconductor plant showed a 30 percent increase in breast cancer rates among female workers.[255] A Danish study of women

ages 20 to 55 employed in solvent-using industries (fabricated metal, lumber, furniture, printing, chemical, textile and clothing industries) showed these women had double the risk of breast cancer.[256] A 1995 U.S. study suggested an increased breast cancer risk associated with occupational exposure to styrene,[257] as well as with several other organic solvents (including carbon tetrachloride and formaldehyde).[258] These results were validated by studies in Finland, Sweden and Italy.[259,260,261,262]

Studies by Duke University and NIEHS researchers found that the solvent ethylene glycol methyl ether (EGME) and its metabolite, 2-methoxyacetic acid (MAA), act as hormone sensitizers both in vitro and in vivo. This means that these solvents increase cellular sensitivity to the effects of exposure to estrogens and progestins. EGME is used in the semiconductor industry and it is a component in varnishes, paints, dyes and fuel additives. Duke and NIEHS scientists found that exposure to EGME/MAA increased the activity of hormones inside cells as much as eightfold. The researchers emphasized caution for women exposed to EGME while taking HRT, oral contraceptives or tamoxifen. Their studies also found similar hormone-sensitizing effects with another compound, valproic acid (an anticonvulsant medication also prescribed for migraines and bipolar disorder).[263,264]

5. Aromatic Amines

Aromatic amines are a class of chemicals found in the plastic and chemical industries. They are also found in environmental pollution, such as diesel exhaust, combustion of wood chips and rubber, tobacco smoke and in grilled meats and fish.[265] There are three types of aromatic amines: heterocyclic, polycyclic and monocyclic. One type of monocyclic amine, o-toluidine, is known to cause mammary tumors in rodents.[266,267] Heterocyclic amines are formed, along with PAHs, when meats or fish are grilled or otherwise cooked at high temperatures. Since the female breast may be most vulnerable to carcinogens during a critical window of development between menarche and first full-term pregnancy, exposure to heterocyclic amines during adolescence may increase the risk of breast cancer.[268]

6. 1,3-Butadiene

1,3-butadiene is an air pollutant created by internal combustion engines and petroleum refineries. It is also a chemical used in the manufacture and processing of synthetic rubber products and some fungicides. In addition, 1,3-butadiene is found in tobacco smoke.

The EPA determined that 1,3-butadiene is carcinogenic to humans by inhalation. The National Toxicology Program classifies 1,3-butadiene as a known human carcinogen.[269] Data from research on animals indicate that females may be more vulnerable to the carcinogenic effects of 1,3-butadiene,[270] which is known to cause mammary and ovary tumors in female mice and rats. This pollutant produces even greater toxic effects in younger rodent populations.[271,272]

Evidence Indicating Probable Environmental Links To Breast Cancer

Scientific research has established a probable link between certain chemicals and breast cancer. These include DDT, polychlorinated biphenyls, polycyclic aromatic hydrocarbons, dioxin and ethylene oxide.

I. DDT/DDE and PCBs

Two types of chemicals known to disrupt hormone function are the organochlorine pesticide DDT (dichloro-diphenyl-trichloroethane) and PCBs (polychlorinated biphenyls), which were used in the manufacture of electrical equipment and numerous other industrial and consumer products. Both DDT and PCBs have been banned in the United States for three decades, yet both are still found in the body fat of humans and animals, as well as in human breast milk.[273,274]

For more than 30 years prior to the EPA's ban on domestic use of DDT in 1972, this extremely toxic and persistent pesticide was sprayed to control insects on farms and in swamps. An early version of DDT contained an estrogen-like form called o,p'-DDT. Today, DDT continues to contaminate much of our farmland and to enter many homes as a residue on food and as dust because it deteriorates very slowly in soil. In fact, a 1995 study reported measurable levels of DDT residue in household dust in 82 percent of homes studied.[275] Although banned in many countries for agricultural use, DDT is still used for malaria control in 17 countries around the world.[276] DDE is the principal metabolite and environmental breakdown product of DDT, some of which is stored in body fat, including breast fat.

A U.S. study examined blood drawn from children and adolescents at the time of active DDT use. Increased risk of breast cancer paralleled increasing concentrations of serum DDT, and the risk of breast cancer was significantly greater in women exposed before age 15 than after.[277]

A connection was also established by laboratory studies that found the estrogen-like form of DDT enhances the growth of estrogen-positive (ER+) breast tumors,[278,279] the most common type of breast cancer. The percentage of breast tumors in the United States that are ER+ rose from 73 percent in 1973 to 78 percent in 1992.[280]

One widely reported study from the Long Island Breast Cancer Study Project did not find an association between DDT/DDE, PCBs and breast cancer.[281] Like many such studies, however, this project measured contaminant levels near the time of breast cancer diagnosis, did not

consider the effect of chemical mixtures and did not assess key metabolites. In addition, researchers on the Long Island Study were looking at levels in blood rather than in fatty tissue, which accumulates higher levels of these compounds for longer periods of time. Levels of DDE in this recent negative study were more than 10 times lower than levels in the earlier positive studies.

Although the EPA banned the use of PCBs in new products in 1976, as many as two-thirds of all of the insulation fluids, plastics, adhesives, paper, inks, paints, dyes and other products containing PCBs manufactured before 1976 remain in daily use.

The science on DDT/DDE and on PCBs is complicated and conflicting. PCBs are classified in three types based on their effects on cells, but there are more than 200 PCB congeners with perhaps as many different effect mechanisms. One type acts like an estrogen. A second type acts like an anti-estrogen. A third type appears not to be hormonally active, but can stimulate enzyme systems of animals and humans in a manner similar to certain drugs (such as phenobarbital) and other toxic chemicals. Therefore, these compounds have the ability to alter normal metabolism, either by disrupting hormones or enzymes. Unfortunately, most research studies have looked at total PCB levels without identifying individual types. In 1999, however, researchers showed that certain types of PCBs promote the proliferation of breast cancer cells in culture by stimulating the production of key proteins or structures in cancerous tissue.[282]

Numerous studies have identified PCBs as carcinogenic. Although the EPA banned the use of PCBs in new products in 1976, as many as two-thirds of all of the insulation fluids, plastics, adhesives, paper, inks, paints, dyes and other products containing PCBs manufactured before 1976 remain in daily use. The remaining one-third has been discarded, which means that these toxic compounds eventually make their way into landfills and waste dumps.[283]

Despite the fact that some studies have failed to link organochlorines and breast cancer, some evidence suggests that some of these compounds may have their greatest impact on women with greater susceptibilities. Researchers evaluating data from the Nurses' Health Study revisited the issue of PCBs and breast cancer risk and revised their conclusion concerning the link between PCBs and DDE and breast cancer. Based on studies of PCBs and DDE in blood, they had previously concluded that exposure to these chemicals was unlikely to explain high breast cancer rates.[284] In 2002, new evidence regarding variations in individual susceptibility due to genetic differences prompted these researchers to call for additional studies.[285]

A Canadian study measured DDE and specific types of PCBs in breast biopsy tissue and showed that, compared with healthy women, premenopausal women with breast cancer had significantly higher levels of certain PCBs (known as 105 and 118), while postmenopausal women with breast cancer had higher levels of other PCBs (known as 170 and 180).[286] A 2004 Belgian case-control study of 60 women found significantly higher total

blood levels of PCBs in women with breast cancer than in presumably healthy women, particularly PCB 153, which has shown estrogenic activity in animal and in vitro studies.[287]

A 2003 New York study implicated PCBs in breast cancer recurrence among women with non-metastatic breast cancer. The study found that women with the highest levels of one PCB congener in their adipose tissue were almost three times as likely to have recurrent breast cancer as women with lower levels.[288]

2. Polycyclic Aromatic Hydrocarbons (PAHs)

Polycyclic aromatic hydrocarbons (PAHs) are compounds found in soot and fumes from combustion of diesel and other fuels. Various studies have shown that PAHs appear to play a role in the development of breast cancer.

One of the several studies from the Long Island Breast Cancer Study Project found that PAHs create a distinctive type of damage on genetic material—referred to as a fingerprint—where the compounds directly bind up with the basic building blocks of DNA into what is known as a DNA adduct.[289] Women with the highest PAH body burdens had a 50 percent increased risk of breast cancer. This Long Island study validated the earlier work of researchers at Columbia University who also found a close relationship between DNA damage from exposure to PAHs in breast tissue and increased risk of breast cancer.[290]

A recent case-control study in western New York indicated that early life exposure to high levels of PAHs is associated with increased risk of premenopausal breast cancer.[291] Another study of women with occupational exposure to PAHs and benzene showed an elevated risk of premenopausal breast cancer.[292] Some PAHs also may cause estrogenic effects in addition to DNA damage.[293,294]

A new study from Italy suggests that PAHs may also play a role in male breast cancer, particularly with gene-environment interactions. The study focused on male breast cancer patients who had a BRCA1 or BRCA2 mutation and showed that the most frequent occupation among this group was truck driving, which involves chronic exposure to PAHs in diesel exhaust.[295]

Tobacco smoke also contains PAHs, which may explain a potential link between increased breast cancer risk and both active and passive smoking. Researchers at Japan's National Cancer Center recently reported the results of a study involving 21,000 women between the ages of 40 and 59. They found that both active and passive smoking increases the risk of breast cancer in premenopausal women.[296] A large study of California teachers revealed an increased risk of breast cancer among smokers, particularly those who began smoking during adolescence or at least five years before their first full-term pregnancy, or who were long-time or heavy smokers.[297] Four earlier studies also suggest that women who begin smoking cigarettes as adolescents face increased risks of breast cancer.[298,299,300,301]

Until recently, we had more evidence linking secondhand smoke than active smoking to breast cancer risk. Current evidence suggests that both exposures increase breast cancer risk by about the same amount, even though passive smokers receive a much lower dose of carcinogens than do active smokers.[302,303] One possible explanation for this is that smoking acts as an anti-estrogen and damages the ovaries. Researchers believe that

the resulting lower level of estrogen acts to lower breast cancer risk, while at the same time carcinogens in cigarette smoke increase a smoker's risk of breast cancer. Passive smokers, on the other hand, do not get a large enough dose of smoke to depress estrogen levels. A 2005 report from the Air Resources Board of California's Environmental Protection Agency concluded:

> Overall, the weight of evidence (including biomarker, animal and epidemiological studies) is consistent with a causal association between environmental tobacco smoke (ETS) in breast cancer, which appears to be stronger for premenopausal women.[304]

It is important to note that tobacco smoke contains hundreds of chemicals[305] including two known human carcinogens (polonium-210,[306] a radioactive element, and vinyl chloride), as well as benzene, toluene and 1,3-butadiene, all of which are known to cause mammary tumors in animals.

3. Dioxin

Of all toxic chemicals, dioxin may be the most ubiquitous—and the most toxic. The body fat of every human being, including every newborn, contains dioxin. Dioxin (along with a variety of other chemicals) is formed by the incineration of products containing PVC (polyvinyl chloride), PCBs and other chlorinated compounds. Dioxin also comes from industrial processes that use chlorine and combustion of diesel and gasoline, which contain chlorinated additives.

Dioxins are known human carcinogens and hormone mimickers. One of the dioxins (2,3,7,8-tetra chlorodibenzo-para-dioxin—TCDD dioxin) has been classified by the International Agency for Research on Cancer (IARC) as a Group 1 carcinogen (i.e., known human carcinogen).[307] In 2000, after more than a decade of delays, the U.S. Environmental Protection Agency officially declared TCDD dioxin to be a known carcinogen.

People are exposed to dioxin primarily through consumption of animal products: meat, poultry, dairy products and human breast milk.[308] Dioxin enters the food chain when vehicle exhaust or soot from incinerated chlorinated compounds falls on field crops later eaten by farm animals. It is then passed to humans though dairy and meat products.

Until recently, only one study linked dioxin to increased risk of breast cancer—an English study that implicated the toxin in the development of mammary tumors in laboratory mice.[309] However, a recent follow-up study on women exposed to a chemical plant explosion in 1976 in Seveso, Italy makes a more compelling case for a connection between dioxin and breast cancer.[310] Scientists analyzed blood samples taken and stored at the time of the explosion and correlated the results with subsequent cases of breast cancer. They found that a tenfold increase in TCDD dioxin levels was associated with more than twice the risk of breast cancer. Of the 981 women in the study, just 15 have developed breast cancer to date, but the results are compelling because the stored samples measured dioxin levels at the time of actual exposure. Researchers continue to follow the Seveso women and expect to find additional breast cancer cases.

Another recent study showed that intrauterine exposure to TCDD disrupted the development of the rat mammary gland in a way that predisposed offspring to mammary cancer. The mammary gland never fully matured, which prolonged its window of vulnerability to cancer-causing chemicals.[311] This study validated findings by U.K. scientists in which dioxin exposure of the pregnant mouse caused proliferation of terminal end buds of the female offspring's mammary gland, making the gland more vulnerable to carcinogen exposure.[312]

4. Ethylene Oxide

Ethylene oxide is a fumigant used to sterilize surgical instruments. It is also used in some cosmetic products.[313] Ethylene oxide is a known human carcinogen and one of 47 chemicals that the National Toxicology Program identifies as mammary carcinogens in animals. (See Appendix.)

Scientists from the National Institute for Occupational Safety and Health (NIOSH) studied breast cancer incidence in 7,576 women exposed to ethylene oxide while working in commercial sterilization facilities. They found an increased incidence of breast cancer among these women in direct proportion to their cumulative exposure.[314]

Further research is needed, but we will never be able to study and draw conclusions about the potential interactions of exposure to every possible combination of the nearly 100,000 synthetic chemicals in use today.... By implementing precautionary policies, Europeans are creating a model that can be applied in the U.S. to protect public health and the environment. To ignore the scientific evidence is to knowingly permit tens of thousands of unnecessary illnesses and deaths each year.

— Richard Clapp, Genevieve Howe and Molly Jacobs, "Environmental and Occupational Causes of Cancer," 2005

Evidence Indicating Possible Environmental Links To Breast Cancer

Chemicals

Scientists have determined that a number of chemicals are possibly linked with increased breast cancer risk. These include heptachlor, triazines, ingredients in some sunscreens, the group of chemicals known as phthalates and food additives.

1. Heptachlor

Heptachlor is an insecticide widely used in the United States throughout the 1980s, especially for termite control. In 1988, the U.S. EPA restricted use of heptachlor to certain applications for controlling fire ants, but agricultural use continued until 1993 because growers were allowed to use up pre-existing stocks.[315]

Heptachlor still contaminates both soil and humans. Its breakdown product, heptachlor epoxide, (HE) is known to accumulate in fat, including breast tissue. Levels are highest in women 20 years of age and older, but HE is also found in the bodies of adolescents ages 12 to 19 years old[316] and in 8 out of 10 samples of umbilical cord blood from newborn infants.[317]

Although HE does not act like estrogen, it affects the way the liver processes estrogen, thus allowing levels of circulating estrogens to rise, thereby increasing breast cancer risk. HE also has been shown to disrupt cell-to-cell communication in human breast cells in tissue culture.[318] The body's cells need to communicate with each other to regulate their growth. By disrupting cell growth regulation, HE may increase the risk of breast cancer.

Heptachlor is one of many pesticides that have been used on Hawaiian pineapple fields since the late 1950s. After the fruit was harvested, the chopped up leaves, called "green chop," were sold to dairy farmers in Oahu to use in cattle feed, a practice that continued until 1982. Thus, heptachlor contaminated the local milk and dairy supply for years. Between 1981 and 1984, heptachlor levels in Oahu milk and dairy products exceeded the FDA standard (0.3 parts per million [ppm]) tenfold. Follow-up studies found that heptachlor levels in the breast milk of women who had consumed Oahu dairy products averaged 200 ppm and in some cases exceeded 400 ppm.

Breast cancer rates in Hawaii are among the highest in the world. Between 1975 and 1985, breast cancer incidence increased 35 percent among all racial groups in Hawaii. After 1987, breast cancer incidence peaked among white women in Hawaii and declined gradually since

then, although incidence is still rising among Asian and Pacific Islanders living in Hawaii.[319] Heptachlor continues to contaminate soil and crops such as cucumbers in some parts of Hawaii.

2. Triazine Herbicides

Triazine herbicides are the most heavily used agricultural chemicals in the United States. Triazines include atrazine, simazine and cyanazine. All three have been shown to cause mammary cancer in animals.

Simazine, another of the triazine herbicides, is widely used in Florida, California and the Midwest, where it contaminates surface and groundwater. Some lawn chemicals contain simazine. Research suggests that simazine may contribute to breast cancer. In 1994, the EPA banned the use of simazine as an algicide in swimming pools, hot tubs and whirlpools, citing "unacceptable cancer and non-cancer health risks to children and adults."[320]

One study reported an increase of breast tumors in female rats that were fed simazine.[321] Although these rats did not have elevated levels of estrogens, they did have elevated levels of prolactin (another hormone known to play a role in the development of breast tumors in animals).[322] Researchers are trying to determine if simazine can change hormone levels in animals, thus contributing to breast tumor formation.

About 80 million pounds of atrazine are applied annually in the United States, primarily to control broadleaf weeds in corn and sorghum crops in the Midwest.[323] Atrazine is banned in the European Union. Atrazine was once classified by the U.S. Environmental Protection Agency as a carcinogen but industry pressure forced a lengthy and controversial risk assessment process, resulting in the re-registration of atrazine as a permissible chemical.

Elevated levels of atrazine are found each spring and summer in both drinking water and groundwater in the Midwest.

Atrazine is a known endocrine disruptor. Research has shown that atrazine exposure disrupts pituitary-ovarian function, including a decrease in circulating prolactin and luteinizing hormone levels.[324] Exposure to atrazine during gestation delays development of the rat mammary gland in puberty, widening the window of sensitivity to breast carcinogens.[325]

3. Sunscreens (UV Screens)

Growing concern about exposure to ultraviolet (UV) radiation from the sun and the risk of skin cancer has led to widespread use of sunscreens. Research has found that sunscreens contain some chemicals (also used in various cosmetics) that are not only estrogenic but also lipophilic (fat-seeking). Studies show these chemicals are accumulating in wildlife and humans.[326]

A new study by German scientists found that 3-(4-methylbenzylidene)-camphor (4-MBC) accelerates cell proliferation in estrogen-dependent breast cancer cells (**MCF-7**). This finding indicates that 4-MBC has the potential to alter physiological and developmental processes mediated by estrogen receptor signaling mechanisms.[327] Earlier, Swiss researchers who tested six frequently used UV sunscreens found that five of them showed estrogenic activity in breast cancer cells and three showed estrogenic activity in laboratory animals.[328]

4. Phthalates

Phthalates are a group of endocrine-disrupting chemicals commonly used to render plastics soft and flexible. They are found in soft plastic "chew toys" marketed for infants and also in some varieties of nail polish, perfumes, skin moisturizers, flavorings and solvents. Phthalates have been found in indoor air and dust,[329] as well as in humans. Levels are highest in children ages 6 to 11 years and in women.[330]

Some phthalates have hormone-disrupting effects. Recent research by Korean scientists shows that three types of phthalates significantly increase cell proliferation in MCF-7 breast cancer cells. The types include butyl benzyl phthalate (BBP), di(n-butyl) phthalate (DBP) and di(2-ethylhexyl) phthalate (DEHP). In addition, the scientists reported that these three phthalates inhibited the anti-tumor action of tamoxifen in MCF-7 breast cancer cells.[331]

Studies of circulating levels of estrogen, testosterone and other hormones and their relationship to breast cancer indicate that hormonal factors are central to breast cancer risk.[332,333,334] Much remains to be learned about phthalates before a direct connection to breast cancer risk can be established. However, we know that many phthalates disrupt hormonal processes and therefore may increase breast cancer risk.[335]

5. Food And Food Additives (rBST And Zeranol)

Modern food-production methods have opened major avenues of exposure to environmental carcinogens and endocrine-disrupting compounds. Pesticides sprayed on crops, antibiotics used on poultry and hormones injected into cattle, sheep and hogs expose us involuntarily to contaminants that become part of our bodies. Research suggests that some of these exposures may increase breast cancer risk.

The U.S. and Canadian beef, veal and lamb industries have used synthetic growth hormones since the 1950s to hasten the fattening of animals. A study by researchers at Ohio State University suggests these hormones may elevate the risk of breast cancer.

Consumption of animal products also may hold inherent risks because animal fat can retain pesticides and other environmental toxicants consumed by the animal. These lipophilic chemicals become more concentrated as they move from plants to animals and finally to humans.

The U.S. and Canadian beef, veal and lamb industries have used synthetic growth hormones since the 1950s to hasten the fattening of animals. A study by researchers at Ohio State University suggests these hormones may elevate the risk of breast cancer.[336] Concerns about this risk have led the European Union to ban imports of U.S. and Canadian beef since 1999.[337]

a. Bovine Growth Hormone (rBGH)/ Recombinant Bovine Somatotropin (rBST)

Despite opposition from physicians, scientists and consumer advocacy groups, in 1993, the Food and Drug Administration approved Monsanto's genetically engineered hormone product, recombinant bovine growth hormone (rBGH), for injection in dairy cows to increase milk production. This hormone quickly found its way (without labeling) into the U.S. milk supply, and from there into ice cream, buttermilk, cheese, yogurt and other dairy products. Since its introduction, rBGH (subsequently renamed recombinant bovine somatotrophin, rBST) has proven controversial because of its potential carcinogenic effects.

Drinking any type of cow's milk noticeably raises body levels of Insulin Growth Factor 1 (IGF-1), a naturally occurring hormone in both cows and humans. Elevated levels of IGF-1 have been associated with increased risk of breast cancer. A prospective study of American women found that premenopausal women with the highest levels of IGF-1 in their blood (drawn before cancer developed) were seven times as likely to develop breast cancer as women with the lowest levels. No increased risk was noted in postmenopausal women.[338] Three studies reported in 2005 by scientists in Sweden,[339] the United Kingdom[340] and the United States[341] also showed an association between circulating levels of IGF-1 and the risk of breast cancer in premenopausal women. These studies confirm earlier research linking elevated levels of IGF-1 with increased breast cancer risk.[342,343,344]

Injecting a cow with rBST stimulates additional production of IGF-1, which increases cell division and decreases cell death (apoptosis). Both these changes increase cancer risk.[345,346] Thus drinking milk from cows injected with rBST further elevates levels of IGF-1.

Proponents of rBST argue that IGF-1 is harmless because it occurs naturally in humans, is contained in human saliva and is broken down during digestion. However, animal evidence indicates that digestion does not break down IGF-1 in milk because casein, the principal protein in cow's milk, protects IGF-1 from the action of digestive enzymes.[347]

b. Zeranol (Ralgro)

One of the most widely-used hormones in U.S. beef cattle is zeranol (Ralgro), a nonsteroidal growth promoter with estrogenic activity.

Ohio State University scientists found that zeranol exhibited estrogenic activity in normal breast epithelial cells and breast cancer cells. Abnormal cell growth was significant even at zeranol levels 30 times lower than the FDA has approved as safe.[348] A more recent experimental study from these researchers demonstrated that zeranol is comparable to natural estrogen (17-beta estradiol) and the synthetic estrogen diethylstilbestrol (DES) in its ability to transform MCF-10A human breast epithelial cells. These results demonstrate that zeranol can create neoplastic changes in breast cells in vitro.[349]

A recent Harvard study of dietary fat intake in 90,000 women suggests cause for concern about hormones in the meat industry. Scientists reported that premenopausal consumption of red meat may increase the risk of breast cancer later in life. The study found that the risk of breast cancer was one-third higher among women with the highest animal fat intake, derived primarily from red meat and milk.[350]

Danish researchers compared the potency of zeranol to other endocrine disruptors and concluded, "the very high potency of zeranol… suggests that zeranol intake from beef products could have greater impact on consumers than the amounts of the known or suspected endocrine disruptors that have been found in food."[351]

Non-ionizing Radiation (Electromagnetic Fields)

Everyone in the industrialized world is exposed to electromagnetic fields (EMFs) every day. EMFs are a type of non-ionizing radiation, i.e., a type of low-frequency radiation without enough energy to break off electrons from their orbits around atoms and ionize (charge) the atoms. The mechanisms by which EMFs can affect health are not completely understood. Microwaves, radio waves, radar and power frequency radiation associated with electricity are examples of EMFs. Electric lighting generates electromagnetic fields. Fluorescent lighting and all low-voltage lighting produce particularly high fields compared to incandescent lighting, however. In addition, computers and other electric and electronic equipment all create electromagnetic fields of varying strengths.

The International Agency for Research on Cancer (IARC) has classified EMFs as possible human carcinogens. In 1998, a National Institute of Environmental Health Sciences (NIEHS) EMF Working Group recommended that low-frequency EMFs, such as those from power lines and electrical appliances, be classified as possible human carcinogens.[352] Research studies, however, have not been conclusive about the relationship between EMFs and breast cancer.[353]

Some research suggests that EMF exposure lowers the body's level of melatonin, a hormone secreted by the pineal gland during darkness. Melatonin appears to have anti-cancer properties. For example, adding melatonin to cancer cells in a laboratory dish will cause them to stop growing. Placing the same dish in an electromagnetic field will cause the cells to start growing again.[354] In vitro studies have shown that EMF exposure interferes with the ability of tamoxifen to inhibit the growth of breast cancer cells in culture.[355]

Research has shown that exposure to light at night also decreases melatonin levels. This finding led to the hypothesis that night-shift work (working at night in a lighted environment) may increase the risk of breast cancer by lowering melatonin levels. Although this hypothesis remains controversial, at least three studies suggest a link between night-shift work and increased risk of breast cancer.[356,357,358] A recent prospective study from Harvard indicated that higher melatonin levels were associated with a lower risk of breast cancer.[359]

The potential interaction of the hormonal effects of night-shift work together with other environmental exposures such as solar ionizing radiation and (until recently) secondhand smoke may help explain the elevated risk of breast cancer among flight attendants. Studies in Iceland, Sweden and California found varying degrees of increased incidence of breast cancer among flight attendants.[360,361,362]

In 2003, Norwegian researchers reported an increased risk of breast cancer among female radio and telegraph operators exposed to radiofrequency (one type of EMF) and extremely low frequency EMF. Premenopausal women showed an increased risk of estrogen-receptor-positive tumors and postmenopausal women had an increased risk of estrogen-receptor-negative tumors.[363]

Research on EMF exposure has shown increased mortality from breast cancer in women employed in the telephone industry.[364] Further, premenopausal women appear to be at higher risk than postmenopausal women.[365]

In 2004, a Norwegian study of residential and occupational electromagnetic field (EMF) exposure found a 60 percent increase in breast cancer risk among Norwegian women of all ages living near high voltage power lines. Occupational exposure also increased risk, but not as noticeably as residential exposure. Women under 50 who were exposed to EMFs both at home and at work had a modest increase in risk of breast cancer.[366,367]

A 2003 study suggested that EMF exposure from electric bedding (electric blankets, mattress pads and heated waterbeds) may increase the risk of breast cancer in African American women.[368] Researchers from Walter Reed Army Medical Center and Meharry Medical College compared 304 African American women with breast cancer to 305 African American women who did not have the disease. They found that the longer a woman used an electric bedding device, the greater her risk of breast cancer. Most earlier studies on electric bedding use among Caucasian women did not show an association with increased breast cancer risk.

Although breast cancer is rare in men, numerous studies point to a connection between EMF exposure and male breast cancer.[369,370,371,372,373] A recent literature review on male breast cancer also identifies exposure to EMFs as a risk factor.[374]

Moving Forward

Advance The Research Agenda

Federal funding for breast cancer research since 1991 totals $6.8 billion.[375] However, only a small percentage has been directed toward studying environmental connections to breast cancer. The relatively few environmental studies that have been undertaken usually defined "environment" to include nutrition, exercise, tobacco and alcohol use and other lifestyle factors. In other words, most so-called "environmental" studies have defined the word very broadly and have focused largely on voluntary exposures and individual behaviors.

In addition to the National Cancer Institute, approximately 35 other federal and state agencies, private foundations and numerous pharmaceutical and biotech companies conduct or fund breast cancer research. There is no coordination or monitoring of this research and little funding is devoted to research on preventable, environmental causes of breast cancer.

Research into possible environmental causes of breast cancer must not only continue but also expand. We urgently need breast cancer research methods and approaches that reflect the reality of human exposure to chemicals and radiation in the environment.

One encouraging research development is the funding of four new breast cancer and environmental research centers by the National Cancer Institute and the National Institute of Environmental Health Sciences. The agencies allocated $5 million each year for seven years, beginning in 2004, to study environmental links to breast cancer. The four sites include the University of California San Francisco, Fox Chase Cancer Center, University of Cincinnati and Michigan State University.

The Sister Study, launched in 2004, may help uncover the reasons underlying racial disparities in breast cancer rates. This long-term prospective study aims to enroll a diverse population of 50,000 women between the ages of 35 and 74 whose sisters have been diagnosed with breast cancer but who do not themselves have breast cancer. Studying this large group of women with higher than normal risk of breast cancer has the potential to yield new understanding of the roles of genetics and environment in the development of breast cancer. The study is actively enrolling women. More information is available at www.sisterstudy.org.

Priorities For Advancing The Breast Cancer Research Agenda:

1. Study The Interplay Between Timing Of Exposures, Multiple Exposures, Low-Dose Exposures, Chronic Exposures (Including Occupational Exposures) And Cumulative Exposures.

Researchers are only beginning to focus attention on these emerging and promising areas of science. Recent research has confirmed the importance of timing of exposure to environmental contaminants in increasing breast cancer risk. In studying pollutants, researchers need to consider not only those that mutate DNA but also those that alter tissue organization and disrupt normal development, which may lead organisms to develop cancer.

Scientists, policy makers and advocates must heed the comments of two EPA toxicologists in designing future research on environmental links to cancer:

> …There have been epidemiological studies investigating the association of environmental chemicals, including both organochlorines such as PCBs and atrazine, with breast cancer incidence. These particular studies have measured the levels of exposure of these chemicals in adult women who develop breast cancer. Could we be trying to correlate exposure and effect at the wrong time? If it is prenatal or early life stage exposure that is critical to disease susceptibility, why are we measuring environmental chemicals in people once they have developed breast cancer? The critical exposure window may have been much earlier.[376]

We are all exposed to hundreds, perhaps thousands, of chemicals every day, many of which may interact either additively or synergistically. Studying one or two chemicals at a time in isolation will not yield meaningful results. The combined effects of the multiplicity of exposures we experience must be investigated.

We also need further research on the effects of low-dose exposures, which can be more harmful than high-dose exposures, especially during critical windows of vulnerability. The same applies to the long-term effects of chronic exposures at home, school, work and play, and the cumulative effects over time of repeated exposures.

The technology exists to assess and monitor human exposures and health outcomes over weeks, months, even years. For example, monitoring umbilical cord blood in newborns and tracking health outcomes over time could enhance our understanding of the health effects of these exposures. Two of the Breast Cancer and Environmental Research Centers are studying girls between the ages of 7 and 9—tracking their exposures by periodic collection of biospecimens. Ideally, researchers would track these girls over time to see who develops breast cancer. This is just one example of the type of research we need.

2. Study Exposures Of Women At Home And In The Paid Workplace.

Many women in the United States have two places of work: in the home and in the (paid) workplace. To accurately assess the environmental exposures that may increase breast cancer risk, researchers need to consider exposures at both sites, individually and collectively.

Household Exposures

Many of the products and innovations that make modern life more convenient also make it more toxic.[377] Many cleaning products contain hazardous chemicals as do pesticides and products for lawn, garden, pet and pool care.[378] Spray paints and paint removers may contain methylene chloride, known to cause mammary cancer in laboratory animals.[379]

Many personal care products used by women and families, including cosmetics, sunscreens and shampoos, include endocrine-disrupting compounds (such as phthalates and parabens) that could increase breast cancer risk.

Nearly 90 percent of chemicals used in cosmetics and personal care products have never been tested for their effects on human health.[380] The Food and Drug Administration has no authority to regulate these chemicals. The only entity reviewing chemicals in cosmetics sold in the United States is the industry-funded Cosmetics Ingredient Review Panel, which has no regulatory authority and to date has reviewed only 11 percent of the ingredients in cosmetics.[381,382]

Exposures In The Paid Workplace

Since World War II, the number of women employed outside the home has increased steadily; today, women make up nearly half of the U.S. workforce (46 percent).[383] We need more studies of women in the paid workplace because occupational exposures to certain environmental agents are chronic and also can be more intense than in non-occupational settings. For example, one of the earliest studies on workplace exposures found that more than half a million women were occupationally exposed to ionizing radiation and that tens of thousands were exposed to carcinogenic chemicals.[384] Despite these findings, however, relatively few recent studies have been carried out in the United States to identify occupational exposures associated with breast cancer. Most occupational research on women comes from Scandinavia and Canada, and much of it reports risk by job type rather than by specific exposures.

The limited research evidence to date shows an increased risk of breast cancer among two broad occupational categories: (1) those workers who regularly work with toxic chemicals, such as chemists, clinical laboratory technicians, dental hygienists, paper mill workers, meat wrappers and cutters, microelectronics workers and telephone workers, and (2) professionals who are generally in higher socioeconomic groups such as school teachers, social workers, physicians, dentists and journalists.[385,386,387] (See sidebar, page 46.)

Non-ionizing radiation (electromagnetic fields or EMF) is the most pervasive environmental exposure in the developed world. More research is needed to characterize the potential of these exposures in homes, schools and various work environments to increase the risk breast cancer and other diseases. Yet, consumers do not have easy access to information on the levels of electromagnetic radiation emitted by appliances in their homes or equipment in their workplaces. There has been little federally-funded research on EMFs in the United States since 1998. Ongoing research in Sweden, Norway and other European countries continues to link EMF exposure to increased risk of breast cancer and other cancers.

A growing body of evidence shows an association between night-shift work and increased risk of breast cancer. The studies suggest that exposure to light at night alters hormone function, particularly the production of melatonin, which has anti-cancer properties. Until the actual cancer risk of EMF and light at night can be confirmed or refuted by scientific evidence, research must resume in the United States without further delay.

3. Study Disparities In Health Outcomes And Environmental Exposures.

More studies are needed to explain disparities in breast cancer incidence and mortality between different racial and ethnic groups and to determine whether environmental exposures are contributing to these disparities. For example, white women have the highest incidence of breast cancer but African American women have the highest death rate from the disease. Postmenopausal Hispanic women appear to be at significantly greater risk of breast cancer related to estrogen replacement therapy than non-Hispanic white women.[395] This variation could suggest greater sensitivity to environmental estrogens as well as different exposures. Breast cancer rates are rising rapidly in Asian American women, particularly in Japanese American women.[396]

Throughout the 1990s, the incidence of inflammatory breast cancer (IBC), a relatively rare but extremely aggressive form of the disease, increased in both white and black women, but incidence was higher for black women.[397] Another study showed that premenopausal IBC patients were younger at menarche and at the time of their first live births than their non-IBC counterparts.[398]

Few research studies on breast cancer include actual assessment of environmental exposures. However, according to CDC scientists, blacks have higher body burden levels of some chemicals than whites or Mexican Americans, such as PCBs, mercury, lead, PAHs, dioxin and phthalates. Mexican Americans have higher levels of the pesticides DDT/DDE, lindane and 2,4,5 TCP.[399] Biomonitoring clearly shows differences in exposures among communities of color that must be considered in evaluating the causes of breast cancer.

Socioeconomic status also affects environmental exposures, which in turn affect cancer incidence and mortality. One former director of the National Cancer Institute declared that "poverty is a carcinogen."[400] The unfortunate reality in the United States is that poverty is three times as common among people of color as among white people,[401] and five-year cancer survival is 10 percentage points lower among the poor than in those who live in more affluent areas.[402] Those who live below the poverty line suffer multiple environmental injustices: substandard housing, under-employment except in high-exposure low-level dangerous jobs, disproportionate exposure to industrial pollution, lack of adequate health insurance and a compromised ability to deal with the collective impact of these conditions. Underserved and overexposed, people in these communities are at high risk for breast cancer and other cancers. Community-based participatory research[403] can help identify communities exposed to cumulative risks and give community members tools to work toward risk reduction and pollution prevention.

Occupations Associated With Increased Risk Of Breast Cancer[388,389,390,391,392,393,394]

- Aircraft and automotive workers
- Barbers and hairdressers
- Chemists
- Clinical laboratory technicians
- Computer and peripheral equipment operators
- Crop farmers and fruit and vegetable packers
- Dental hygienists
- Dentists
- Dry cleaning workers
- Flight attendants
- Food, clothing and transportation workers
- Homemakers
- Journalists
- Librarians
- Nurses, particularly chemotherapy nurses
- Paper mill workers
- Physicians
- Publishing and printing industry workers
- Meat wrappers and cutters
- Microelectronics workers
- Radiologic technologists
- School teachers
- Social workers
- Telephone workers

4. Develop Less Invasive, More Effective Breast Cancer Screening Methods.

Ionizing radiation is the longest-established environmental cause of breast cancer and other cancers. Despite undeniable evidence,[404,405,406] mammography continues to be a gold standard for breast cancer screening. The American Cancer Society and the National Cancer Institute now recommend that women begin annual mammography screening at age 40, and even earlier if their family history, genetic predisposition or previous medical treatment puts them at high risk of developing breast cancer. The authors of this report, however, call for annual mammography beginning at menopause (usually age 50 or older) for most women, in part due to the risks of unnecessary exposure to ionizing radiation.

Recommendations that women at high risk for breast cancer increase their exposure to one of the only proven causes of the disease highlights the urgent need for an alternative to mammography that does not involve radiation exposure. The screening recommendation for women who have already undergone radiation therapy for Hodgkin's disease further illustrates the contradiction in current medical practice. Four studies in 2003 found a greatly increased risk of breast cancer among young women who had received radiation treatment for Hodgkin's disease.[407,408,409,410] These studies confirmed findings from many earlier studies. Every year, 3,500 women are diagnosed with Hodgkin's disease and treated with radiation. The American Cancer Society (ACS) suggests that these women consider undergoing annual mammograms as young as 30, ignoring the risk of 10 extra years of radiation exposure, in addition to the radiation therapy that has already put them at high risk for breast cancer.

ACS makes a similar screening recommendation for women with the BRCA1 and BRCA2 gene mutation. However, the ACS's "Guidelines for Breast Cancer Screening Update 2003"[411] includes the following risk assessment:

> Overall risk from single and cumulative diagnostic exposures is small, but risk increases with the amount of exposure and with younger age at exposure. . .[412,413]

It has also been hypothesized that some women at increased inherited risk for breast cancer may also have increased radiation sensitivity, which could increase their risk for radiation-induced breast cancer. This hypothesis may be plausible because studies of BRCA1 and BRCA2 suggest that these genes code for functions related to repair of radiation damage to DNA.[414,415,416,417,418]

Surely women at particularly high risk for breast cancer should not be repeatedly exposed to a known breast carcinogen as a screening method.

Women need a more effective method for breast cancer screening, one that works for women of all ages and does not expose them to radiation. Finding an alternative to mammography, a technology now more than half a century old, must be a top research priority. It is time to redirect scarce resources to answer this critical need.

Women also need better information about the benefits and harms of mammography screening. Researchers at the Nordic Cochrane Centre in Copenhagen, Denmark found the information provided by professional advocacy groups (including the American Cancer Society, the Susan G. Komen Foundation and Y-ME National Breast Cancer Organization) to be "severely biased in favour of screening. Few websites live up to accepted standards for informed consent."[419] Web sites of three of the consumer organizations studied (including Breast Cancer Action) mentioned the harms of screening, overdiagnosis and treatment, and were found to be "much more balanced and comprehensive than other sites."

Women need a more effective method for breast cancer screening, one that works for women of all ages and does not expose them to radiation. Finding an alternative to mammography, a technology now more than half a century old, must be a top research priority. It is time to redirect scarce resources to answer this critical need.

Implement Policy Changes

While research proceeds, scientists, public health professionals and activists call for fundamental changes in both the public and private sectors regarding exposure to radiation and the production, use and disposal of chemicals found to increase the risk of breast cancer or suspected of doing so. Failure to act on the evidence summarized in this report could be tantamount to ignoring the costly history lesson of smoking and lung cancer.

The Centers for Disease Control and Prevention (CDC) have documented the invasion of 148 chemicals into the bodies of Americans without our knowledge or consent. Some of these chemicals, such as polycyclic aromatic hydrocarbons (PAHs), heptachlor (an insecticide) and atrazine (an herbicide) are associated with increased risk of breast cancer.[420] Many of them, such as atrazine, cadmium and various phthalates are known endocrine disruptors and may put developing fetuses at greater risk of breast cancer in adulthood. The collective impact of chemical mixtures is unknown, but the uninvited presence of chemicals in our bodies is unacceptable.

All scientific work is incomplete—whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone action that it appears to demand at a given time.

— Sir Austin Bradford Hill, Address to the Royal Society of Medicine, 1965

Magnifying or manufacturing scientific uncertainty is another tactic used to delay or prevent public health and environmental protection.... Policy decisions should be made with the best available evidence and must not wait until every piece of evidence is in and until every conceivable doubt is erased.

— David Michaels, American Journal of Public Health, 2005

Breast Cancer Is A Public Health Issue

There is no shortage of advice for women about things they can do in their personal lives to reduce the risk of breast cancer. However, many factors contributing to the disease lie far beyond an individual's control and can only be addressed by government policy and private sector changes. In addition, avoiding involuntary exposures at home and at work is simply not an option for many people. Most workers cannot afford to walk away from potentially hazardous jobs. Moreover, organic or chemical-free produce and meat are not available in every corner of the country, even if we could all afford the extra cost.

Breast cancer is more than a personal issue; it is a public health crisis that demands action by society as a whole. Hundreds of non-governmental organizations are involved in public education campaigns to help people understand the mounting evidence linking environmental exposures with breast cancer, other cancers and other chronic diseases.[421] Once informed, the public can be mobilized to action, using this evidence to justify measures to protect human health and the health of future generations.

The Need For A Precautionary Approach

The public's health cannot and should not have to wait for absolute proof that certain chemicals cause breast cancer before moving to reduce the risk of such harm occurring. Too many people will suffer from this disease if we delay action until a "scientific standard" of proof is met. Such a standard requires a 95 percent certainty of cause and effect. While this strict standard is supported by industry when policy changes under consideration would have an impact on profits, less stringent standards are followed in other settings. California's Environmental Quality Act (CEQA) requires only "potential for significant impact"—10 to 30 percent likelihood—as a basis for action.

What may work for science and industry does not serve, in this case, to protect public health. The public can only be protected from environmental hazards when some evidence of harm—not conclusive proof—is sufficient cause for action. That standard is known as the precautionary principle. Public health policy based on the precautionary principle says that indication of harm, rather than proof of harm, serves as the trigger for policy action. By that standard, there is ample evidence of the need to reduce or, in some cases, eliminate exposure to certain toxic chemicals.

Understood by doctors as "first, do no harm," the precautionary principle is sometimes abbreviated as "better safe than sorry." The precautionary principle provides that:

> When an activity raises threats of harm to the environment or human health, precautionary measures should be taken even if some cause-and-effect relationships are not fully established scientifically… The process of applying the precautionary principle must be open, informed and democratic and must include potentially affected parties. It must also involve an examination of the full range of alternatives, including no action.[422]

The precautionary principle mandates that manufacturers and industries that use or emit toxic chemicals assess the health consequences and environmental impacts *before* introducing them to the marketplace.

Understood by doctors as "first, do no harm," the precautionary principle is sometimes abbreviated as "better safe than sorry."

To reduce the risk of breast cancer and ultimately end the epidemic, fundamental and immediate public policy changes based on the precautionary principle must be made. We can afford to wait no longer. The following 10-point plan moves us closer to this goal.

A 10-Point Plan For Reducing The Risk Of Breast Cancer And Ultimately Ending The Epidemic

1. Establish Environmental Health Tracking (EHT) Programs At State And Federal Levels.

Environmental Health Tracking (EHT) programs at both the state and federal levels could play a pivotal role in reducing environmentally related chronic disease. These programs would provide the information needed to improve existing pollution- and disease-prevention programs. EHT programs would investigate the interplay between chemicals exposure and resultant health outcomes in humans, with the ultimate goal of developing policies and practices that would eliminate contaminants that lead to adverse health outcomes. These programs would integrate multiple databases such as human body burden data (biomonitoring), chemical release data, geographic distribution patterns of exposure and health outcome data. Environmental health data need to be shared and integrated in a standardized manner and disseminated to the public in a timely, accessible and useful way.

A Nationwide Health Tracking Network (NHTN) is needed to connect state systems tracking chronic diseases, environmental exposures and other risk factors so that the causes of priority chronic diseases can be identified, addressed and ultimately eliminated. The annual findings of the NHTN should be made available to the public as education to help prevent chronic disease. The NHTN should also provide grants to help states develop the necessary infrastructure to participate in the Nationwide Network.

Environmental Health Tracking programs are needed in every state because each state has unique exposures and rates of disease. For example, the CDC National Health And Nutrition Examination Survey (NHANES) provides a kind of aerial photograph of the nation's health but it does not offer a snapshot of what's happening in communities at ground level or a systematic method of monitoring trends over time in a particular state.

While high uncertainty may obscure both the probability of a risk and the magnitude of harm, uncertainty does not eliminate risk. Unrecognized risks are still risks; uncertain risks are still risks; and denied risks are still risks.

— John Cairns, Jr., Environmental Health Perspectives, 1999

In order to obtain more complete data on chemical, geological and physical hazards, monitoring states need federal funding to develop the necessary infrastructure for health tracking, which includes:

- State laboratories capable of performing biomonitoring of human samples for an array of contaminants, including certain pesticides, brominated flame retardants and mercury;
- State-initiated Health and Nutrition Examination Surveys to provide data on a range of health indicators and environmental exposures; and
- State Human Exposure Assessment Surveys (HEXAS) to identify exposures in the indoor environment, where many pollutants gather and concentrate.

2. Practice "Healthy Purchasing" By Adopting Precautionary Purchasing Laws At Local, State And Federal Levels.

Businesses, government, consumers and hospitals should purchase products that are free from chemicals linked to cancer, such as chlorine-free paper and plastic products made without polyvinyl chloride. Such subtle changes in purchasing practices would mean that fewer cancer-causing chemicals would enter our homes, be dumped in our landfills and pollute our air and water. Further, these actions will encourage industry to provide non-hazardous products that consumers want.

Local, state and federal governments can and should lead the way by adopting environmentally-preferable purchasing practices, thereby creating an example for individuals, businesses and hospitals to follow. In 2002, the Los Angeles Unified School District, the second largest in the United States, adopted an Integrated Pest Management Policy based on the precautionary principle. The California General Services Division of State Architects (DSA) has launched a list of environmentally-preferable building products to be used in school construction. See www.eppbuildingproducts.org for more information.

In 2003, San Francisco adopted a precautionary principle ordinance as a policy framework for decision-making. This led to the 2005 passage of a precautionary purchasing ordinance in San Francisco that would require the city to choose the safest alternatives when purchasing city vehicles, janitorial products and other commodities. Also in 2003, Berkeley, California adopted a precautionary principle resolution that mandated the drafting of a city ordinance.

In 2005, New York became the first state to require schools to use "green" cleaning products. Also in 2005, Massachusetts' Alliance for a Healthy Tomorrow secured funding in the state budget for an analysis of safer alternatives to five toxic chemicals: lead, formaldehyde, perchloroethylene, hexavalent chromium and di-(2-ethylhexyl) phthalate (DEHP). This funding will be used by the Toxic Use Reduction Institute (TURI) at University of Massachusetts-Lowell to analyze the uses of each chemical in Massachusetts, potential human health and environmental impacts and the potential of any and all alternative chemicals or technologies to serve as substitutes for the toxic substances.

3. Protect Workers From Hazardous Exposures

When occupational exposures are known or suspected of posing a health hazard to workers and communities, immediate action is necessary to eliminate these exposures. Much of what we know about chemicals that cause cancer comes from studies of workers. Chemicals to which workers are exposed ultimately enter the general environment and affect communities by being carried home on work clothes, added to consumer products, dumped into toxic landfills or released into air or water.[423] Fenceline communities (people living near industrial sites) are at greatest risk of harm from chemical exposures and these are almost always communities of color. We must ensure that no population is disproportionately burdened by chemical exposures.

All industries manufacturing or using toxic chemicals should follow the example set forth in the Silicon Principles, developed by the Silicon Valley Toxics Coalition and the Campaign for Responsible Technology.[424] These principles include:

- **Establishing a comprehensive toxics use reduction program**, including phasing out chlorofluorocarbons (compounds used as propellants and refrigerants) and other chlorinated solvents, carcinogens, reproductive toxicants and neurotoxicants.
- **Developing comprehensive health monitoring and health and safety education programs** that are sensitive to diversity of the workforce and available for public inspection.

4. Educate The Public About The Health Effects Of Radiation And How To Reduce Exposure To Both Ionizing And Non-Ionizing Radiation

Health professionals and the public need to understand that (1) exposure to ionizing radiation can cause cancer; (2) exposure to even low levels of radiation are cumulative over a lifetime and can cause genetic damage; and (3) the younger an individual is at the time of exposure, the greater the risk of cancer development. Medical procedures involving radiation exposure involve both risks and benefits, and patients are entitled to know both in order to provide informed consent.[425] Physicians and others referring patients for a radiological procedure should tell the patient what radiation dose is involved, just as they currently tell the patient the dosage of a prescribed medication.

Public education also is needed about the risks of non-ionizing radiation (EMF) exposure, how people can measure EMF levels in their environment and how they can mitigate them if necessary. This educational effort should identify prudent avoidance measures for consumers as well as for certain labor and professional groups, such as teachers, nurses and flight attendants. An informed public can help shape public policy to reduce EMF exposure at the local, state and national level.

5. Hold Corporations Accountable For Hazardous Practices

Corporations wield enormous economic, social and political power throughout the world. This power includes deciding when, how and where to manufacture their products, often without regard for social or environmental consequences. Because corporate wealth buys influence in government, corporations are able to shape laws and public policy to serve the needs of industry at the expense of public health. These realities have allowed corporate polluters to contaminate communities across the United States and around the globe, leaving sickness and death in their wake.

If we are to reverse the epidemic of breast cancer and other cancers, corporations must be held accountable for practices that endanger public health. Market-based corporate accountability campaigns such as the Campaign for Safe Cosmetics (www.safecosmetics.org) and "Think Before You Pink" (www.thinkbeforeyoupink.org) can make a difference. Both Web sites offer information about alternatives to products with toxic ingredients. Exposing the fact that manufacturers of personal care products are using harmful ingredients—chemicals that can cause cancer and birth defects—can literally shift the market by increasing consumer demand for safe, non-toxic products.

Government must act to hold corporations accountable for hazardous practices. All environmental laws should be based on the "polluter pays" principle.

6. Offer Local, State And Federal Incentives For Clean Green Practices

Companies should not only be held accountable for releasing cancer-causing chemicals into our environment and into our bodies but should also be rewarded for instituting new policies and processes that are healthier for our environment. Many companies already understand that being "green" builds consumer loyalty and increases profitability and some companies are committed to practicing sustainability in doing business. Offering additional incentives to corporations that encourage them to eliminate harmful chemicals in their products and processes will help them initiate new policies.

Such incentives might include a labeling system to highlight companies that use pollutant-reducing technology, prioritizing "green" companies when awarding government contracts, tax credits for companies that reduce their use of natural resources, grants to small businesses for one-time purchase of equipment or materials that would help them reduce their use of cancer-causing chemicals and non-monetary public recognition awards.

7. Strengthen Right-To-Know Legislation And Public Participation In Decisions About Toxic Exposures

The public and workers are entitled to full disclosure about chemicals to which they may be exposed and to full participation in decisions about how or if hazardous chemicals are to be used. Information must be clear, current and easily accessible in all relevant languages and must include chemicals and materials, quantities of chemicals produced, used, released and exported, as well as chemical hazard, use and exposure information. California's Proposition 65, the Safe Drinking Water and Toxic Enforcement Act of 1986,[426] is one example of important right-to-know legislation. Proposition 65 lists all chemicals known to cause cancer, birth defects or other reproductive harm, and requires disclosure of this information in public settings.

We should strive to reduce or eliminate exposures to all chemicals and myriad, multiple exposure circumstances known to cause cancer in humans and/or in animals.

— James Huff, European Journal of Oncology, 2000

Every person has a right to know which environmental chemicals have invaded his or her body without consent, the likely source of the exposure and the potential health affect of chemical exposure. Monitoring the body burden of chemicals in workers and members of the general public is a valuable tool in assessing human exposure to chemicals. A biomonitoring program should reflect the principles of community-based participatory research, involving the community from the outset and providing support and practical information to those who agree to be tested.

8. Enforce Existing Environmental Protection Laws

Existing environmental protection laws need to be enforced and, in some cases, toughened. As a recent GAO report[427] recommended, EPA needs additional authority and resources to do its job in protecting public health and the environment from hazardous chemicals. Other environmental protection laws such as the Clean Air Act, the Clean Water Act and the Federal Insecticide, Fungicide and Rodenticide Act must be strengthened, not weakened. Sufficient funding must be appropriated for regulatory agencies and commissions, such as the EPA and the Consumer Products Safety Commission, to increase environmental surveillance and enforcement of existing regulations.

9. Require Greater Transparency In Funding Of Scientific And Medical Training, Research And Publications

History provides many examples of how corporate interests have trumped public interest in government, law, public policy and science: tobacco, lead, diethylstilbestrol, HRT and asbestos. Despite, in many cases, knowing the dangers of these products, industry continued to promote their "benefits" for decades, citing their own "scientific" studies as proof that products were safe. Industry practices such as these have harmed generations of men, women and children.

Recent evidence has exposed physicians, scientists and government regulatory agencies whose relationships with private industry, particularly pharmaceutical manufacturers and biotechnology companies, have compromised drug safety, clinical trials and other research. According to a report by the inspector general of the U.S. Department of Health and Human Services, conflicts of interest and other ethical violations are common among scientists at the National Institutes of Health (NIH).[428]

Policy changes are needed to establish and enforce ethical standards as well as to prevent conflicts of interest in employment and appointments to government regulatory agencies such as the NIH, EPA and FDA. For example, scientists who represent the interests of industry should not be appointed to science advisory boards of research or regulatory agencies.

Greater transparency in the funding of scientific research and publications is needed, especially to expose potential conflicts of interest that arise when corporations that stand to gain economically from a study's findings are involved in the study itself.

10. Create A Comprehensive Chemicals Policy Based On The Precautionary Principle

One of the most critical public health and environmental challenges facing the United States and the global community is the growing rates of breast cancer and other cancers, developmental disorders, asthma and other chronic diseases caused in part by exposure to toxic chemicals and radiation. International efforts have been underway for more than a decade to develop a precautionary approach to chemicals regulation that would include phasing out chemicals that cause cancer, reproductive harm or genetic damage. This approach would require toxic-use reduction planning and clean-production planning by all polluters and government agencies. However, the United States has failed to develop such a policy. In fact, a new report from the U.S. Government Accountability Office (GAO) found that U.S. chemicals regulatory policy, based on the Toxic Substances Control Act (TSCA), fails to protect public health and the environment from toxic chemical exposures.[429]

International Efforts To Create Change

REACH

The new policy proposed by the European Union (EU) known as REACH (Registration, Evaluation and Authorization of Chemicals), offers an excellent model for comprehensive chemicals regulation. REACH uses the precautionary principle as its guiding principle. It requires that manufacturers show that chemicals can be used safely prior to receiving government authorization for their release into commerce. In many cases, such a policy would prevent harm from occurring. REACH would apply not just to chemicals but also to products that contain harmful chemicals, including cleaning solvents and cosmetics and personal care items. The final draft of legislation was published on October 29, 2003, and is expected to become law in 2006.

The Paris Appeal

In support of the REACH policy, hundreds of members of the European Parliament, scientists, physicians, ethicists and citizens from Europe, Canada and the United States signed the International Declaration on Chemical Pollution Health Dangers in May 2004, also known as the Paris Appeal. The signatories call on "national decision-makers, European Authorities, international organizations and specifically the United Nations" to ban all products that are certainly or probably carcinogenic, mutagenic or contain reproductive toxicants for humans, and apply the precautionary principle to all chemicals that are persistent and bio-accumulative. Other recommendations can be found on the following Web site: http://appel.artac.info/anglais.htm.

The EU Cosmetics Directive

Since October 2004, cosmetics manufactured and sold in the EU are prohibited from containing any chemical known to be a carcinogen, mutagen or reproductive toxicant. Requiring the same standards of companies that sell cosmetics and personal products in the United States would necessitate extensive independent research into the health effects of ingredients in these products.

The POPS Treaty

The Persistent Organic Pollutants (POPs) treaty,[430] negotiated under the auspices of the United Nations Environment Program, targets hexachlorobenzene, endrin, mirex, toxaphene, chlordane, heptachlor, DDT, aldrin, dieldrin, PCBs, dioxins and furans. The agreement became legally binding on May 17, 2004, when France became the 50th nation to ratify it. Although the United States is a signatory to this agreement, the U.S. Senate has not ratified the treaty.

State Efforts To Create Change

State initiatives are proving effective in targeting certain high-production-volume chemicals shown to be accumulating in humans. For example, California and Maine passed the nation's first laws banning certain flame retardants and New York and Washington state have followed their lead. Legislation that would mandate disclosure to the state Department of Health Services of any ingredients in cosmetics that cause cancer or reproductive harm was enacted in California in 2005. Collaborative efforts in states such as Massachusetts, Washington, Maine, New York and California are working toward statewide chemicals policy reform campaigns.

In Massachusetts, for example, the Alliance for a Healthy Tomorrow, which has more than 140 member organizations, is actively promoting a state-level "Safer Alternatives to Toxics" program. In New York, the Citizens' Environmental Coalition is leading the Alliance for a Toxic-Free Future to create a unified approach for initiatives that will protect human health and the environment from persistent toxic chemicals. In Washington state, the Toxic Free Legacy Coalition led by the Washington Toxics Coalition passed a tough mercury pollution bill and is working with the state's Department of Ecology in a coordinated effort to phase out the most toxic, persistent chemicals.

Other efforts are underway in the United States to educate and promote discussion about a REACH-like chemicals policy at local, state, regional and federal levels. For example, the Louisville Charter for Safer Chemicals[431] is a set of principles agreed upon in Louisville, Kentucky in May 2004 by a network of environmental health and justice organizations working on chemical policies and campaigns. (See sidebar.)

Louisville Charter Core Principles

- **Embrace Safer Substitutes and Solutions** by seeking to eliminate the use and emissions of hazardous chemicals by altering production processes and substituting safer chemicals.
- **Phase Out Persistent, Bioaccumulative or Highly Toxic Chemicals** by prioritizing for elimination chemicals that accumulate in humans or animals that are slow to degrade, or that are highly hazardous to humans or the environment.
- **Act on Early Warnings** in order to prevent harm from new or existing chemicals when credible evidence of harm exists, even when some uncertainty remains regarding the exact nature, magnitude or mechanism of the harm.
- **Require Comprehensive Safety Data for All Chemicals** as a prerequisite for a chemical to remain on or be placed on the market.

Cancer prevention depends on reducing or eliminating exposures to substances and processes that cause cancer. A policy such as REACH or the Louisville Charter would help reverse the epidemic of breast cancer. Initial steps could include expanding the authority of U.S. Environmental Protection Agency to regulate chemicals as recommended in the Government Accountability Office Report and giving the FDA authority to regulate the ingredients in cosmetics and personal care products before they are allowed on the market.

Conclusion

We ignore at our peril the evidence that radiation and chemicals are contributing to the growing human and economic costs of breast cancer. Halting the scourge of this disease demands that we take action based on existing evidence to protect the health of people and the planet. Waiting for absolute proof only means more needless suffering and loss of life. It is in our power to change the course we are on. It is time to act on the evidence.

Appendices

Appendix 1: Chemicals Shown To Induce Mammary Tumors In Animals

Source: U.S. National Toxicology Program, 2005.

- Acronycine
- Benzene
- 2,2-Bis(Bromomethyl)-1,3-Propanediol
- 1,3-Butadiene
- 2-Chloroacetophenone (CN)
- Chloroprene
- C.I. Acid Red 114
- C.I. Basic Red 9 Monohydrochloride
- Clonitralid
- Cytembena
- 2,4-Diaminotoluene (2,4-Toluene Diamine)
- 1,2-Dibromo-3-Chloropropane
- 1,2-Dibromoethane
- 2,3-Dibromo-1-Propanol
- 1,1-Dichloroethane
- 1,2-Dichloroethane
- 1,2-Dichloropropane (Propylene Dichloride)
- Dichlorvos
- 3,3'-Dimethoxybenzidine Dihydrochloride
- 3,3'-Dimethylbenzidine Dihydrochloride
- 2,4-Dinitrotoluene
- Ethylene Oxide
- Furosemide (Lasix)
- Glycidol
- Hydrazobenzene
- Indium Phosphide
- Isophosphamide
- Isoprene
- Leucomalachite Green
- Malachite Green
- Methylene Chloride
- Methyleugenol
- Nithiazide
- 5-Nitroacenaphthene
- Nitrofurazone
- Nitromethane
- O-Nitrotoluene
- Ochratoxin A
- Phenesterin
- Procarbazine Hydrochloride
- Reserpine (Serpasil)
- Sulfallate
- 2,4- & 2,6-Toluene Diisocyanate
- O-Toluidine Hydrochloride
- 1,2,3-Trichloropropane
- Urethane
- Urethane AND Ethanol Combination

Appendix 2: Substances Listed In The U.S. National Toxicology Program's 11th Report On Carcinogens

Part A. Known to be Human Carcinogens

Aflatoxins
Alcoholic Beverage Consumption
4-Aminobiphenyl
Analgesic Mixtures Containing Phenacetin
Arsenic Compounds, Inorganic
Asbestos
Azathioprine
Benzene
Benzidine
Beryllium and Beryllium Compounds
1,3-Butadiene
1,4-Butanediol Dimethanesulfonate (Myleran(r))
Cadmium and Cadmium Compounds
Chlorambucil
1-(2-Chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea (MeCCNU)
bis(Chloromethyl) Ether and Technical-Grade Chloromethyl Methyl Ether
Chromium Hexavalent Compounds
Coal Tar Pitches
Coal Tars
Coke Oven Emissions
Cyclophosphamide
Cyclosporin A
Diethylstilbestrol
Dyes Metabolized to Benzidine
Environmental Tobacco Smoke
Erionite
Estrogens, Steroidal
Ethylene Oxide
Hepatitis B Virus
Hepatitis C Virus
Human Papillomas Viruses: Some Genital-Mucosal Types
Melphalan
Methoxsalen with Ultraviolet A Therapy (PUVA)
Mineral Oils (Untreated and Mildly Treated)
Mustard Gas
2-Naphthylamine
Neutrons
Nickel Compounds
Radon
Silica, Crystalline (Respirable Size)
Smokeless Tobacco
Solar Radiation
Soots 233
Strong Inorganic Acid Mists Containing Sulfuric Acid
Sunlamps or Sunbeds, Exposure to
Tamoxifen
2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD); "Dioxin" 241
Thiotepa
Thorium Dioxide
Tobacco Smoking
Vinyl Chloride
Ultraviolet Radiation, Broad Spectrum UV Radiation
Wood Dust
X-Radiation and Gamma Radiation

Part B. Reasonably Anticipated to be a Human Carcinogen

Acetaldehyde
2-Acetylaminofluorene
Acrylamide
Acrylonitrile
Adriamycin® (Doxorubicin Hydrochloride)
2-Aminoanthraquinone
o-Aminoazotoluene
1-Amino-2,4-dibromoanthraquinone
1-Amino-2-methylanthraquinone
2-Amino-3,4-dimethylimidazo [4,5-*f*]quinoline (MeIQ)
2-Amino-3,8-dimethylimidazo [4,5-*f*]quinoxaline (MeIQx)
2-Amino-3-methylimidazo [4,5-*f*]quinoline (IQ)
2-Amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP)
Amitrole
o-Anisidine Hydrochloride
Azacitidine (5-Azacytidine(r), 5-AzaC)
Benz[*a*]anthracene
Benzo[*b*]fluoranthene
Benzo[*j*]fluoranthene
Benzo[*k*]fluoranthene
Benzo[*a*]pyrene
Benzotrichloride
Bromodichloromethane
2,2-bis-(Bromoethyl)-1,3-propanediol (Technical Grade)
Butylated Hydroxyanisole (BHA)
Carbon Tetrachloride
Ceramic Fibers (Respirable Size)
Chloramphenicol
Chlorendic Acid
Chlorinated Paraffins (C12, 60% Chlorine)
1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosourea
bis(Chloroethyl) nitrosourea
Chloroform
3-Chloro-2-methylpropene
4-Chloro-*o*-phenylenediamine
Chloroprene
p-Chloro-*o*-toluidine and *p*-Chloro-*o*-toluidine Hydrochloride
Chlorozotocin
C.I. Basic Red 9 Monohydrochloride
Cisplatin
Cobalt Sulfate
p-Cresidine
Cupferron
Dacarbazine
Danthron (1,8-Dihydroxyanthraquinone)
2,4-Diaminoanisole Sulfate
2,4-Diaminotoluene
Diazoaminobenzene
Dibenz[*a,h*]acridine
Dibenz[*a,j*]acridine
Dibenz[*a,h*]anthracene
7*H*-Dibenzo[*c,g*]carbazole
Dibenzo[*a,e*]pyrene
Dibenzo[*a,h*]pyrene
Dibenzo[*a,i*]pyrene
Dibenzo[*a,l*]pyrene
1,2-Dibromo-3-chloropropane
1,2-Dibromoethane (Ethylene Dibromide)
2,3-Dibromo-1-propanol
tris(2,3-Dibromopropyl) Phosphate
1,4-Dichlorobenzene
3,3´-Dichlorobenzidine and 3,3´-Dichlorobenzidine Dihydrochloride
Dichlorodiphenyltrichloroethane (DDT)
1,2-Dichloroethane (Ethylene Dichloride)

Dichloromethane (Methylene Chloride)
1,3-Dichloropropene (Technical Grade)
Diepoxybutane
Diesel Exhaust Particulates
Diethyl Sulfate
Diglycidyl Resorcinol Ether
3,3´-Dimethoxybenzidine
4-Dimethylaminoazobenzene
3,3´-Dimethylbenzidine
Dimethylcarbamoyl Chloride
1,1-Dimethylhydrazine
Dimethyl Sulfate
Dimethylvinyl Chloride
1,6-Dinitropyrene
1,8-Dinitropyrene
1,4-Dioxane
Disperse Blue 1
Dyes Metabolized to 3,3´-Dimethoxybenzidine
Dyes Metabolized to 3,3´-Dimethylbenzidine
Epichlorohydrin
Ethylene Thiourea
di(2-Ethylhexyl) Phthalate
Ethyl Methanesulfonate
Formaldehyde (Gas)
Furan
Glass Wool (Respirable Size)
Glycidol
Hexachlorobenzene
Hexachlorocyclohexane Isomers
Hexachloroethane
Hexamethylphosphoramide
Hydrazine and Hydrazine Sulfate
Hydrazobenzene
Indeno[1,2,3-*cd*]pyrene
Iron Dextran Complex
Isoprene
Kepone(r) (Chlordecone)
Lead and Lead Compounds
Lindane and Other Hexachlorocyclohexane Isomers
2-Methylaziridine (Propylenimine)
5-Methylchrysene
4,4´-Methylenebis(2-chloroaniline)
4-4´-Methylenebis(*N,N*-dimethyl) benzenamine
4,4´-Methylenedianiline and Its Dihydrochloride Salt
Methyleugenol
Methyl Methanesulfonate
N-Methyl-*N´*-nitro-*N*-nitrosoguanidine
Metronidazole
Michler´s Ketone [4,4´-(Dimethylamino)benzophenone]
Mirex
Naphthalene
Nickel (Metallic) (See Nickel Compounds and Metallic Nickel)
Nitrilotriacetic Acid
o-Nitroanisole
Nitrobenzene
6-Nitrochrysene (See Nitroarenes (selected))
Nitrofen (2,4-Dichlorophenyl-*p*-nitrophenyl ether)
Nitrogen Mustard Hydrochloride
Nitromethane
2-Nitropropane
1-Nitropyrene
4-Nitropyrene
N-Nitrosodi-*n*-butylamine
N-Nitrosodiethanolamine
N-Nitrosodiethylamine
N-Nitrosodimethylamine
N-Nitrosodi-*n*-propylamine
N-Nitroso-*N*-ethylurea
4-(*N*-Nitrosomethylamino)-1-(3-pyridyl)-1-butanone
N-Nitroso-*N*-methylurea
N-Nitrosomethylvinylamine
N-Nitrosomorpholine
N-Nitrosonornicotine
N-Nitrosopiperidine
N-Nitrosopyrrolidine
N-Nitrososarcosine
Norethisterone
Ochratoxin A
4,4´-Oxydianiline
Oxymetholone
Phenacetin
Phenazopyridine Hydrochloride
Phenolphthalein
Phenoxybenzamine Hydrochloride
Phenytoin
Polybrominated Biphenyls (PBBs)
Polychlorinated Biphenyls (PCBs)
Polycyclic Aromatic Hydrocarbons (PAHs)
Procarbazine Hydrochloride
Progesterone
1,3-Propane Sultone
_-Propiolactone
Propylene Oxide
Propylthiouracil
Reserpine
Safrole
Selenium Sulfide
Streptozotocin
Styrene-7,8-oxide
Sulfallate
Tetrachloroethylene (Perchloroethylene)
Tetrafluoroethylene
Tetranitromethane
Thioacetamide
4,4´-Thiodianaline
Thiourea
Toluene Diisocyanate
o-Toluidine and *o*-Toluidine Hydrochloride
Toxaphene
Trichloroethylene
2,4,6-Trichlorophenol
1,2,3-Trichloropropane
Ultraviolet A Radiation
Ultraviolet B Radiation
Ultraviolet C Radiation
Urethane
Vinyl Bromide
4-Vinyl-1-cyclohexene Diepoxide
Vinyl Fluoride

Glossary

AGE-ADJUSTED RATE—Cancer incidence and mortality statistics are weighted (age-adjusted) to match the age distribution of the population during a given census year. This allows for comparison of rates between different regions of the country. Unless rates are age-adjusted, a region with more older people would have a higher rate of breast cancer than a region with younger population.

AROMATIC AMINE—A pollutant from the chemical and plastics industries, and a byproduct of high temperature cooking of meat and fish. Many aromatic amines are known to cause mammary tumors in animals.

CARCINOGEN—Any substance or process known to cause cancer.

CASE-CONTROL STUDY—A research study that looks at two groups of people, one group that has a disease (cases) and one that does not have the disease (controls) but is otherwise similar in age, lifestyle and education to the cases. The goal is to help identify potential causes of the disease. For example, women who have breast cancer might be compared with women who do not have breast cancer to see whether use of pesticides at home was more common among cases than among controls.

DIOXIN—The name given to a group of highly toxic chemicals created by industrial processes that use chlorine, such as the manufacture of paper or the incineration of polyvinyl chloride (PVC) plastics.

DNA ADDUCT—A marker of exposure to a particular carcinogen such as those found in PAHs or tobacco smoke, creating an altered form of DNA. If normal repair mechanisms are successful, the DNA returns to its original structure. If mis-repaired, the adduct results in a mutation, increasing the risk of cancer.

ELECTROMAGNETIC FIELDS (EMFs)—Non-ionizing radiation that includes electrical fields, magnetic fields, radiofrequency transmissions and microwaves.

ENDOCRINE DISRUPTING CHEMICALS/COMPOUNDS (EDCs)—Chemicals such as dioxin that disturb the body's finely tuned hormonal (endocrine) balance. Any disruption in hormonal activity can interfere with an organism's ability to grow, develop and function normally. Some EDCs act like the hormone estrogen and may be referred to as xenoestrogens.

EPIDEMIOLOGY—The study of the distribution and determinants of disease frequency in human populations.

EPITHELIAL CELLS—Most internal and external surfaces of the body are covered with epithelial tissue, including the ducts and lobules of the breast. The majority of breast cancers originate in the epithelial cells of the ducts and are called ductal carcinoma.

ESTRADIOL—The most potent of the three principal types of estrogen hormones; the other types are estriol and estrone. Estradiol is produced by the ovaries, the cortex (outer layer) of the adrenal glands and, during pregnancy, by the placenta. Estradiol is also produced by the male testes.

ESTRIOL—A weaker estrogen produced in the ovaries and peripheral body fat when androgens (male hormones) are converted to estrone by the action of aromatase. Estriol is the metabolite of estrone and estradiol.

ESTROGEN-DEPENDENT—Tumors that grow in the presence of natural or synthetic estrogen are said to be estrogen-dependent or estrogen-receptor-positive (see next page). Tamoxifen is often used to treat such tumors because it reduces estrogen levels in the breast.

ESTROGEN-RECEPTOR—The majority of breast cancers have receptors on their cellular surfaces that respond either to estrogen or progesterone. Tumors are tested to see whether these receptors are present before treatment is prescribed. Estrogen- and progesterone-receptor-positive tumors grow in response to estrogen exposure, and thus may be effectively treated by hormonal drugs such as tamoxifen. Estrogen-receptor-negative tumors are more aggressive than estrogen-receptor-positive tumors and do not respond to hormonal treatments.

GENISTEIN—A phytoestrogen (from plants) found in most soy products.

HISTOLOGICALLY NORMAL—Cells that show no structural abnormalities when examined under a microscope.

HORMONE SENSITIZERS—Chemicals that increase cells' susceptibility to the effects of exposure to hormones such as estrogen.

IN VITRO—Derived from the Latin for "in glass," in vitro studies are those conducted in an artificial environment, on cells in a laboratory dish, for example, rather than in a living organism.

IN VIVO—Studies conducted in a living organism such as humans or other animals.

LIPOPHILIC—Fat-seeking, a term most often applied to chemicals, such as DDT and PCBs, that enter the fatty tissues of the body including the breast.

MCF-7 BREAST CELLS—One of the oldest breast cancer cell lines, immortalized by the Michigan Cancer Foundation on the seventh withdrawal from the breast cancer of a nun, Sister Catherine Frances, who died of breast cancer in 1970. (See Steingraber S (1997). Living downstream: An ecologist looks at cancer and the environment. Reading, MA: Addison-Wesley, p. 121-122.)

MCF-10A BREAST CELLS—A cell line derived from nonmalignant human breast epithelial cells, which retains many of the characteristics of normal breast epithelium.

METABOLITE—A chemical that has been converted from its original form by the body's own chemical processes. For example, the pesticide DDT is converted to DDE in the body.

ORGANOCHLORINES—Any chemical composed of carbon, hydrogen atoms and chlorine. Many pesticides such as DDT and chlordane are organochlorines, which persist in body fat for years. They may also be endocrine disruptors and xenoestrogens and, just as with naturally occurring estrogens, are believed to promote growth of cancer cells.

NEOPLASTIC CHANGES—Alterations in cell structure or function, such as accelerated proliferation, that increase the likelihood of cancer development.

PARABENS—Endocrine-disrupting compounds used as preservatives in thousands of cosmetic, food and pharmaceutical products.

PARTS PER MILLION (PPM)—A standard unit of measurement, used in biomonitoring studies to determine the concentration of a chemical in blood or urine. One part per million is equal to one microgram per milliliter or one milligram per liter.

PERSISTENT ORGANIC POLLUTANTS (POPs)—Organic chemicals that are persistent in the environment and in our bodies, usually in fatty tissues. These include polychlorinated biphenyls (PCBs) and organochlorines.

PHTHALATES—A group of hormone-mimicking chemicals used to render plastics soft and flexible and found in many household products as well as cosmetics.

PHYTOESTROGENS—Plant estrogens that mimic the estrogen hormones and are commonly found in whole grains, dried beans, peas, fruits, broccoli, cauliflower and soy products. (See genistein.)

PINEAL GLAND—A small endocrine gland in the midbrain that secretes many substances including the hormone melatonin, which is secreted only during darkness and appears to have anti-cancer properties.

POLYBROMINATED DIPHENYL ETHERS (PBDEs)—Flame retardants used in hundreds of consumer products including furniture, computers, televisions and automobiles.

POLYCHLORINATED BIPHENYLS (PCBs)—A group of highly toxic, synthetic chemical compounds once used as insulation fluid in electrical transformers, lubricating oil in pipelines, components of plastics and mixed with adhesives, paper, inks, paints and dyes.

POLYCYCLIC AROMATIC HYDROCARBONS (PAHs)—Byproducts of combustion, including high-temperature cooking of meats and fish, the burning of cigarettes and other tobacco products and the combustion of fuels such as diesel, gasoline and heating oil.

POLYVINYL CHLORIDE (PVC)—A type of plastic also referred to as vinyl, used in construction materials, packaging, medical products, appliances, cars, toys, credit cards and rainwear. It contains heavy metals such as lead and cadmium as well as phthalates, all of which can be ingested by children when vinyl toys are sucked or chewed.

POPULATION-BASED (ECOLOGIC) STUDY—A research study that investigates the incidence or mortality of a particular disease or other condition among members of the general population of cities, counties, states or countries. The individuals who participate in the study are usually selected by random digit dialing or some other randomized computer method, which avoids selection bias, such as individuals who want to participate in research but are not necessarily representative of a significant portion of the population. These studies do not take into account personal characteristics such as diet and other lifestyle factors or personal history including weight, reproductive history and family history of disease.

PROSPECTIVE STUDY/PROSPECTIVE COHORT STUDY—A long-term research study that enrolls participants and studies them before diseases or disorders develop. The Nurses Health Study at Harvard is one such study. A cohort is a distinct population group, such as daughters whose mothers took DES during pregnancy or women who had repeated fluoroscopy examinations for scoliosis during adolescence.

PROGESTIN—An artificial (synthetic) progesterone, added to estrogen in hormone replacement therapy (HRT) to reduce the risk of uterine cancer, and used to treat metastatic breast cancer.

PROGESTERONE-RECEPTOR—See Estrogen-Receptor entry.

RADIATION—Energy transmitted in the form of rays, waves or particles. There are two types of radiation: ionizing and non-ionizing. Ionizing radiation can strike genetic material and break off ions, thereby changing the way new cells are formed. Exposure to ionizing radiation occurs during medical procedures such as X-rays and other radiological diagnostic tests, during mining and processing of uranium or other radioactive ores, from nuclear weapons manufacture and testing, from nuclear accidents such as those at Chernobyl and Three Mile Island and from hazardous waste produced by nuclear power plants. Non-ionizing radiation is electromagnetic radiation, which includes electromagnetic fields from power lines and electric appliances, microwaves and radiofrequency radiation from cellular phones and transmission towers and antennas (explained in the section on non-ionizing radiation, p. 40). How non-ionizing radiation affects our health is not clearly understood but it is thought to be related to altered hormone function.

RELATIVE RISK—The risk of breast cancer (or other disease) in an individual who may have several risk factors such as family history, age and race, compared with the average risk in a diverse population regardless of risk factors.

SELECTION BIAS—Unless research study participants are randomly selected (see Population-Based Study entry), results of a study may be biased by who chooses or is chosen to participate as a research subject.

SYNERGY—The interaction of two or more elements or forces that results in an effect greater than the sum of the individual effects. This is a key concept in understanding why current regulation of hazardous chemicals does not take real-world exposures into account. Chemicals are often regulated as if people were exposed to them one at a time when, in fact, we face multiple chemical exposures every day in air, water and food, and at home and in the workplace.

TAMOXIFEN (Nolvadex)—A hormonal therapy used to treat estrogen- and progesterone-receptor-positive breast cancer and to reduce the risk of breast cancer in women at high risk of developing the disease.

XENOESTROGENS—Chemicals that mimic the action of the hormone estrogen but come from outside the body (xeno means foreign), such as organochlorine pesticides.

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430 Complete information on the POPs treaty, including current sign-on status, can be found on http://irptc.unep.ch/pops/default.html. The U.S. Senate has yet to vote on ratification.

431 In May 2004, Louisville, Kentucky hosted a meeting of groups and individuals whose common goal is to work together on chemical policies and campaigns to protect human health and the environment from harmful chemicals. Participants named the charter after this city, which is home to Rubbertown, the site of 11 industrial facilities responsible for one-third of all reported toxic releases in Kentucky. The surrounding community is 60 percent African American and has lived with this toxic legacy for nearly a century. www.louisvillecharter.org.

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