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2008

FIFTH EDITION

State of the Evidence

The Connection Between Breast Cancer and the Environment

Edited by Janet Gray, Ph.D.

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Dedication

This 2008 edition of *State of the Evidence: The Connection between Breast Cancer and the Environment* is dedicated to Nancy Evans, Breast Cancer Fund Health Science Consultant and longtime environmental health advocate. Nancy was the principal editor of the first four editions of this report and is an invaluable editorial team member of this publication.

We are all indebted to Nancy, a 17-year breast cancer survivor, for her brilliance and courage in articulating the personal and political ramifications of breast cancer through her editorial work, her writing and filmmaking, including the award-winning film, *Rachel's Daughters: Searching for the Causes of Breast Cancer*. In 2000, she was honored as a Breast Cancer Fund Hero with the Bella Abzug Advocacy Award.

Her dedication and commitment to environmental health and breast cancer advocacy — and the science that supports it — continue to guide all of us toward the vision of a world in which women do not live in fear of losing their lives or breasts to breast cancer. Nancy's sense of humor, passion and friendship inspire so many of us to continue this work. We are blessed to have her in our family.

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Executive Summary

Breast cancer strikes more women in the world than any other type of cancer except skin cancer. In the United States, a woman's lifetime risk of breast cancer has increased steadily and dramatically over the decades of the 20th century.[1,2] Between 1973 and 1998, breast cancer incidence rates in the United States increased by more than 40 percent.[3] Today, a woman's lifetime risk of breast cancer is one in eight.[4]

In the United States, a woman's lifetime risk of breast cancer increased steadily and dramatically over the decades of the 20th century.[1,2] Between 1973 and 1998, breast cancer incidence rates in the United States increased by more than 40 percent.[3] Today, a woman's lifetime risk of breast cancer is one in eight.[4]

The increasing incidence of breast cancer over the decades following World War II paralleled the proliferation of synthetic chemicals. An estimated 80,000 synthetic chemicals are used today in the United States; another 1,000 or more are added each year.[5] Complete toxicological screening data are available for just 7 percent of these chemicals.[6] Many of these chemicals persist in the environment,[7,8] accumulate in body fat and may remain in breast tissue for decades.[9] Many have never been tested for their effects on human health.

The most recent breast cancer incidence data (2003 - 2004)[10,11] indicate a significant decline in breast cancer incidence for women in the U.S., although this effect may be relevant only for women over the age of 50 with a particular sub-type (estrogen receptor postitive, or ER+) of the disease.[12,13,14] The most widely discussed explanation for this decrease is the sharp decline in use of post-menopausal hormone replacement therapy (HRT), especially following the 2002 discovery of HRT's association with increased risk for breast cancer.[15,16]

A recent survey conducted at the Massachusetts-based Silent Spring Institute indicated that 216 chemicals and radiation sources have been recognized by national and international regulatory agencies as being implicated in breast cancer causation.[17] Many other chemicals, especially those classified as endocrine-disrupting compounds (EDCs), are not listed by the regulatory agencies, the researchers said; yet the scientific evidence linking EDCs to breast cancer risk is substantial and growing.[18,19]

In *State of the Evidence 2008*, we examine the increasingly sophisticated and compelling data linking radiation and myriad chemicals in our environment to the current high rates of breast cancer. While we acknowledge the importance of commonly discussed risk factors for breast cancer — primary genetic mutations,[20] reproductive history[21] and

lifestyle factors such as weight gain,[22] alcohol consumption[23, 24] and lack of physical exercise[25] — we assert that these commonly discussed factors alone do not address a large portion of the risk for the disease.[26]

An important body of scientific evidence demonstrates that exposure to common chemicals and radiation may contribute to the staggering incidence of breast cancer. In our daily lives, we are rarely exposed to these substances in isolation; the pervasiveness of many of these substances means we likely have multiple, low-level exposures over the course of weeks, months, even years. There are several examples in recent scientific literature demonstrating that *mixtures* of environmental chemicals, chemicals and radiation, or complex combinations of chemicals and particular genetic or hormonal profiles may alter biological processes and possibly lead to increases in breast cancer risk. These new data show that we need to begin to think of breast cancer causation as a complex web of often interconnected factors, each exerting direct and interactive effects on cellular processes in mammary tissue.

When examining the effects of lifestyle factors, environmental chemicals and radiation on future breast cancer induction, scientists now know that the *timing, duration and pattern of exposure* are at least as important as the dose. A growing body of evidence from both human and animal models indicates that exposure of fetuses, young children and adolescents to radiation and environmental chemicals puts them at considerably higher risk for breast cancer in later life.[27, 28] Issues of timing reflect the fact that mammary cells are more susceptible to the carcinogenic effects of hormones, chemicals and radiation during early stages of development, from the prenatal period through puberty, adolescence, and on until the first full-term pregnancy.[29]

Summarizing findings of more than 400 epidemiological and experimental studies, *State of the Evidence 2008* demonstrates that a significant body of scientific evidence links exposures to radiation and synthetic chemicals to an increased risk of breast cancer. The report also addresses some of the ongoing methodological complexities in breast cancer research.

The Moving Forward section of the report was written for breast cancer prevention, women's health and environmental health and justice advocates as well as others interested in developing policy and research agendas at the state and federal levels that call for the identification and elimination of the environmental links to breast cancer.

This report builds on the data suggesting that recent declines in cancer incidence rates are associated with decreases in HRT use. At the same time, it recognizes that over the past 30 years there have been significant improvements in cleaning our environment of some contaminants associated with breast cancer risk. These new data offer real promise for the future that by decreasing exposures to carcinogens, such as exogenous estrogens, estrogen mimics and endocrine disruptors, we may continue to lower breast cancer levels — and actually prevent the devastating disease — in the future.

Hormones and Endocrine Disrupting Compounds Linked to Breast Cancer

There is broad agreement that exposure over time to natural **estrogens** in the body increases the risk of breast cancer. **Hormone replacement therapy (HRT)**[30] and hormones in **oral contraceptives (OC)**[31, 32] and some other pharmaceuticals also increase this risk. The National Toxicology Program now lists steroidal estrogens (the natural chemical forms of estrogen) as known human carcinogens.[33] 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. Other **endocrine disrupting compounds (EDCs)** may disrupt normal biological processes by disturbing not only the actions of the estrogens, but also those of other hormones including the androgens and thyroid hormone. All of these disruptions may increase the risk for breast cancer.

EDCs are present in many pesticides, fuels, plastics, detergents, industrial solvents, tobacco smoke, prescription drugs, food additives and personal care products.[34, 35] Chronic exposure to widespread and persistent xenoestrogens may help explain the increase in breast cancer in industrialized countries around the world.

Examples of EDCs that have been shown to affect the risk for breast cancer in humans, or the risk of mammary cancer in animals include:

- **Numerous pesticides**:
  - The banned, but still pervasive, insecticide **DDT**;
  - **Dieldrin** and **aldrin**, insecticides that are currently banned but were pervasive from the 1950s to 1980s, when exposure may have affected subsequent risk of breast cancer for exposed women;
  - The triazine herbicides, including **atrazine**, a chemical banned in Europe but widely applied in the U.S. on many major agricultural crops;
  - The banned but, until a decade ago, widely applied insecticide **heptachlor**;
- **Bisphenol A**: one of the most pervasive chemicals in modern life, used to make polycarbonate plastic, epoxy resins and dental sealants;
- **Polyaromatic hydrocarbons (PAHs)**: ubiquitous byproducts of combustion;
- **Tobacco smoke**: both active and passive exposures;
- **Dioxins**: byproducts of incineration, manufacturing processes and vehicle exhaust that have contaminated the food supply (including crops, meat and dairy products);
- **Alkylphenols**: industrial chemicals used in the production of detergents and other cleaning products;
- **Metals**: including copper, cobalt, nickel, lead, mercury, cadmium and chromium;
- **Phthalates**: chemicals used to make plastics more flexible, also found in some cosmetics;
- **Parabens**: anti-microbials found in some cosmetics and other personal care products;
- **Food additives**: recombinant bovine somatotropin (**rBST**) and **zeranol**, compounds administered to cattle and sheep to enhance growth.

Other Chemicals of Concern Linked to Breast Cancer

Not all chemicals exert their cancer-causing effects on mammary tissue through disruption of hormones. Some chemicals that are found widely in our environment exert carcinogenic effects by causing direct damage to mammary cell DNA, or by altering a cell's ability to respond to internal or environmental challenges that increase the probability of the development of cancer. Examples of some of these other chemicals of concern include:

- **Benzene**: high-volume petrochemical solvent inhaled from gasoline fumes, vehicle exhaust, tobacco smoke and industrial burning;
- **Other organic solvents**: including those used in the production of electronics, computer components, textiles, furniture and printing;
- **Polyvinyl chloride (PVC)**: used extensively for medical products, food packaging, appliances, toys, water pipes and many other products;
- **1,3-butadiene**: byproduct of petroleum refining and vehicle exhaust, also used in processing of synthetic rubber;

- **Ethylene oxide:** surgical instrument sterilizer, also found in some cosmetics;
- **Aromatic amines**: byproducts of manufacturing plastics, pesticides, dyes and polyurethane foams, as well as high-temperature grilling of foods.

Radiation Linked to Breast Cancer

Both ionizing (**X-rays and gamma radiation**) and non-ionizing radiation (especially **electromagnetic fields [EMF]**) have been implicated in an increased risk for breast cancer.

- **Ionizing radiation**: the longest-established environmental cause of human breast cancer. Radiation increases the risk of breast cancer, both by directly damaging DNA and by disrupting normal cellular and intra-cellular processes. Radiation may also enhance the ability of hormones or other chemicals to cause cancer.[36, 37]
- **Non-ionizing radiation** (EMF): including microwaves, radio waves, radar and artificial light. The mechanisms by which EMF can affect health are not completely understood. However, the most widely studied model is built on the finding that EMF exposure and increased light-at-night (LAN) lower the body's level of melatonin, a hormone secreted by the pineal gland during darkness.[38] Through complex interactions with estrogens and cell signaling pathways,[39] melatonin appears to have anti-cancer properties.[40]

New Research Included in *State of the Evidence 2008*

- In studies of both U.S.[41] and European[42] women with *BRCA1* or *BRCA2* mutations, groups of women with higher incidence of the disease were born in recent decades that parallel increasing exposures to a wide variety of synthetic chemicals shown to increase risk for breast cancer. These data confirm an earlier study reporting this cohort effect.[43]
- Several recent studies have confirmed the results first reported in 2001-02, that use of combined estrogen-progestin hormone replacement therapy (HRT) increases the risk of breast cancer in post-menopausal women. These cancers tend to have low proliferation rates (mitotic indices) and favorable prognostic outcomes.[44, 45, 46]
- Use of oral contraceptives (OC) within the past five years led to significant increases in breast cancer incidence in both Hispanic and non-Hispanic white groups. The effect was magnified for women of both groups when OC use had continued for more than 20 years. In agreement with earlier studies, and again for both Hispanic and non-Hispanic white women, significant increases in estrogen receptor negative (ER-) tumors were observed.[47]
- Scientists interested in the long-term health effects of exposure to the banned pesticide DDT looked at blood DDT levels in young women at the time they gave birth. These blood levels served as markers of DDT exposures during their youth. Researchers then followed the women for two decades after they had given birth, noting cases of non-invasive or invasive breast cancer before the women reached age 50, and deaths from breast cancer before age 50. Exposure to DDT during childhood and early adolescence was associated with a fivefold increase in risk of developing breast cancer before the age of 50.[48]
- Prenatal exposure to the pesticide atrazine delays development of the rat mammary gland in puberty, widening the window of sensitivity to breast carcinogens.[49] Similarly, exposure of rats late in pregnancy to a mixture of metabolites of atrazine also leads to persistent changes in mammary gland development in the pups that were exposed during gestation. These abnormalities in prenatally exposed rats persist into adulthood.[50]
- The insecticide heptachlor has been implicated in increased risk for breast cancer. Recent

studies of body burdens of its major metabolite, heptachlor epoxide (HE), show that high levels of HE in breast milk[51] and fat tissue from breast biopsies[52] are associated with increased incidence of breast cancer.

- An overview of the scientific literature has confirmed that exposure to environmental tobacco smoke increases breast cancer risk in pre-menopausal women.[53]
- Several studies of both rat and mouse models have demonstrated that even brief exposures to environmentally-relevant doses of bisphenol A (BPA), either prenatally or around the time of birth, lead to changes in mammary tissue structure predictive of later development of tumors. Exposure also increased sensitivity to estrogen at puberty.[54, 55, 56, 57]
- Early prenatal exposure to BPA leads to abnormalities in mammary tissue development that are observable during gestation.[58] Prenatal exposure of rats to BPA also increased the number of pre-tumorous changes in mammary tissue, and an increased number of mammary tumors following adulthood exposures to a sub-threshold dose (lower than that needed to induce tumors) of a known carcinogen.[59]
- Prenatal exposure to the dioxin TCDD alters subsequent mammary gland development in ways that predispose rats to develop mammary cancers as adults.[60]
- Higher accumulations of iron, nickel, chromium, zinc, cadmium, mercury and lead have been found in cancerous breast biopsies as well as in serum samples of women diagnosed with cancer as compared with healthy women.[61, 62]
- A recent laboratory rat study demonstrated that application of octyl-methoxycinnamate (OMC) to the skin enhances the penetration of the endocrine-disrupting herbicide 2,4-D.[63] OMC is a chemical commonly found in sunscreen lotions.
- A case-control study of 128 female 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.[64]
- Recent studies examining occupational exposures to benzene among enlisted women in the U.S. Army[65] and women in different professions in Israel[66] show significant increases in breast cancer rates among women with the highest benzene exposures.
- Benzene administration to laboratory mice induces mammary tumors. These animals have more mutations of genes that are responsible for suppressing the development of tumors.[67]
- A recent questionnaire study found an association between higher lifetime consumption of grilled meats and fish and increased incidence of post-menopausal breast cancer.[68] Heterocyclic aromatic amines (HAAs) are formed, along with polycyclic aromatic hydrocarbons (PAHs), when meats or fish are grilled or otherwise cooked at high temperatures.
- Studies of both breast milk and cells from the ducts of women's breasts revealed the presence of DNA adducts in association with HAAs.[69, 70] These DNA adducts are indicators of problems in DNA repair in cells, one of the early hallmarks of tumor development.
- Laboratory studies of HAAs in systems using cultured human breast cancer cells demonstrate that these chemicals can mimic estrogen, and can also have direct effects on cell division processes in ways that can enhance the development of tumors.[71]
- Increases in breast cancer have been observed in women living in areas surrounding the

Chernobyl nuclear power plant in the former Soviet Union, which exploded in 1986 and caused massive radiation contamination. The most devastating effects have been found in women who were younger at the time of the accident.[72]

- Recent genetic data indicate that women with some gene mutations that may make them more likely to develop breast cancer (e.g., *ATM*, *TP53* and *BRCA1/2*) may be especially susceptible to the cancer-inducing effects of ionizing radiation exposure.[73, 74]
- Girls and adolescents treated with radiation for non-Hodgkin's lymphoma[75] or for acne[76] had an increase in rates of breast cancer several decades later.
- A recent study of female radiology technologists who had sustained daily exposures to ionizing radiation demonstrated an increased risk of breast cancer. The findings hold for those women who began working during their teens or, independent of age, worked in the field earlier than the 1940s, when exposure levels were substantially higher than they have been in more recent decades.[77, 78]
- Post-menopausal women whose earlier breast cancers were treated with radiation therapy have increased risks of radiation-induced secondary cancers of the breast.[79, 80]
- A recent population-based case-control study in the United States looked at breast cancer risk in women who were exposed on the job to low, medium or high levels of EMF in their respective work environments. Small but significant increases in breast cancer incidence were found.[81]
- A major case-control study from Poland found an increased risk for breast cancer in women working in white-collar jobs, such as marketing, advertising, management, engineering, social science and economics. Increased risk was also found in blue collar workers, such as machine operators in a variety of settings. No single chemical or other exposure can be linked to the occupations with excess risk, leading the authors to conclude that possible associations of these occupations with EMF deserve further attention.[82]
- *The BioInitiative Report*, a new analysis of science on the health effects of EMF exposure, summarizes the evidence on breast cancer and other cancers as well as neurodegenerative diseases. This groundbreaking document is based on a review of more than 2,000 studies and calls for strengthening safety standards to avoid future cancers and other diseases and disorders in adults and children.

Moving Forward: Breast Cancer Fund's Policy and Research Recommendations

Together, we must move forward to identify and eliminate the environmental causes of breast cancer. The Moving Forward section provides a call to action for advocates and policy makers. It offers a menu of different ways, from crafting state and federal policy to research initiatives, that supporters can be active in breast cancer prevention. The evidence is clear and growing. There are actions we can take today to reduce the public's exposures to toxic chemicals and radiation.

Framework of This Report

Introduction

Goals of the Report

A major goal of *State of the Evidence 2008* is to examine the increasingly sophisticated and compelling data linking radiation and various chemicals in our environment to the current high rates of breast cancer incidence. We acknowledge the importance of many widely understood risk factors for breast cancer, including primary genetic mutations,[83] reproductive history[84] and lifestyle factors such as weight gain,[85] alcohol consumption[86, 87] and lack of physical exercise.[88] Yet we begin with an understanding that these factors alone still do not address a considerable portion of the risk for breast cancer.[89] A substantial body of scientific evidence indicates that exposures to common chemicals and radiation, alone and in combination, may contribute to the unacceptably high incidence of breast cancer.

A second goal of this report is to outline how the growing scientific data connecting certain environmental chemicals and radiation to breast cancer incidence can inform and direct new research and public policy to reduce environmental exposures. We hope to inspire advocates, educators, legislators, scientists and citizens to work together to decrease our exposures to environmental toxins and thereby lower the incidence of breast cancer in the future.

What We Mean by "Environment"

We recognize that the term "environment" encompasses all external factors that can affect health, including 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 focus on people's exposures to environmental agents such as pesticides, dioxin, secondhand tobacco smoke, plasticizers and other chemicals, as well as many forms of radiation. So, for example, we will not discuss the often complicated and inconclusive literature examining possible relationships between diet, stress or obesity and risk for breast cancer.[90] But we will consider the reality of pesticides, herbicides, hormones and chemicals leaching from packaging materials into foods, thereby enhancing the total exposures of people to synthetic chemical compounds that have been implicated in increased risk for breast cancer.

Although we may have some control over our personal use of many of these chemicals, exposures to some of these chemicals are involuntary.[91] On a daily basis, we are all exposed to agents in air, food, water, soil, medications, common household products, personal care products and the workplace. Learning more about the scientific evidence will direct the public — as individual consumers and as members of communities — to push for targeted new research and policy change at the local, state and federal levels.

In bringing this broad focus to environmental causes of breast cancer, we expect that we will not only lower the future incidence of breast cancer for our children and grandchildren, but we will also be joining in the collective effort to turn the tables on a number of other diseases. Unfortunately, the environmental exposures discussed in this report are not only implicated in the rising incidence of breast cancer, but also in a number of other cancers and asthma, as well as several reproductive, neurodegenerative and learning disorders.[92, 93, 94, 95, 96]

Background

Breast Cancer Statistics

Breast cancer now strikes more women in the world than any other type of cancer except skin cancer. In the United States, a woman's lifetime risk of breast cancer increased steadily and dramatically from the 1930s, when the first reliable cancer incidence records (starting in the state of Connecticut) were established, through the end of the 20th century.[97, 98] Between 1973 and 1998, breast cancer incidence in the United States increased by more than 40 percent.[99] Today, a woman's lifetime risk of breast cancer is one in eight.[100]

Women who move from countries with low breast cancer rates to industrialized countries soon acquire the higher risk of their new country.

The most recent incidence data (2003, 2004)[101,102] indicate a significant decline in breast cancer incidence for women in the U.S., although this effect may be relevant only for women over the age of 50 with a particular sub-type (estrogen receptor positive or ER+) of the disease.[103, 104, 105] The most widely discussed explanation for this decrease is the sharp drop in use of post-menopausal hormone replacement therapy (HRT) over the past few years. The decline in use of HRT was especially notable following the 2002 announcement linking HRT with increased risk for breast cancer.[106, 107]

The incidence of breast cancer varies considerably by a number of factors, including age and ethnicity. In the U.S. between 2000 and 2004, white[108] women had the highest overall annual incidence rate for the disease (132.5 cases per 100, 000 women), followed by African American (118.3 per 100,000), Hispanic (89.3 per 100,000), Asian American/Pacific Islander (89.0 per 100,000) and American Indian/Alaska Native (69.8 per 100,000) women. Yet these data have a number of distinct patterns. The great majority of women diagnosed with breast cancer are 45 years of age or older, and a higher rate of the disease is found for white women as compared to African American women for all ages older than 45. Nevertheless, there is a higher incidence rate for African American than white women for ages 35 years and younger. [109] Most importantly, younger women in general, and younger African American women in particular, present with forms of the disease that are more aggressive and more difficult to treat effectively.[110, 111]

Looking at national mortality data and aggregating across all possibly affected organs, cancer is the leading cause of death for U.S. women between the ages of 40 and 79, and the second most prevalent cause of death for all other ages. Cancer of the breast results in the highest mortality rates of any cancers in women between the ages of 20 and 59 years. Although rates of mortality from breast cancer remain high for older women, the elderly are more likely to succumb to lung cancer than breast cancer.[112, 113]

Globally, more than 1.15 million women were diagnosed with breast cancer in 2002.[114,115] The highest rates are found in the industrialized nations of North America and western Europe, while lower rates are generally found in western Asia, southern Africa and South America, although even in these areas cancer of the breast is the most commonly diagnosed cancer in women.[116] In northern Africa, as in many countries that are either developing or in transition, breast cancer rates are escalating sharply.[117,118,119] While some of the changes in rates may be associated with improved ability to detect the disease along with changes in lifestyle and reproductive histories, migration studies suggest that much of the variability in international incidence rates might be environmentally related.

Migration Studies

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 immigrate 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.[137, 138] A generation later, the risk for their daughters approaches that of U.S.-born women. Hispanic women born in the U.S. have a significantly higher rate of breast cancer than do immigrant Hispanic women. The longer those Hispanic women spend in the U.S., the greater their risk for breast cancer. This is especially true for women who immigrated before the age of 20.[139]

Similarly, a Swedish study of people with many different cancers showed that age at immigration 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."[140]

Immigration to industrialized countries may alter many factors. 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, or a combination of these factors. Emigration may also affect reproductive behavior, such as the use of oral contraceptives[141] or when and if a woman decides to have children. Moving to a more industrialized society may also increase exposure to chemicals in pollution, consumer products like cosmetics and cleaning products, and solvents used in industry that have been implicated in increased risk of breast cancer, for example.

A growing body of evidence from both human and animal models (see page 21) indicates that exposure of fetuses, young children and adolescents to radiation and environmental chemicals puts them at considerably higher risk for later-life breast cancer diagnosis.[142] These data are consistent with the role of environmental exposures, especially at

Breast Cancer Rates Are Falling?

Recent data indicate a significant decrease in breast cancer incidence in the United States. These data are cause for excitement, the first indications in decades that the sum of factors leading to the development of breast cancer may be receding. Most notably, several reports in the recent scientific literature have associated these decreases in (ER+, post-menopausal) breast cancer rates to very recent decreases in use of post-menopausal hormone replacement therapy (HRT).

There could be other factors contributing to this decline. It has been three decades since many pesticides, including DDT, have been banned. Although we all carry remnants of DDT's earlier large-scale usage, concentrated exposures during critical periods of breast development are much lower than they were for young girls several decades ago.

Similarly, federal and state regulations have succeeded in removing from common use several other chemicals that have been implicated in the rising risk for breast cancer. For example, our air is generally cleaner than it was 35 years ago, reducing exposure to PAHs and other air pollutants linked to breast cancer. And smoking restrictions in workplaces and public spaces have greatly reduced our exposures to secondhand smoke, a factor that is especially important for young children and adolescents.

As always, patterns of disease incidence, including breast cancer, need to be watched for the short term and the longer term. Still, declines in breast cancer rates provide real promise for the future that by decreasing exposures to exogenous estrogens, estrogen mimics, endocrine disruptors and other carcinogens, we may continue to lower the levels of breast cancer and eventually prevent the disease in the future.

young ages, in affecting the later incidence of breast cancer in women who have immigrated to relatively industrialized areas from regions of the world with lower risks of breast cancer.

Gene-Environment Interactions

Another indicator that environmental changes over the past several decades may be influencing breast cancer risk comes from studies looking at incidence rates in women with primary genetic mutations related to the disease. Inherited mutations of the two "breast cancer genes," *BRCA1* and *BRCA2*, have received much attention recently though they may account for a relatively small fraction — no more than 10 percent — of the current breast cancer diagnoses.[143] These mutations do greatly increase the risk for breast cancer, especially among members of families already devastated by having several relatives also diagnosed with either breast or ovarian cancers. However, having a mutation in either of these primary genes associated with breast cancer does not necessarily mean that a woman will develop the disease.

Women with an inherited mutation on the *BRCA1* or *BRCA2* genes have a 60 to 82 percent probability of being diagnosed with breast cancer in their lifetimes.[144] This suggests that the likelihood of developing breast cancer is influenced by something beyond the identified mutations, or the lifestyle and environmental factors that are often shared by members of the same family. In other words, differences in personal and environmental exposures probably contribute significantly to whether the *BRCA1* or *BRCA2* mutations are associated with a diagnosis of breast cancer.

In studies of both U.S.[145, 146] and European[147] women with *BRCA1* or *BRCA2* mutations, those who demonstrated higher incidence of the disease were born in recent decades that parallel increasing exposures to a wide variety of synthetic chemicals implicated in increased risk for the disease. For example, women who are *BRCA1* carriers who were born after 1940 have nearly twice as much breast cancer by ages 40 and 50 as those born earlier.[148] Thus these younger women were more likely than their older relatives to have been exposed to radiation or chemicals during the sensitive periods of their early development.

In other studies, scientists have explored the relative contributions of genetic and environmental factors by examining likelihood of disease in twins. In the largest study of twins ever conducted, they found that among twins in which at least one woman developed breast cancer, environmental exposures unique to that woman made the most significant contribution to the development of the cancer. Inherited genes contributed 27 percent, shared environmental factors 6 to 9 percent, and non-shared environmental factors 60 to 67 percent of the risk.[149] These data indicate that 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.[150, 151]

Most recently, scientists have worked to understand contributions that a wide variety of genes might make to alter breast cancer risk and have identified several candidate genes in the past few months.[152, 153, 154, 155] How these genetic profiles might interact with one another, or with reproductive, lifestyle or environmental factors in increasing breast cancer risk, remains to be examined.

Chemicals in our Environment and in our Bodies

As suggested above, the rising incidence of breast cancer in the decades following World War II paralleled the proliferation of synthetic chemicals. An estimated 80,000 synthetic chemicals are used today in the United States, another 1,000 or more are added each year.[156] Yet, complete toxicological screening data are available for just 7 percent of these chemicals and more than 90 percent have never been tested for their effects on human health.[157]

A recent survey of these substances indicated that 216 chemicals and radiation sources have been registered by international and national regulatory agencies as being experimentally implicated in breast cancer causation.[158, 159] Many of these chemicals persist in the environment,[160, 161] accumulate in body fat and may remain in breast tissue for decades.[162] (See Appendix 1 for a listing of chemicals that have been registered by the International Agency for Research on Cancer [IARC] as carcinogens, and that have also received ratings by regulatory agencies regarding induction of human breast and animal mammary tumors. The equivalent of breast tissue in non-human animals is called mammary tissue.)

Studies by the U.S. Centers for Disease Control and Prevention of chemical body burdens show that all Americans carry many contaminants in their bodies, and that women have higher levels of many of these chemicals than do men.[163] Some of these contaminants, including chemicals used in common fuels, solvents and industrial processes, have been linked to mammary tumors in animals.[164, 165]

Many of these chemicals recently have been shown to be detectable in young girls (age 6 to 8 years) living in New York, Ohio and California.[166] In biological samples from pregnant women and mothers who have recently given birth, some of these chemicals are found in maternal blood, placental tissue and breast milk, indicating that maternal burdens of environmental contaminants are being passed on to their young during pregnancy and breastfeeding.[167, 168, 169, 170] This is of great concern, given increasing evidence that chemical exposures during prenatal through adolescent periods have profound lifelong impacts on breast tissue development and possible susceptibility to cancer later in life.

Breast Cancer Incidence and Mortality by Race and Ethnicity

Racial disparities in health cannot be explained solely by poverty status, access to health care or environmental factors. Their complex etiology is dependent on interactions between all these factors plus genetics.[120]

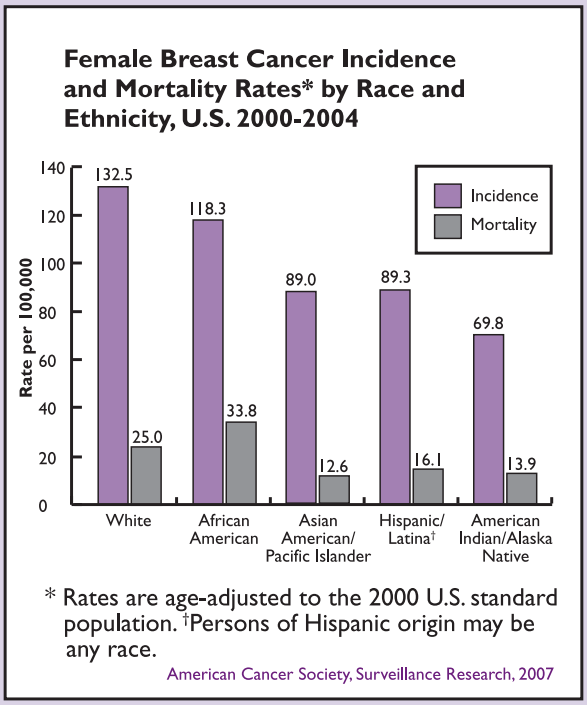
Breast cancer incidence and mortality rates vary widely among racial/ethnic groups, among various age groups and among the populations of counties, states and countries. Globally, incidence is highest among white women of European descent who live in industrialized countries. Still, a global view is like an aerial photograph: it doesn't show the details of what's happening on the ground — in communities, and in individuals.

Although diversity is increasing in the U.S., medical and scientific research on diverse populations has not kept pace. Much of current breast cancer diagnosis and treatment is based on research in white women. Breast cancer among women of color is only beginning to be addressed. Even so, evidence shows genetic variations affect susceptibility to environmental exposures as well as the characteristics of the tumors themselves. It is also clear that breast cancer is more aggressive in some racial/ethnic groups than in others.

Incidence

White (non-Hispanic) women of all ages have the highest incidence of breast cancer of any racial/ethnic group in the United States. American Indian/Alaska Natives have the lowest incidence of the disease.[121] Latinas have a much lower incidence of breast cancer than either black or white women, but the figure is rising.

Black women younger than age 35 have a higher incidence of breast cancer than their white



American Cancer Society. *Breast Cancer Facts and Figures 2007-2008*. Atlanta: American Cancer Society, Inc.

counterparts, and a less favorable prognosis. They have more aggressive tumors: typically estrogen-receptor negative, progesterone-receptor negative, HER2 negative and basal-type tumors, sometimes referred to as "triple-negative" tumors. Triple-negative tumors do not respond to hormonal therapies such as tamoxifen.[122, 123] In addition, young black women present with more advanced breast cancer at diagnosis, including larger tumors and more lymph node involvement.[124]

Throughout the 1990s, the incidence of inflammatory breast cancer (IBC), a rare type that primarily affects pre-menopausal women, increased in both black women and white women.[125] However, the incidence of IBC is higher among black women. Because IBC does not cause a lump in the breast, it may be misdiagnosed as an infection, leading to delays in treatment.

And research suggests that breast cancer risk factors are different for black women and white women. Early age at first birth and having four or more children before age 45 appears to increase the risk of breast cancer in black women, while in white women early childbearing reduces breast cancer risk.[126] Use of oral contraceptives may increase the risk of breast cancer in black women, apparently by raising levels of insulin-like growth factor-1 (IGF-1), which is associated with increased risk of breast cancer. On the other hand, oral contraceptive use suppresses levels of IGF-1 in white women.[127]

Mortality

Black women have the highest breast cancer mortality rate of any racial/ethnic group. Asian Americans, particularly Japanese Americans and Chinese Americans, have the best survival rates.[128] The reasons for these disparities are not clearly understood. However, socioeconomic factors undoubtedly play a role in both environmental exposures and access to care. According to CDC scientists, blacks have higher body burden levels than whites or Mexican Americans of some chemicals, 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.[129] Biomonitoring can provide important information about differences in exposures that must be considered in investigating the causes of breast cancer.

Breast cancer is the leading cause of cancer death in Latinas in the U.S. Like young black women, Latinas are also disproportionately affected by aggressive triple-negative tumors.[130] Environmental exposures may be contributing to the rising rates, particularly among farm workers.[131] Research also shows that hormone therapy may pose a greater risk of breast cancer in post-menopausal Latinas than in their white counterparts.[132]

American Indian/Alaska Native (AI/AN) women have the lowest incidence of breast cancer and

one of the lowest mortality rates. However, the American Cancer Society urges caution in interpreting these statistics, stating: "Cancer incidence rates among the American Indian population have been monitored more systematically in the Southwest than in other geographic regions and may not reflect the cancer experience of American Indians or Alaska Natives residing elsewhere." [133] The National Cancer Institute's SEER (Surveillance Epidemiology and End Results) data for AI/AN populations predominantly reflect the cancer rates for those living on reservations covered by the New Mexico registry and in urban areas in California. Therefore, it is possible that many cases of breast cancer may go unreported, particularly among women living in rural reservations with limited access to health care.

Research Implications

Research on breast cancer in racial/ethnic populations needs to recognize that genetic, cultural and historical diversity exists within those populations. For example, African Americans comprise a heterogeneous group, based on the region of Africa from which their ancestors came.[134] Hispanic/Latino Americans include people from Cuba, Mexico, Puerto Rico, Central and South America, Dominican Republic and other countries. Asian/Pacific Islander Americans include many nationalities—Chinese, Filipinos, Koreans, Hawaiians, Indians, Japanese, Samoans, Vietnamese and others. The American Indian/Alaska Native population represents more than 500 diverse tribes with different cultures, socio-demographic factors and languages.[135]

Reporting cancer statistics according to broad racial and ethnic groupings may mask wide variations for specific groups within those broad categories. For example, a study of Asian American women in Los Angeles found that breast cancer risk among women of Japanese and Filipino ancestry is twice that of Chinese and Korean women. Asian women, who have relatively low breast cancer rates in their native countries, experience increasing breast cancer incidence after immigrating to the U.S.[136]

A more detailed understanding of breast cancer among women of color is urgently needed. Research needs to move beyond examining patterns of mammography screening among various ethnic groups. Future research should include occupational studies and biomonitoring to determine exposures, as well as analyses to determine tumor characteristics within various racial/ethnic groups.

Main Themes: Mixtures and Timing of Exposures Matter

In examining the complex and sometimes controversial evidence related to environmental risks and breast cancer, two themes recur. The first theme is that mixtures matter. In real life, we are not exposed to single chemicals absent our biological or social histories. The effort to study and understand these interactions is extremely difficult, and yet growing evidence supports the need for this level of examination of the multiple factors that may increase risk for breast cancer.[171] The second recurring theme is that timing of exposure matters. Growing scientific evidence from human epidemiological studies and animal-based toxicological studies indicates that exposures to environmental chemicals and radiation during early development may predispose a woman to higher risk of breast cancer.

Mixtures Matter

It is very difficult to design and conduct reliable, long-term studies examining the possible effect of individual chemicals on risk for a disease as complex as breast cancer. The time between exposures and development of the disease may be several decades; women may not know to what chemicals they have been exposed; and women are not exposed to chemicals in isolation. Scientists increasingly recognize that to understand the risks underlying a particular disease, they need to focus on the "lived experiences of local populations"[172] or individuals at risk. In reality this is a very difficult task. For that reason, human epidemiological studies are complemented by animal toxicology studies, allowing for greater control and ease of manipulation of environmental chemicals, hormones, gene mutations and other factors — alone and in combination — to study possible later development of mammary tumors.

Women are not exposed to chemicals in isolation.

Many of the environmental chemicals that are thought to be important in increasing breast cancer risk interfere with numerous biological processes, including those ordinarily regulated by one of the female hormones, estradiol. For that reason, scientists often refer to these chemicals as having estrogenic properties or as being endocrine (or hormone) disruptors, depending on how they alter biological systems.

Numerous animal studies indicate that the kinds of mixtures to which an animal (including, presumably, a woman) is exposed matter in determining ultimate risk.[173] Unfortunately, though, only a few combinations and doses of chemicals have been tested. This is perhaps not surprising: Koppe and colleagues have calculated that it would require 166 million experiments to test all combinations of three out of the 1,000 (of about 80,000) most common synthetic chemicals currently in use.[174] While only a few of those studies have been conducted, several of them indicate either additive (to illustrate, 2 + 3 = 5) or synergistic (2 + 3 = 9) effects of mixtures of low levels of chemicals in a number of systems that are relevant to exploring risk for breast cancer.

To further complicate things, each chemical alone may have different effects depending on the concentration and timing of exposures. Nevertheless, there are several examples in the recent scientific literature demonstrating that mixtures of environmental chemicals, chemicals and radiation, or complex combinations of chemicals and particular genetic or hormonal profiles may alter biological processes and possibly lead to increases in breast cancer risk.

For example, in a variety of different types of experimental systems, two different weak estrogenic pesticides — dieldrin and toxophene — showed either additive[175] or synergistic[176] effects,

depending on the doses used and the particular conditions of the experiments. Similarly, combinations of very low doses of common chemical surfactants (used to solubilize or disperse other chemicals) and herbicides led to highly synergistic effects in a natural wildlife fish model that, like human breast tissue, is sensitive to estradiol and related estrogenic compounds.[177] Another study examined the effects of four very different types of environmental chemicals: a pesticide residue (*o,p*'-DDT), a plant estrogen (genestein, found in soy), and two alkylphenol surfactants (sudsing agents and chemical dispersers; 4-*n*-octylphenol and 4-nonylphenol). Clear additive effects across the four chemicals were observed.[178]

Another study that looked at the combined effects of 11 different environmental contaminants — all added at levels so low that they did not have any effects by themselves — showed that the various chemicals had additive effects with each other and also with naturally occurring estradiol.[179] Similarly, at levels found in the environment, the ubiquitous plasticizer bisphenol A significantly increased the effects of estradiol.[180] These results show that even at low concentrations, environmental chemicals may exacerbate some of the biological effects of natural estrogens.

Even at low concentrations, environmental chemicals may exacerbate some of the biological effects of natural estrogens.

Together these toxicology studies suggest that many of the chemicals of concern may mimic or functionally increase the action of natural estrogens. We know that excess exposure to estradiol and its related compounds explains how many commonly discussed risk factors such as reproductive history (age at first menstruation, number of children, age at menopause, contraceptive and hormone replacement history, etc.), diet and alcohol consumption might all be related to risk for breast cancer.[181]

In studies of mammary tissue development, mixtures of chemicals commonly found in the environment made rat mammary tissue more susceptible to dietary estrogens after birth. This led to profound tissue abnormalities that, in other studies,[182] have been associated with mammary tumors. Similarly, pretreatment of young rats with a low dose of radiation led to increased malignancy and numbers of mammary tumors after subsequent exposure to a known chemical carcinogen.[183]

Recent large clinical studies of women with breast cancer have explored the effects of exposures to environmental chemicals and radiation in combination with other factors. The data from these studies illustrate how complex the interactions among breast cancer risk factors may be. The data also help clarify why large epidemiological studies examining the effects of different chemicals on breast cancer risk in women may have contradictory results.

For example, in a study examining the possible link between organochlorine pesticide residues and breast cancer among African American and white women in North Carolina, higher blood (plasma) levels of the chemicals did not correspond to a diagnosis of breast cancer. But the data did suggest that risk factors such as race/ethnicity, body mass, reproductive history and social factors might make some women more susceptible to the carcinogenic effects of the organochlorine pesticides.[184]

A number of other studies are beginning to suggest that specific combinations of genes may make some women more vulnerable to certain environmental carcinogens. This supports the conclusion that for many women, genetic and other commonly discussed factors may interact with environmental carcinogens in causing a large number of breast cancer cases. These differences do not only occur in primary breast cancer genes

Rather than looking for single, direct causes underlying the disease, we will be better served to recognize the multiple and perhaps often interacting factors that may influence risk.

like *BRCA1* or *BRCA2*. That is, they are not indicated in heritable transmission of the disorder from generation to generation in the way that the *BRCA* gene mutations are. Nevertheless, these mutations may make a woman more susceptible to the effects of environmental carcinogens.[185, 186, 187]

Taken together, these complex studies make clear that breast cancer causation is not simple to understand. Indeed, rather than looking for single, direct causes underlying the disease, we will be better served to recognize the multiple and perhaps often interacting factors that may influence risk. It is time to go beyond looking for simple linear cause-effect relationships between risk factors and breast cancer, or even trying to think of a pie chart that we can slice up into proportions of risks accounted for by different types of factors. We instead need to begin to think of breast cancer causation as a complex web of often interconnected factors, each exerting both direct and interactive effects on cellular and extra-cellular processes in mammary tissue.

Timing of Exposures Matters

Two decades of research on laboratory animals, wildlife and isolated cell systems have shown the inadequacy of the long-held belief that "the dose makes the poison." In fact, lower exposures to chemicals sometimes may have more profound effects than higher ones, and that makes research into environmental risks and disease even more challenging.[188]

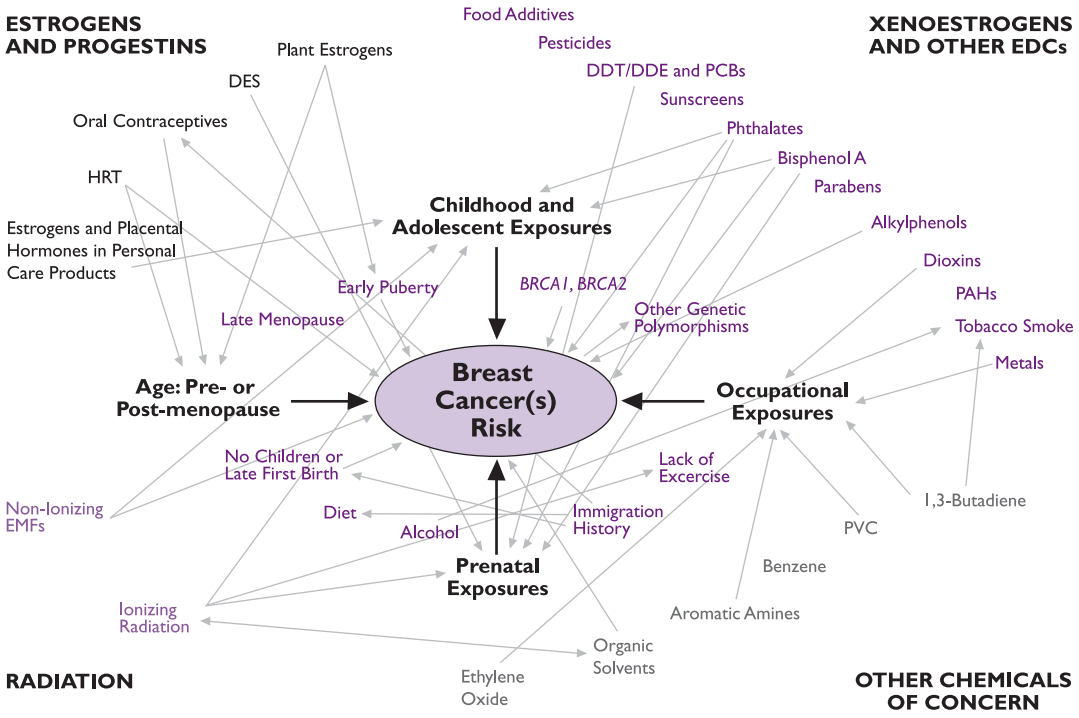
Nevertheless, when examining the effects of lifestyle factors, environmental chemicals and radiation on future breast (mammary) cancer induction, scientists now know that the timing, duration and pattern of exposure are at least as important as the dose. A substantial body of data from the scientific literature using animal models supports this conclusion.[189] Issues of timing reflect the fact that mammary cells are more susceptible to the carcinogenic effects of hormones, chemicals and radiation during early stages of development, from the prenatal period through puberty and adolescence, and on until the first full-term pregnancy.[190]

Prenatal Exposures

The tragic legacy of diethylstilbestrol (DES), a synthetic estrogen prescribed to prevent miscarriage, shows that cancer can have its earliest beginnings in the womb.[191] An estimated 5 to 10 million American women took DES between 1938 and 1971,[192] not knowing that the result would be structural abnormalities in their daughters' reproductive tracts leading to later infertility and increased vaginal and cervical cancer rates.[193] Evidence over the past decades indicates that for both the mothers[194, 195] who took the drug, and for their daughters who were exposed prenatally,[196] exposure to DES is also associated with an increased risk for breast cancer.

It is relatively difficult to look back on medical records and determine what drugs a mother might have taken during pregnancy, and therefore to what pharmaceutical agents her daughter might have been exposed during her prenatal development. But such clearly recorded information does not exist regarding the multiple exposures of the real world. It is exceedingly difficult to separate fetal exposures to environmental chemicals and radiation from sustained exposures over a lifetime. Rarely are environmental exposures so limited in time as prenatally, and if they are, there are huge problems remembering and recording them 30 to 60 years later, when breast cancer is diagnosed. This makes

Complexity of Breast Cancer Causation



Arrows indicate just some of the many links among risk factors, exposures and breast cancer.

studying their effects on breast cancer risk almost impossible, at least with traditional epidemiological tools for assessing exposures, such as questionnaires and use of existing records.

Recent data do indicate that changes in the fetal environment, resulting in increased exposure to estrogens or estrogen-mimicking chemicals, lead to higher incidence of breast cancer in adulthood. These studies look at indirect markers of fetal estrogen exposure, mainly birth weight of infants. Higher birth weight is associated both with increased maternal estrogens during pregnancy and risk of breast cancer, especially pre-menopausal cancer, in later life.[197]

Interestingly, severe maternal famine during pregnancy — especially during the first trimester — also leads to a several-fold increase in breast cancer rates in daughters.[198] Although the mechanisms underlying this effect are not understood, the results support the notion that prenatal events can have profound effects on subsequent risk for breast cancer.

There is at least one study that has more directly examined the effects of environmental contaminants at around the time of birth and later development of breast cancer in women. Polycyclic aromatic hydrocarbons (PAHs) are products of incineration found in air pollution, vehicle exhaust (particularly diesel), tobacco, smoke and grilled foods. They have been shown to be carcinogenic and to increase risk for breast cancer by altering estrogen-mediated cell systems.[199] A recent study in western New York examined air-monitoring records from 1959 to 1997 to establish PAH levels

In utero exposure to environmental estrogens may predispose the developing fetus to mammary gland carcinogenesis in adulthood.

in residential areas. This case-control study of 3,200 women (ages 35 to 79 years) showed that exposures to high levels of PAHs at the time of their birth were associated with an increased risk of post-menopausal breast cancer decades later.[200]

Data from animal studies support the notion that prenatal exposures to environmental chemicals can increase the later risk for breast cancer. Bisphenol A (BPA) is a chemical found widely in food packaging and containers. It has recently been shown that 95 percent of people tested had measurable levels of BPA in their urine, demonstrating how ubiquitous the chemical is and how prevalent it is within our bodies.[201] Fetal exposure of mice to low-dose BPA changed the timing of DNA synthesis in the epithelium (cells lining the ducts of the mammary tissue) and in the stroma (connective tissue) of their mammary glands, increased the number and extension 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.[202, 203] These results suggest that alterations in mammary gland structure that are observed in puberty and adulthood in perinatally exposed animals have their origins in fetal development. These data are particularly important because of the very low doses of BPA that resulted in abnormal mammary gland development, and because the effects were found in the absence of co-treatment of the experimental animals with any other cancer promoter. 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."[204]

Most importantly, prenatal exposures of mice to bisphenol A led to preneoplastic (intraductal hyperplasias) and neoplastic (carcinoma in situ) lesions in mammary glands that were visible at the onset of puberty.[205] Following brief post-pubertal exposure to a known carcinogen, adult animals that also had been exposed prenatally to low doses of bisphenol A developed more precancerous and cancerous abnormalities in their mammary tissues.[206] Similarly, laboratory studies have shown that prenatal exposures to either the dioxin TCDD[207, 208, 209] or a breakdown product of the commonly used herbicide atrazine[210] alter subsequent mammary gland development in ways that predispose rats to develop mammary cancers as adults. These studies demonstrate a common critical window of prenatal exposure for these persistent effects in the adult mammary gland.

Together these data demonstrate that in both women and in relevant rodent models, exposure during gestation can lead to aberrations in development of breast/mammary tissues in ways that greatly increase the risk for developing breast/mammary cancer later in life.

Childhood and Adolescent Exposures

Again, it is difficult to identify environmental chemicals to which women were exposed during childhood and adolescence, although we know better those to which women were exposed later (or earlier) in life. However, a very recent study shows that exposure to the now banned, but once widely used, pesticide DDT during childhood or early adolescence led to a fivefold increase in breast cancer risk before age 50.[212]

There are also numerous studies demonstrating that exposure to the carcinogenic effects of ionizing radiation,[213, 214] and possibly alcohol consumption, diet and lack of physical exercise during childhood and adolescence could play a role in later-life breast cancer. The few studies examining exposures to environmental chemicals in animal models (mice or rats) are inconclusive, and peri-pubertal

(equivalent to human puberty and adolescence) effects of most chemicals have not been studied.[215]

The connection between childhood or adolescent exposures to radiation and breast cancer is clearer. In women, links between radiation exposure and breast cancer have been confirmed in atomic bomb survivors.[216, 217, 218] Rates of breast cancer were highest among women who were younger than age 20 when the United States dropped atomic bombs on Hiroshima and Nagasaki.[219] Following the accidental contamination in 1986 by massive amounts of radiation in the area surrounding Chernobyl in the former Soviet Union, increases in breast cancer have been observed in women living in surrounding areas. The most devastating effects have been found in women who were younger at the time of exposure, although is still too early to learn of the physiological ramifications of the accident on women who were girls or teens at the time of the accident.[72]

What is known is that adolescent girls whose treatment for scoliosis was monitored with repeated X-rays to their backs later suffered significantly higher rates of breast cancer than women who did not receive multiple X-rays. Similar exposures of older women with scoliosis did not have the same cancer-promoting effect.[220]

X-ray treatment of children, adolescents and very young adult women with Hodgkin's lymphoma led to significant increases in breast cancer risk in later adulthood, with most of the cancers developing in the area that had previously been irradiated.[221, 222] Girls and adolescents treated with radiation to combat non-Hodgkin's lymphoma had a similar increase in rates of breast cancer several decades later.[223] For women who had repeated fluoroscopic exposures while being treated as young girls for tuberculosis, younger age and increasing dose of radiation exposure were both associated with higher incidence of breast cancer in adulthood.[224] When women who had been treated with radiation for enlarged thymus glands during infancy were

The Falling Age of Puberty in U.S. Girls

Girls today get their first periods, on average, a few months earlier than did girls 40 years ago, but their breasts develop one to two years earlier. Over the course of a few decades, the childhoods of U.S. girls have been significantly shortened.

Early puberty is a known risk factor for breast cancer. The younger girls are when they get their first period, the greater their risk of breast cancer later in life. In fact, first menstruation (menarche) before age 12 raises breast cancer risk by 50 percent compared to menarche at age 16.[211] It is not completely clear how early puberty increases breast cancer risk but there are some clues. Early puberty is associated with an increased exposure to estrogen (which raises breast cancer risk), which in turn expands the window of vulnerability for breast cancer development between first menstruation and first pregnancy.

In 2007, the Breast Cancer Fund commissioned *The Falling Age of Puberty in U.S. Girls: What We Know, What We Need to Know,* by Sandra Steingraber, Ph.D., to further examine the reasons for the declining age of puberty. It reviews the published literature in a dozen fields of study, describes the state of the evidence for possible contributing factors and explores the mental and physical health consequences of early puberty. To learn more and download the report, visit www.breastcancerfund.org/pubertyreport.

compared with their non-treated sisters for the incidence of breast cancer decades later, a significantly higher incidence of breast cancer was found among the women who had received early X-ray treatments.[225]

Regarding diet and later risk for breast cancer, few if any reliable and replicable effects have been found looking across all age ranges.[226] Still, there is substantial evidence that high dietary intake during adolescence of animal fats, but not vegetable fats,[227, 228] may lead to increased breast cancer incidence later in life. Possible protective effects of genistein or soy intake are strongest when the compounds were taken as regular parts of diet during puberty (in rats)[229] or adolescence (in girls).[230] Similarly and with clearer evidence, physical activity during adolescence is associated with a decrease in later breast cancer risk,[231] reinforcing the importance of metabolic and related hormonal status during this stage as influencing later risk for breast cancer.

We need more research to better understand the impact of exposures of our children — from their earlier points of development through adolescence — on susceptibility to breast cancer and other diseases. In the meantime, advocates and policy makers should err on the side of precaution to minimize and, where possible, eliminate exposures to the damaging effects of ionizing radiation and environmental toxicants.

Breast Cancer or Breast Cancers?

In this report, as is true in so much of the public and scientific conversation about breast cancer, we discuss breast cancer as if it were a single disease. In reality, there are several different presentations of the disease and increasing sophistication in how some scientific studies differentiate among subtypes of the disorder. Sometimes the site of cancer origin within the breast (duct vs. lobe) is compared. Of the two most common forms of breast cancer, ductal cancer is more common (about 85 percent of breast cancers), but lobular may be more difficult to diagnose, leading on average to larger, more aggressive tumors at the time of diagnosis.[232] Another type of breast cancer, inflammatory breast cancer, is a relatively rare (between 1 and 6 percent of cases in the U.S., although incidence is much higher in Northern Africa) but exceedingly aggressive form of the disease that presents with rapid swelling, reddening and irritation of the breast tissue with or without an underlying solid breast lump.[233]

The tumor types described above are all forms of invasive breast cancer, or cancer that has spread beyond the confines of the ducts or lobes of the mammary system. Many research studies only look at women with invasive breast cancer. On the other hand, with increased use of mammography over the past two decades, diagnoses of ductal carcinoma in situ (DCIS) have increased by four to five times. DCIS is diagnosed when there is the appearance of abnormal cells contained within the walls of the ducts of the breast. At the time of diagnosis, DCIS is not life-threatening (only invasive cancer is). However, some DCIS will eventually transform into invasive cancers and, at present, clinicians cannot predict with reliability in which women this will happen. As a result, many women with DCIS are treated as though they have an early form of invasive cancer, undergoing both surgical and/or radiation treatments.[234]

Breast cancers often are distinguished by the age of the woman at her diagnosis, with age 50 generally used as an arbitrary marker for the transition from pre-menopausal to post-menopausal stages of a woman's reproductive life. Sometimes more precise information about menopausal status is gleaned either from the woman or from her medical records. Menopausal status is important because it marks the gradual but important downward shift in secretion of estrogens in the body. As we have seen, total exposures to estrogens, estrogen mimics and endocrine system disruptors — from any of a number of different sources — have been associated with increased risk for breast cancer later in life.

…it is important to acknowledge that approximately 1 percent of all diagnoses of breast cancer are in men.

Using a number of biological markers (genes or proteins found in cells that have been associated with mechanisms underlying breast cancer; see Table, page 27) as a basis, a different set of breast cancer subtypes has recently been established: basal, HER2 over-expression, luminal A, luminal B, normal and unclassified.[235, 236] The basal subtype (ER negative, PR negative , HER2 negative) is only found in about 15 percent of breast cancers but has been shown to be aggressive, unresponsive to treatment and ultimately indicative of a poor prognosis.[237, 238] Data published from the Carolina Breast Cancer study (2006) indicated a significant increase in this aggressive subtype of the disease in pre-menopausal African American women, a probable contributor to the poorer prognosis of women in this category relative to others of the same age but different racial/ethnic backgrounds.[239]

Finally, it is important to acknowledge that approximately 1 percent of all diagnoses of breast cancer are in men. The scientific literature indicates that many of the risk factors for men are similar to those for women, with a combination of

genetic, hormonal and environmental factors being involved.[240] Among the environmental issues that have been linked to male breast cancer are occupational exposures to gasoline and vehicle combustion, PAHs, EMF and some industrial solvents.[241, 242, 243, 244] Nevertheless, nearly all scientific research has been directed toward an understanding of breast cancer and its causes in women or female animals and, therefore, this will be the focus of this report. It is hoped that a better understanding of the complex causes underlying female breast cancer will also illuminate the factors influencing its development in males.

Breast Cancer Molecular Markers

This table provides brief information on some of the molecular markers found in different forms in breast cancer, along with brief descriptions of the significance of these markers.

Molecular Marker	Description	Biological Significance
Estrogen receptor ER+ ER-	Protein needed for many cellular actions of estrogens.	Actions can be blocked by anti-estrogens (e.g., tamoxifen).
Progesterone receptor PR+ PR-	Protein that is a product of activation of the estrogen receptor.	Necessary for cellular actions caused by progesterone.
HER2 HER2+ HER2-	Cell membrane protein that is important in translation of messages leading to increased cell growth and proliferation.	Actions can be blocked by drugs (e.g., Herceptin).
BRCA1, BRCA2	Genes that were identified in the early 1990s as important in the inherited transmission of breast cancer in a minority (5 to 10 percent) of cases.	Encode proteins involved in the repair of DNA mutations.
Other genes *p53* *FGFR2 et al.*	Genes that are involved in the encoding of proteins that alter cell pathways involved in the development of breast cancer.	Mutations may influence susceptibility to environmental, hormonal or other factors.

State of the Methodology

Trying to understand the factors underlying a complex disease such as breast cancer is very difficult. As described above, there are many presentations or forms of the disease, which may be related to different risk factors. Women with different genetic profiles may be differently susceptible to the disease-enhancing effects of various biological, lifestyle and environmental exposures. Many of the exposures that may be relevant in understanding risks for the disease may have occurred decades before diagnosis and most exposures do not occur in isolation, but rather as components of mixtures of factors that accumulate to affect disease incidence.

While recognizing these considerations, a substantial scientific literature has developed that implicates the role of environmental factors in the current high incidence of breast cancer. No single method or research design can determine definitively that a particular environmental exposure (or genetic profile, or lifestyle factor) is responsible for an individual's diagnosis of breast cancer; however, the collective data from several types of research studies can inform our understanding of risk for the disease at a broader level. Together the data from epidemiological and experimental laboratory research studies — in animals (in vivo) and in cell cultures (in vitro) — have provided compelling evidence that exposures to a number of environmental agents contribute to an increased risk of breast cancer.

No single method or research design can determine definitively that a particular environmental exposure is responsible for an individual's diagnosis of breast cancer.

Epidemiological Studies

Epidemiological studies of breast cancer are studies of human populations that explore the relationships between environmental exposures and incidence of breast cancer, including conditions under which the disease occurs in particular groups. These studies are critical starting points for developing hypotheses and ultimately thinking about effects of exposures on incidence of disease in people. These studies can also provide powerful tests of specific hypotheses, and several studies can be combined statistically to afford strong evidence for cause-effect relationships. Yet methodological constraints often make these studies difficult to design and more difficult to interpret.

Cases in which robust exposures to environmental chemicals or radiation occur allow for follow-up and examination of changes in rates of diseases such as breast cancer. These cases are essentially limited to unusual situations, usually involving accidental exposures. These include examples like the catastrophic radiation exposure following the dropping of the atomic bombs in Japan; the accidental release of radiation in Chernobyl, Russia; the accidental release of dioxin in Seveso, Italy; or cases of large and sustained occupational exposures to industrial chemicals or radiation.

More commonly, women, adolescents, young girls and fetuses are exposed unknowingly to multiple chemicals at lower doses. This makes it difficult for researchers to compare exposures — what, when and how much — for women who develop, or don't develop, breast cancer. In addition, many of the chemicals of concern may influence factors such as timing of puberty or menopause, and in turn pubertal or menopausal status might influence susceptibility to the effects of environmental factors. As a result of these methodological challenges, our understanding of the complexity of possible environmental effects on breast cancer risk in our mobile, industrial society is often compromised by

These studies are critical starting points for developing hypotheses and ultimately thinking about effects of exposures on incidence of disease in people.

the number of confounding or difficult-to-measure factors.[245]

Scientists are developing a number of methods to try to make epidemiological studies more meaningful. One example is the use by scientists at the Silent Spring Institute in Massachusetts of Geographic Informational Systems (GIS) mapping to overlay extensive historical exposure records, local chemical contamination profiles and detailed questionnaire information about chemical usage and personal health histories.[246, 247, 248] This is time-intensive and expensive work, but it results in detailed individual and community information that can be used to correlate historical exposures and later development of diseases, including breast cancer.

Other important advancements include the increased use of biomonitoring of chemicals in our bodies[249] to study how the chemicals of concern (or their breakdown products, called metabolites) accumulate in our bodies, especially in the extensive fat tissue found in breasts. Monitoring of excretion (urine samples), circulating (blood samples) or salivary levels of chemicals can be fairly easy if done reliably and over time. Direct measurement in breast tissue itself, or even in fat, is more problematic; multiple biopsies over the course of a woman's lifetime are impractical, risky and of ethical concern. Nevertheless, fat samples containing both natural estrogens and lipophilic endocrine disruptors can be removed at the time of surgeries for both breast cancer patients and patients undergoing other types of breast surgery, and meaningful analyses may then be conducted. For example, a recent study has shown that when detailed demographic and body weight data were factored into an analysis of fat-derived samples from surgical patients, increased incidence of breast cancer was associated with higher levels of environmental chemicals (total levels of combined xenoestrogens) in leaner post-menopausal women.[250, 251]

Taking a different, non-invasive approach, regular and reliable measurement of chemicals in placental tissue or cord blood at the time of birth, or in breast milk in early subsequent weeks, can provide information about fetal and perinatal exposures to chemicals at a critical time in a child's development.[252, 253]

Epidemiological studies are generally important both for the initial observations of possible relationships between environmental, lifestyle and demographic factors and disease, leading to the formulation of hypotheses related to those observations, as well as for more complex quantitative analyses of some of those relationships. More detailed understanding of underlying mechanisms comes from experimental research, conducted on models including animal (usually rats or mice) or cell-culture (e.g., tumor or pre-tumor cells grown in Petri dishes) systems.

Experimental Studies – Animal (In vivo) Studies

Use of rodent models allows scientists to expose animals to known amounts and combinations of environmental chemicals at identified periods in the animal's development. Studies of this sort have been critical in learning about risks underlying mammary cancers within the context of otherwise healthy, biologically intact animals. Rodents are particularly susceptible to chemically induced cancers, making them a good system to study the cellular and inter-cellular processes involved in the initiation and progression of mammary tumors. Their shorter lifespan and comparable profile of development make mice and rats good models for studying effects of early exposures to environmental toxins on susceptibility to tumor development.[254, 255]

Rodent models have been critical in understanding

some of the complexity of tumor development,[256] with growing evidence that cancer cannot be explained by an accumulation of genetic mutations in the tissue, but instead that changes in the development and interactions between different cell types (e.g., epithelial and stromal cells) may predispose the organism to cancer. [257, 258] This shift in focus toward examining the more complex biological context in which cancer develops is essential to our understanding of the ways that environmental factors affect molecular, sub-cellular and tissue organizational systems, and lead to greater breast cancer susceptibility.

Limitations of animal models include the observations that rodents have considerably shorter lifespans than humans; given the long latency between exposures and diagnosis of breast cancer often observed in humans, these differences may be important. Rats and mice also have some significant differences from humans in the rates and processes of progression of mammary/breast tumors.[259]

Even so, rats and mice provide important models for examining complex biological processes related to tumor formation in living animals and have been critical in the identification of environmental chemicals that are associated with increased risk for breast cancer.

Experimental Studies – Cell (In vitro) Studies

Much of the basic biology of breast cancer cells has been studied in isolated cell systems in which human breast cancer or pre-cancerous cells have been removed by biopsy and then grown and allowed to proliferate (sometimes eventually for hundreds or even thousands of generations of daughter cells) in containers in the laboratory. These cell systems are well characterized, representing a variety of different biomarker (genes or proteins that are identifiable and related to risk for breast cancer; see table, page 27) profiles. For example, some cell lines are ER+ and PR+, while others are receptor negative.[260] Studies of these cell lines have allowed scientists to compare susceptibility and behavior of the cells under a variety of different conditions and to monitor carefully the cellular and molecular events that characterize the processes by which normal cells are transformed to cancerous cells.

Because multiple tests of initially identical cells can be run concurrently under different conditions, effects can be observed relatively easily and rapidly, without requiring the use of live animals. With the addition of stromal cells, nutrients and other factors found in the normal environment of the breast tissue, more complex processes in breast tumor cells can now be studied.[261, 262]

The major limitation to cell culture or in vitro studies is simply that they are run under such artificial conditions. No matter how many cell types and nutrients are added, the complexity of a living biological system is not met. These cell studies are run without normal feedback from all the other cells and physiological systems of the body. Proper development and function of mammary cells in culture only occurs in the presence of the full range of cells, extra-cellular matrix and support enzymes normally present in intact mammary tissue.[263]

As we turn to the evidence supporting the conclusion that exposures to environmental chemicals and radiation contribute to the current high incidence of breast cancer, it is important to remember the issues of complexity that have been addressed in this opening Framework. It is also important to recognize the strength of the accumulated data that come from a wide variety of experimental models. The data are simply too powerful to be ignored.

Evidence Linking Environmental Factors and Breast Cancer

In June 2007, scientists at the Silent Spring Institute in Massachusetts released a comprehensive review of the scientific evidence examining environmental contaminants that have been identified by national and international regulatory agencies as increasing mammary tumor development in animal models. Among the 216 identified carcinogenic substances identified were industrial chemicals, chlorinated solvents, combustion products, pesticides, dyes, ionizing radiation, drinking water disinfection byproducts, pharmaceuticals, hormones, natural products and research chemicals.[264] The Silent Spring database is a rich resource, covering many more specific chemicals than we will cover in this report. We strongly recommend examining it for a more extensive overview of the field. A second paper, also from the Silent Spring Institute, comprised a review and critical analysis of the complex epidemiological data examining links between several of these chemicals and breast cancer incidence in women.[265]

In the sections below, we address many of the chemicals to which we might be exposed on a regular basis. The evidence is divided into three main sections, examining the links of the following to breast cancer:

- **Hormones and endocrine disrupting compounds**
- **Other chemicals of concern**
- **Radiation**

Within the discussion of each chemical, group of chemicals and type of radiation, we give a brief overview of the substances under discussion, including where they are found and how they may exert their effects on breast cancer risk. This is followed by evidence from epidemiological (human) and/or laboratory (animal and in vitro cell culture) studies.

Additionally, where applicable we describe and note (see sidebar for key to notations) the ratings for the substances by either the International Agency for Research on Cancer (IARC) or the National Toxicology Program (NTP). IARC is the division of the World Health Organization that evaluates and designates risk categories for substances that may be linked to human cancers.[266] The NTP, a program within the National Institute of Environmental Health Sciences of the National Institutes of Health, provides carcinogenicity ratings based on scientific evidence in both animals and humans.[267] Not all chemicals have been rated by IARC or NTP.

Finally, we also note which chemicals are classified as endocrine disrupting compounds (EDCs).

Key to Evidence in this Section

Institution	Rating Category
International Agency for Research on Cancer (IARC)	■ Known ■ Probable □ Possible
National Toxicology Program (NTP)	● Known ● Reasonably Anticipated
	◇ Endocrine Disrupting Compound

Compounds Linked to Breast Cancer	IARC			NTP		
	KNOWN	PROBABLE	POSSIBLE	KNOWN	REASONABLY ANTICIPATED	ENDOCRINE DISRUPTING COMPOUNDS
Evidence Linking Hormones and Endocrine Disrupting Compounds to Breast Cancer						
Estrogens and Progestins						
Hormone Replacement Therapy (HRT) and Oral Contraceptives	X			X		
Diethylstilbestrol (DES)	X			X		
Estrogens and Placental Hormones (Progestins) in Personal Care Products	X			X		
Xenoestrogens and Other Endocrine Disrupting Compounds (EDCs)						
Dioxins	X			X		X
Persistent Organochlorines: DDT/DDE and PCBs						
DDT/DDE			X	X		X
PCBs		X			X	X
Pesticides						
Triazine Herbicides: Atrazine						X
Heptachlor			X			X
Dieldrin and Aldrin						X
Other Pesticides						X
Polycyclic Aromatic Hydrocarbons (PAHs)		X			X	X
Tobacco Smoke: Active and Passive Exposures	X			X		X
Bisphenol A (BPA)						X
Alkylphenols						X
Metals	X			X		X
Phthalates						X
Parabens						X
Sunscreens (UV Filters)						X
Growth Promoters Used in Food Production						
Recombinant Bovine Growth Hormone (rBGH)/ Recombinant Bovine Somatotropin (rBST)						X
Zeranol (Ralgro)						X
Evidence Linking Other Chemicals of Concern to Breast Cancer						
Benzene	X			X		
Other Organic Solvents		X			X	
Vinyl Chloride	X			X		
1,3-Butadiene		X		X		
Ethylene Oxide	X			X		
Aromatic Amines		X			X	X

Evidence Linking Hormones and Endocrine Disrupting Compounds to Breast Cancer

Estrogens and Progestins

Background

The female ovary, or reproductive gland, produces two major types of hormones: estrogens and progestins. These hormones have both complementary and opposing effects that, together, are important in the regulation and maintenance of the menstrual cycle, pregnancy and the development of the breast in preparation for lactation (milk production).

The most abundant estrogen secreted by the ovary is estradiol (others include estriol and estrone), while the most common progestin is progesterone. Extensive exposures to both hormones, but especially to estradiol, have been implicated in increased risk for breast cancer[268] and it is believed that many environmental chemicals exert their carcinogenic effects by mimicking or disrupting hormone-regulated pathways, especially estrogen.

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, which originates from secretions of the testes or adrenal glands.[269]

Hormones like estradiol and progesterone are lipophilic, or fat-loving. This means that they can accumulate in fatty tissues of the body. Breasts are composed primarily of fat and therefore are repositories both for natural steroid hormones as well as for many environmental contaminants that are also lipophilic. Breast tissue also contains several enzymes (chemicals that facilitate the conversion of compounds to other structures) including aromatase, which converts local androgenic hormones to estrogens within the breast. The activity of aromatase is elevated in breast cancer tissue as compared to normal breast tissue.[270]

Hormone Replacement Therapy (HRT) and Oral Contraceptives ■ ●

Over the past several decades, pharmaceutical companies have developed a variety of mixtures of natural and synthetic ovarian hormones used mainly for contraception or post-menopausal hormone replacement therapy (HRT). The International Agency for Research on Cancer (IARC) has listed estrogens as known human carcinogens since 1987,[271] and their component hormones since 1976. In 2002, the National Toxicology Program (NTP) added HRT and estrogens used in oral contraceptives to the list of known human carcinogens.[272]

These classifications confirm scientific evidence that has been collected since the 1930s linking steroidal estrogens to increased cancer risk.[273] Data now show that when a woman's natural estrogens are supplemented by oral contraceptives and/or HRT, her risk of breast cancer increases.[274, 275, 276] 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 who have used only one.[277, 278] The effect may be most pronounced for pre-menopausal women who have taken both oral contraceptives and hormone therapy.[279]

Hormone Replacement Therapy (HRT)

In 2002, a large study designed to explore the benefits and risks of combined estrogen plus progestin HRT in post-menopausal women was halted before the end of study period. This project, called the Women's Health Initiative (WHI), enrolled more than 16,000 women ages 50 to 79. 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.[280]

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.

More recent analyses clarify that the increased risk of breast cancer in the WHI study is found for women taking the combined estrogen-progestin formula, but not for those women taking estrogen-only HRT supplements.[281]

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.[282]

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.

Also in 2003, researchers in the Million Women Study (MWS) in the United Kingdom reported that the use of all types of post-menopausal HRT significantly increased the risk of breast cancer. Again, 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).

Timeline of the History of Sex Hormones and the Use of Estrogen for Menopause

1930s	1940s - 1950s	1960s	1970s
Commercial production and sale of hormones as drugs triggers debates on potential danger of induction of malignancies.	Doubts arise regarding safety of menopausal hormones. Nevertheless, Premarin is a commercial success as women begin using HRT.	Changes in women's status and life expectancy encourage menopausal therapy. *Feminine Forever* (published 1966), promotes HRT as allowing women to avoid "estrogen deficiency" and conserve femininity.	Rise of women's movement and women's health movement. Feminist criticism of the pill and of HRT focuses on dangers of hormone therapy (including DES, banned in 1971). Reports of increased incidence in endometrial cancer in U.S. women using HRT (1975) cuts number of HRT prescriptions in half.

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.[283]

Several other studies have confirmed the basic result that use of combined HRT increases risk of breast cancer in post-menopausal women. Examination of cancer histology in women taking combined HRT at the time of diagnosis reveals an increased presentation of breast cancer of lobular origin,[284, 285] but also of cancers with low proliferation rates (mitotic indices) and favorable prognostic outcome.[286, 287, 288]

Oral Contraceptives

Numerous studies have shown an increased risk of breast cancer in women using oral contraceptives.[290, 291, 292, 293, 294] The risk is greatest among current and recent users, particularly those who have used them for more than five years and especially those who started using birth control pills earlier in life, pre-menopausal women, those with a family history of breast cancer[295] and possibly for women with *BRCA1* or *BRCA2* mutations.[296, 297] As with HRT, current use of oral contraceptives has been associated with an increase in breast tumors originating in the lobular tissue,[298] as well as with the estrogen receptor negative (ER-) (no or low estrogen receptor) profile of the disease.[299]

A recent study examined possible effects of oral contraceptive use on later risk for breast cancer in Hispanic and non-Hispanic white women. Statistically, Hispanic women have somewhat lower rates of breast cancer than do white women, and they are more likely to have breast cancer that is estrogen receptor positive estrogen receptor negative (ER+). Despite these group differences, use of oral contraceptives in the past five years has led to significant increases in breast cancer incidence in both groups. The effect was magnified for women of both groups when OC use continued for more than 20 years. Mirroring other study evidence, and again for both Hispanic and non-Hispanic white women, significant increases in ER tumors were observed.[300]

Post-menopausal women who used oral contraceptives for eight or more years, but who

1980s	1990s	2000s
Progestin-estrogen treatment widely introduced for women with intact uterus. HRT is presented as preventive therapy, shifting emphasis from "young and sexy forever" to "healthy forever." From early 1980s, steady increase in use of HRT (measured by number of prescriptions and sale of drugs), despite persistence of critical voices. By end of 1980s, HRT prescriptions exceed pre-1975 volume.	Steady increase in HRT use continues, strongly promoted by most doctors and sustained, especially in U.S., as individualized preventive medicine. Scientists, feminist scholars and advocates continue to question this approach. WHI — the first large randomized prospective clinical trial of menopausal hormones — begins, partly in response to feminist criticism of HRT.	HERS study reports surprising results on cardiovascular disease. WHI interrupted early, based on finding of excess cancer and cardiovascular incidents in trial's experimental group. In 2002 and 2003, HRT prescriptions decreased sharply in English-speaking countries. In 2004, decreased incidence of breast cancer among U.S. women attributed partially to drop in HRT use. Decrease occurred primarily in women 50 and older, principal users of HRT; decline most evident in estrogen-receptor-positive tumors.[289]

have discontinued use for at least a decade, show no significant increase in breast cancer rates.[301, 302]

Diethylstilbestrol ■ ●

The clearest evidence that a synthetic estrogen can increase risk for cancer decades later comes from the tragic experience with diethylstilbestrol (DES). Between 1938 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 compared to those who were not exposed to DES in the womb.[303, 304, 305] Research indicates that DES exposure is also associated with an increased risk of breast cancer in the women who took it during the 1950s.[306, 307]

In a follow-up study of daughters who were exposed prenatally to DES, a nearly two-fold increase in breast cancer risk was observed in women older than age 40.[308, 309] An even greater effect was found for women over the age of 50, although there were still relatively few of the daughters who had yet reached that age.[310]

Estrogens and Placental Hormones (Progestins) in Personal Care Products ■ ●

Placental extracts, probably with high concentrations of progesterone[311] and estrogenic chemicals, are sometimes used in cosmetics and hair care products, particularly products marketed to women of color. Addition of hormones and extracts is advertised to promote growth and thickness of hair. However, research indicates that use of these products in infants and children may also be linked to precocious puberty or early sexual maturation.[312, 313, 314] Early puberty is a risk factor for breast cancer later in life.[315] Scientists have recently proposed that use of these hormone-altered products might be contributing to the increased incidence of breast cancer, especially among young African American women.[316]

Phytoestrogens (Plant Estrogens)

The prevailing evidence against synthetic estrogens must also be understood alongside evidence about the effects of plant estrogens (phytoestrogens). Foods such 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 and are associated with healthy diets, the data are more conflicting as to whether the plant estrogens are beneficial, harmful or neutral when it comes to affecting breast cancer risk.[317, 318]

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.[319] Some human and laboratory studies suggest that long-term consumption of plant-based estrogens, especially during childhood and adolescence, may help reduce a woman's later risk of breast cancer.[320]

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.[321] Other data suggest that these two soy-based phytoestrogens may have opposing effects on the efficacy of the breast cancer drug, tamoxifen.[322, 323] Overall, the evidence on whether dietary phytoestrogens increase or decrease breast cancer risk in adult women remains incomplete and inconclusive. It may be unwise for women, especially those with estrogen receptor positive breast tumors, to increase their phytoestrogen intake.

Xenoestrogens and Other Endocrine Disrupting Compounds (EDCs)

Background

The substances described in the Estrogens and Progestins section above mostly were developed and distributed *because* of their known hormonal effects. The later consequences for girls and women exposed at different periods during their lives were unanticipated effects of exposures.

In this section we discuss a wide variety of chemicals that have been developed for reasons that are entirely independent of their effects on hormonal systems. Instead these are chemicals that were/are synthesized for their properties as plastic additives, industrial solvents, pesticides and herbicides, or they are chemical byproducts of combustion or industrial manufacturing of commonly used products.

We have learned over the past 20 years that these chemicals also can mimic or alter the activities of the natural hormones, especially the estrogens. They are therefore called "xenoestrogens," meaning stranger or foreign estrogen. The xenoestrogens are members of a larger class of synthetic chemicals known as endocrine disruptors. Endocrine disruptors are substances that mimic or disturb the activity or binding of a much wider group of hormones, including the androgens (for example, testosterone), adrenal hormones (for example, corticosterone), thyroid hormones, etc. Therefore the term "endocrine disruptor" is used to reflect the wide range of effects these compounds may have on the endocrine system, not just as estrogen mimics.

The effects of endocrine disruptors, including xenoestrogens, on reproduction and development have been well-established in a number of wildlife species.[324] Data from humans are more controversial and less conclusive. Given the pervasive nature of many of these chemicals in our physical environment, alone and in mixtures, it is difficult to determine clear relationships between individual chemicals and their effects on risk for cancer or other disorders. As described in the Framework section of this report, complex methodological issues are particularly relevant to understanding the effects of exposure to endocrine disruptors on subsequent risk for breast cancer.

To date, neither the NTP nor IARC have classified most endocrine disruptors as carcinogens in humans. Lack of action reflects controversies in the scientific literature, considerable pressure from industry and failure of the scientific communities and regulatory agencies to agree on methodologies and criteria for classification of these chemicals. For example, the U.S. EPA and other regulatory agencies are still struggling to determine appropriate experimental tests for measuring the hormonal properties of environmental chemicals, much less whether they may be carcinogenic.

Despite the lack of formal classification of many xenoestrogens as chemicals that increase risk for breast cancer, a substantial body of peer-reviewed scientific literature implicates many of these chemicals in the current high rates of the disease. These data come primarily from laboratory studies with animal or cell culture models. But there is also increasing human epidemiological data that support these lab studies.

Scientists have proposed that the primary mechanism by which these chemicals may exert effects on breast cancer risk involve mimicking or disruption of estrogen pathways,[325] so we have included our discussion of these synthetic chemicals in this section, following the Estrogens and Progestins section.

Cell Culture to Human Epidemiological Studies: Evidence that We Should Be Concerned About Endocrine Disruptors

In 1991, researchers at Tufts University discovered that a chemical leaching from polystyrene

laboratory tubes was causing breast cancer cells to grow in vitro, even though no estrogens had been added to the culture. Subsequent investigation identified the substance leached as p-nonyl-phenol, an additive commonly used in plastics, which behaves like a natural estrogen.[326] This landmark discovery generated widespread interest in what we now call xenoestrogens[327] — synthetic agents that mimic the actions of estrogens.

The research on xenoestrogens intensified in 1994 when researchers identified certain pesticides (endosulfan, toxaphene and dieldrin) as xenoestrogens because they caused breast cancer cells to proliferate in cultures.[328] In the last decade and a half, more chemicals have been added to the list of endocrine disruptors or potential disruptors. In 2004, the Commission of the European Communities identified 147 such substances.[329] (See Appendix II for a list of selected endocrine disruptors and their uses in everyday life.)

What about exposures of these xenoestrogens in women? 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.[330] 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 a higher incidence rate. 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.[331]

In examining the environments in which the women lived and worked, researchers found synthetic estrogens in septic tank contents, groundwater contaminated by wastewater and in some private wells.[332] They then tested for a total of 89 hormonally active agents and mammary carcinogens in indoor air and household dust samples from 120 homes. They found 52 different compounds in air and 66 in dust, including phthalates, parabens, alkylphenols, flame retardants, PAHs, polychlorinated biphenyls (PCBs) and bisphenol A, in addition to banned and currently used pesticides.[333]

In the following sections we address in more detail some of the most common xenoestrogens and endocrine disrupting compounds, along with some of the evidence linking them to breast cancer.

Dioxins ■ ● ◇

Of all toxic chemicals, dioxins may be the most widespread. The body fat of every human being, including every newborn, contains dioxins. Dioxins are formed by the incineration of products containing PVC, PCBs and other chlorinated compounds, as well as from industrial processes that use chlorine and from the combustion of diesel and gasoline. Dioxins break down very slowly; they accumulate in fat of wildlife and bioaccumulate across the food chain.

Dioxins are known human carcinogens and endocrine (hormone) disruptors. One of the dioxins (2,3,7,8-tetra chlorodibenzo-para-dioxin [TCDD]) has been classified by IARC as a known human carcinogen.[334] In 2000, the U.S. Environmental Protection Agency officially declared TCDD to be a known carcinogen.

People are exposed to dioxins primarily through consumption of animal products and human breast milk.[335] 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 through dairy and meat products.

There have been very few epidemiological studies examining possible effects of dioxin exposure and breast cancer risk. Most of the studies have been with fairly small numbers of women. Further, comparisons are made looking at dioxin levels at

Of all toxic chemicals, dioxins may be the most widespread. The body fat of every human being, including every newborn, contains dioxins.

the time of diagnosis of breast cancer, not at earlier times when exposures might be influencing cancer initiation. Concentrations of dioxins in breast tissue may change dramatically over the reproductive span of a woman's life. There is a substantial decrease in the amount of dioxin remaining in a woman's breast fat tissue after she has breast fed because, unfortunately, the chemicals have been passed on to her newborn via breast milk. Although the presence of toxic chemicals in breast milk is potentially dangerous, the beneficial nutrients and immune system boosters that are transferred from mother to infant far outweigh the potential toxic transfers.[336]

Not surprisingly, given these methodological issues, study results have been conflicting. However, a recent follow-up study on women exposed to dioxins during a chemical plant explosion in 1976 in Seveso, Italy makes a more compelling case for a connection between dioxin and breast cancer.[337] 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 levels was associated with more than twice the risk of breast cancer. Women who were children at the time of the accident are just beginning to reach the age when breast cancer is most likely to develop and researchers will continue to follow the Seveso women. They expect to find additional breast cancer cases.

Another study examined deaths from cancer among people who had worked in a chemical factory in which they were exposed to high levels of TCDD. There was no increase in overall mortality from cancer for female workers, although there was a significant increase in deaths from breast cancer among those who worked in high exposure regions of the factory.[338]

A number of laboratory studies have demonstrated that when looking at later changes in mammary cancer rates, the timing of exposures to dioxins matters. Although exposing animals to dioxins in adulthood may not affect cancer rates, earlier exposures may have profound effects. Several studies have shown that administration of dioxin (especially TCDD) to pregnant rats leads to structural abnormalities in the development of their pups' mammary tissues and higher incidence of tumors when the pups grow to adulthood.[339, 340, 341, 342]

Persistent Organochlorines: DDT/DDE and PCBs

Two types of chemicals known to disrupt hormone function are dichloro-diphenyl-trichloroethane (DDT), an organochlorine pesticide, and the polychlorinated biphenyls (PCBs), a large group of chemicals that 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 soil, riverbeds and dust particulates in homes. [343 344] Due to their historical overlap in exposures, and because of many similarities in structure and function, the two are often discussed together while their effects on disease have also been explored independently.

DDT/DDE □ ● ◇

DDT was the first widely used synthetic pesticide. It is credited both with the eradication of malaria in the United States and Europe, and with long-term devastating effects on reproductive success in wildlife and adverse health effects in humans.[345] Although banned in many countries for agricultural use, DDT is still used for malaria control in 17 countries.[346] Because of its continued use and its persistence in the environment, DDT is found worldwide. Most animals, including

DDT was the first widely used synthetic pesticide. It is credited both with the eradication of malaria in the United States and Europe, and with long-term devastating effects on reproductive success in wildlife and adverse health effects in humans.

humans, ingest DDT-contaminated foods and retain the chemical and its main metabolite, DDE. Significant concentrations of DDT and DDE are still found in the body fat of humans and animals, in human breast milk and in placenta.[347, 348 349]

Epidemiological data are mixed regarding the effects of DDT/DDE on breast cancer risk. For example, one study from the Long Island Breast Cancer Study Project did not find an association between DDT/DDE (or PCBs) and breast cancer.[350] Like many such studies, however, this project measured contaminant levels near the time of breast cancer diagnosis, without regard to possible exposures during critical early periods of breast development, and did not consider the effect of chemical mixtures or assess key metabolites.

A recent study examined women's year of birth (knowing that DDT use was high in the past, rough historical exposures could be assessed) and blood DDT levels at the time the women gave birth as markers of DDT exposures. Researchers then followed the women over the next two decades, noting cases when women either were diagnosed with invasive or noninvasive breast cancer before the age 50, or died from breast cancer before the age of 50. Results show that exposure to DDT during childhood and early adolescence (younger than age 14) was associated with a fivefold increase in risk of developing breast cancer before the age of 50. As the authors note, "Many U.S. women heavily exposed to DDT in childhood have not yet reached age 50. The public health significance of DDT exposure in early life may be large."[351]

A connection was also established by laboratory studies that found the estrogen-like form of DDT enhances the growth of estrogen-positive (ER+) mammary tumors.[352,353] ER+ tumors are 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, the period when women exposed to DDT as young girls were expected to be exhibiting environmentally altered incidence in breast cancer related to DDT exposure.[354] Another study, looking at chemical levels in breast adipose tissue, did not find an association of DDT/DDE with ER+ tumors. However, data from this study indicated a significant association of higher concentrations of these compounds in breast tissue with tumors were more aggressive and had poorer prognoses.[355]

PCBs ■ ● ◇

Although the EPA banned the use of PCBs in new products in 1976, as many as two-thirds of all insulation fluids, plastics, adhesives, paper, inks, paints, dyes and other products containing PCBs manufactured before the ban remain in daily use. The remaining one-third was discarded, which means that these toxic compounds eventually made their way into landfills and waste dumps.[356]

Levels of PCBs were high before being banned in the U.S., but generally their presence in human tissues has decreased slowly over the past three decades.[357] Exposures were high, though, between childhood and young adulthood for many women who are now facing a diagnosis of breast cancer. A recent study found that both mothers and infants who currently live near PCB-contaminated sites still have high concentrations of several PCBs, a finding that is diminished after dredging and removal of nearby PCB contamination.[358]

The science on PCBs is complicated. There are more than 200 individual PCBs that are classified in three types based on their effects on cells. One type acts like an estrogen. A second type acts like an anti-

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

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.[359] Therefore, these compounds have the ability to alter normal cell function, either by disrupting hormones or enzymes. Most studies have looked at total PCB levels without identifying individual types. A few studies, however, have looked at relationships between cancer status and particular PCBs.

A 2004 case-control study found significantly higher total blood levels of PCBs, particularly PCB 153, in women with breast cancer than in presumably healthy women. PCB 153 has been shown to exhibit estrogen-like activity in animal and in vitro studies.[360] A Canadian study measured several types of PCBs, along with DDE, in breast biopsy tissue. Compared with healthy women, pre-menopausal women with breast cancer had significantly higher levels of PCBs 105 and 118, while post-menopausal women with breast cancer had higher levels of PCBs 170 and 180.[361]

Another report has implicated PCBs in breast cancer recurrence among women with nonmetastatic breast cancer. The study found that women with the highest levels of total PCBs, as well as of PCB 118, in their adipose tissues were almost three times as likely to have recurrent breast cancer as women with lower levels.[362]

Some studies have failed to link PCBs and breast cancer. But new evidence suggests that some of these compounds may have their greatest impact on women with greater susceptibilities, and that looking broadly at large samples will not tell the full story of cancer risk as influenced by PCB exposures. For example, researchers evaluating data from the Nurses' Health Study revisited the issue of PCBs and breast cancer risk and revised their conclusion concerning the links among PCBs, DDE and breast cancer. In studies of PCBs and DDE in blood, they had previously concluded that exposure to these chemicals was unlikely to explain high breast cancer rates.[363] In 2002, new evidence regarding variations in individual susceptibility due to genetic differences prompted these researchers to call for additional studies.[364]

Laboratory studies using in vitro systems of human breast cancer cells have demonstrated that various specific types of PCBs promote the proliferation of breast cancer cells in culture by stimulating estrogen receptor (ER) mediated pathways[365, 366] and the activation of key enzymes and cellular changes that are characteristic of transformation of cells to a malignant state.[367]

Pesticides

A 2006 report from the Long Island Breast Cancer Study Project demonstrated that self-reported lifetime use of residential pesticides was associated with an increase in risk for breast cancer. The increase was found for women who had reported use of chemicals in the aggregate, as well as specifically for use of lawn and garden pesticides.[368] These results are important because they address exposures to chemicals as they happen in ordinary life, and with all the complexities of mixtures and multiple sorts of uses. Many other studies of possible effects of

A 2006 report from the Long Island Breast Cancer Study Project demonstrated that self-reported lifetime use of residential pesticides was associated with an increase in risk for breast cancer.

pesticides try to tease out relationships with single chemicals or classes of chemicals, and the results are often contradictory depending on length and timing of exposures, types of chemical being studied and so forth. Despite that, many pesticides and herbicides have been labeled as human or animal carcinogens (see Appendix I). Many are also found in water supplies,[369] samples of air and dust from homes.[370]

Triazine Herbicides: Atrazine ◇

Triazine herbicides are the most heavily used agricultural chemicals in the United States. Triazines include atrazine, simazine, propazine and cyanazine. Although all have been shown to cause mammary cancer in laboratory rats,[371] there is relatively little scientific data exploring the relationship between simazine or cyanazine and breast cancer. The literature on atrazine is much more extensive.

Dupont, the maker of cyanazine, negotiated with the EPA a gradual phase-out of the pesticide beginning in 1997. Supplies of cyanazine that remained after December 1999 could be used through the end of 2002. Atrazine was banned in the European Union in 2005 because of its high presence in drinking water, its demonstrated harmful effects on wildlife and its potential health effects in humans. Atrazine is still approved for use in the United States. More than 75 million pounds of atrazine are applied annually in the U.S., primarily to control broadleaf weeds in corn and sorghum crops in the Midwest.[372]

Elevated levels of atrazine are found each spring and summer in both drinking water and ground water in agricultural areas.[373 374 375] High levels of triazine (primarily atrazine) in contaminated waters have been associated with an increased risk of breast cancer.[376]

Atrazine is a known endocrine disruptor, causing dramatic damage to reproductive structures in frogs[377] and other wildlife. Research in rodents has shown that atrazine exposure disrupts pituitary-ovarian function, including a decrease in circulating prolactin and luteinizing hormone levels, changes that contribute to the effects of this chemical on increases in mammary tumors.[378 379]

Recent in vitro data suggest that one mechanism by which atrazine exerts its endocrine disrupting effects is by increasing the activity of the enzyme aromatase.[380 381] Aromatase catalyzes (facilitates) the conversion of testosterone and other androgens to estrogens, including estradiol. Androgens are found naturally in women, although at lower levels than in men. The production of estrogens through the aromatase pathway, however, is of sufficient importance in the etiology of breast cancer that a current class of breast cancer drugs aims specifically to block the activity of aromatase.

Exposure to atrazine during gestation delays development of the rat mammary gland in puberty, widening the window of sensitivity to breast carcinogens.[382] Similarly, exposure of rats late in pregnancy to a mixture of commonly formed metabolites of atrazine also leads to persistent changes in mammary gland development in their pups exposed during gestation. These abnormalities persist into adulthood.[383]

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 existing stocks.[384] Heptachlor use was

Atrazine was banned in the European Union in 2005 because of its high presence in drinking water, its demonstrated harmful effects on wildlife, and its potential health effects in humans.

The Connection Between Pesticides and Breast Cancer

Pesticide	Carcinogenic		Hormone Disrupting	Source of Exposure/ Scope of Use
	Animal Mammary Gland Carcinogen *	Human Carcinogenic Risk Classification †	Disrupts Endocrine System/ Estrogenic ‡	
1,2-Dibromo-3-chloropropane	X	IARC Possible; NTP Reasonably Anticipated		Pesticide: banned as soil fumigant in 1985, air pollutant, exposure through ingestion of previously contaminated food and water
2,4-Dichlorophe-noxyacetic acid			X	Pesticide: herbicide
Atrazine (a triazine herbicide)	X	IARC Not Classifiable	X	Pesticide: herbicide, air pollutant, found widely in water bodies, exposure through ingestion of food or water, banned in European Union in 2005, 75 million pounds used annually in U.S. mainly on corn and sorghum
Captafol	X	IARC Probable		Pesticide: fungicide, not currently registered for use in U.S.
Chlordane	X		X	Pesticide: insecticide (ticks and mites), veterinary pharmaceutical, air pollutant, use as insecticide has been banned, persists in meat and fish, found in household dust
Chlorpyrifos			X	Pesticide: insecticide (ticks and mites)
Clonitralid	X			Pesticide: exposure through dermal contact or ingestion of water treated with clonitralid (for water snail and sea lamprey control) or contaminated fish
Cypermethrin			X	Pesticide: insecticide
DDT (Dichloro-diphenyl-trichloroethane)		NTP Reasonably Anticipated	X	Pesticide: contact insecticide, banned in many countries, used for malaria control in others, DDT and metabolite DDE still found in body fat of humans and animals though banned in U.S. in 1973
Dichlorvos	X	IARC Possible		Pesticide: air pollutant, inhalation of air and dermal contact with no-pest strips, sprays or flea collars, ingestion of food prepared where dichlorvos has been used
Dieldrin, Aldrin, Endrin (-drin pesticides)			X	Pesticide: insecticide, 1950s to 1970s dieldrin and aldrin used on corn and cotton, 1987 both were banned, still persist in environment
Fenvalerate	X	IARC Not Classifiable		Pesticide: landscaping/yard products, pet care products
Heptachlor		IARC Possible	X	Pesticide: insecticide, used for termite control through 1980s in U.S., agricultural use continued until 1993 (especially on pineapple)
Lindane		NTP Reasonably Anticipated	X	Pesticide: insecticide
Malathion			X	Pesticide: insecticide
Methoxychlor			X	Pesticide: insecticide, veterinary pharmaceutical
Nifurthiazole	X	IARC Possible		Pesticide
Pentachlorophenol			X	Pesticide: insecticide (termites), wood preservative
Permethrin, Sumithrin			X	Pesticide: insecticide
Simazine (a triazine herbicide)	X	IARC Not Classifiable		Pesticide: air pollutant, widely used to control weeds in food crops and in ponds, algae control in pools and fountains, detected at low levels in air, rainwater and surface water
Sulfallate	X	IARC Possible; NTP Reasonably Anticipated		Pesticide: herbicide, used until early 1990s in U.S., exposure through ingestion of residues in food crops
Toxaphene		NTP Reasonably Anticipated	X	Pesticide: insecticide
Tributyl Tin (chloride)			X	Pesticide: biocide, rodent repellent
Vinclozolin			X	Pesticide: agricultural fungicide, used in vineyards

See citations for this table on page 44.

particularly high in Hawaii, where it was used extensively on pineapple crops and consequently contaminated both local agricultural crops and dairy supplies. Breast cancer rates in Hawaii have increased dramatically for women of all ethnic groups over the past four decades.[385]

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 ages 20 and older, but HE is also found in the bodies of adolescents 12 to 19 years old, [386] and in eight of 10 samples of umbilical cord blood from newborn infants.[387]

High levels of HE in breast milk[388] and fat tissue from breast biopsies[389] have been shown to be associated with increased incidence of breast cancer.

Although HE does not act like estrogen, it affects the way the liver processes estrogen by 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[390] and to increase production of nitric oxide, a chemical that is found naturally in cells and is known to cause damage to DNA.[391]

Dieldrin and Aldrin ◇

From the 1950s until 1970, the pesticides dieldrin and aldrin (which breaks down to dieldrin, the active ingredient) were widely used for crops including corn and cotton. Because of concerns about damage to the environment and, potentially, to human health, the U.S. EPA in 1975 banned all uses of aldrin and dieldrin except in termite control; the agency banned these pesticides altogether in 1987.[392] Thus, most of the human body burden of this chemical comes either from past exposures or lingering environmental residues.

Like many other pesticides found in the environment, dieldrin has been shown to be an endocrine disruptor, both by stimulating estrogen-regulated systems and by interfering with androgen-regulated systems.

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 U.S. CDC, the study examined a rare bank of blood samples taken from women before the development of breast cancer.[393] During the late 1970s and early 1980s, blood samples were taken from approximately 7,500 Danish women ranging in age from 30 to 75. 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

Cites for table, page 43

*Silent Spring Institute's Science Review published in Cancer in 2007 includes information on 216 animal mammary gland carcinogens. www.sciencereview.silentspring.org

†International Agency for Research on Cancer (IARC) carcinogenic risk classification is based on evaluation of potential tumor development at all sites, not only breast/mammary tissue. Categories include: Known, Probable, Possible and others. The National Toxicology Program (NTP), within the National Institute of Environmental Health Sciences of the National Institutes of Health, provides carcinogenicity ratings based on scientific evidence in both animals and humans. Categories include: Known, Reasonably Anticipated, and others. (Report on Carcinogens, Eleventh Edition; U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program.) Not all chemicals have been rated by IARC or NTP.

‡To date, neither the NTP nor IARC have classified most endocrine disruptors as carcinogens in humans. List of endocrine disruptors from: Brody JG, Rudel RA (2003). Environmental pollutants and breast cancer. Environmental Health Perspectives 111: 1007-1019.

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.[394]

Like many other pesticides found in the environment, dieldrin has been shown to be an endocrine disruptor, both by stimulating estrogen-regulated systems and by interfering with androgen-regulated systems. Addition of dieldrin to human breast cancer (MCF-7) cells in vitro can stimulate their growth and proliferation.[395, 396]

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 the disease.

Other Pesticides ◇

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 the disease. 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.[397]

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-trichlorophenoxy propionic 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.[398]

A recent study of farmers and their families shows that children ages 4 to 11 of farmers using 2,4,5-TP on their farms had high levels of the pesticide in their urine samples soon after the chemical had been applied to the fields. This is of concern given the evidence of increased susceptibility of children and young adolescents to the carcinogenic effects of chemicals.[399]

Polycyclic Aromatic Hydrocarbons (PAHs) ■ ● ◇

Polycyclic aromatic hydrocarbons (PAHs) are ubiquitous byproducts of combustion, from sources as varied as coal and coke-burners, diesel-fueled engines, grilled meats and cigarettes. PAH residues are often associated with suspended particulate matter in the air, and thus inhalation is a major source of PAH exposure.[400] In the Silent Spring Institute study of environmental contaminants in house dust, three PAHs (pyrene, benza anthracene and benzapyrene) were found in more than three-quarters of the homes tested.[401]

Like many other environmental chemicals that are associated with breast cancer risk, PAHs are lipophilic and are stored in the fat tissue of the breast.[402] PAHs have been shown to increase risk for breast cancer through a variety of mechanisms. The most common PAHS are weakly estrogenic (estrogen mimicking), due to interactions with the cellular estrogen receptor (ER).[403] However, the major receptor-directed pathway is a different one, with PAHs associating with a protein called the aryl hydrocarbon receptor (AhR), initiating a series of cell changes that lead to altered cell signaling and ultimately to increases in DNA mutations.[404, 405] PAHs can also be directly genotoxic, meaning that the chemicals themselves or their breakdown products can directly interact with genes and cause damage to DNA.[406]

Several epidemiological studies have implicated PAH

exposure in increased risk for breast cancer. One of the studies from the Long Island Breast Cancer Study Project found that women with the highest level of PAH-DNA adducts had a 50 percent increased risk of breast cancer. PAH-DNA adducts are indicators of problems in DNA repair in cells, one of the early hallmarks of tumor development.[407] In an earlier report, researchers explored the presence of PAH-DNA adducts in breast samples taken from women diagnosed with cancer as compared with those diagnosed with benign breast disease. Cancerous samples were twice as likely to have PAH-DNA adducts as were benign samples.[408]

Occupational exposure studies have looked at workers exposed regularly to gasoline fumes and vehicular exhaust, major sources of PAHs (as well as benzene). These occupational exposures are associated with an increased risk of breast cancer for pre-menopausal women[409] and also for men. In the case of male breast cancer, PAHs may specifically increase the risk of breast cancer in men carrying a *BRCA1* or *BRCA2* mutation.[410]

A recent case-control study in western New York indicated that very early life exposure (around the time of birth) to high levels of total suspended particulates, a proxy measure for PAH levels, is associated with increased risk of breast cancer in post-menopausal women.[411]

Tobacco Smoke: Active and Passive Exposures ■ ● ◇

Tobacco smoke also contains PAHs, which may explain a potential link between increased breast cancer risk and both active and passive smoking. Tobacco smoke contains hundreds of other chemicals,[412] including three known human carcinogens (polonium-210,[413] a radioactive element, benzene and vinyl chloride), as well as toluene and 1,3-butadiene, both of which are known to cause mammary tumors in animals.

Researchers at Japan's National Cancer Center recently reported the results of a study involving 21,000 women ages 40 to 59. They found that both active and passive smoking increase the risk of breast cancer in pre-menopausal women.[414]

A large study of California teachers revealed an increased risk of breast cancer among smokers, particularly those who began smoking during adolescence, at least five years before their first full-term pregnancy, or who were long-term or heavy smokers.[415] Several earlier studies also suggest that women who begin smoking cigarettes as adolescents face increased risks of breast cancer.[416, 417, 418, 419 420]

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.[421, 422] One possible explanation for this is that smoking acts as an anti-estrogen and damages the ovaries, thereby lowering estrogen levels. Researchers hypothesize that the lower level of estrogen decreases 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, may 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:

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, and several times that amount is produced globally.

> Overall, the weight of evidence (including biomarker, animal and epidemiological studies) is consistent with a causal association between environmental tobacco smoke (ETS) and breast

cancer, which appears to be stronger for pre-menopausal women.[423]

A recent overview of the scientific literature confirmed the conclusion that where effects of environmental tobacco smoke on breast cancer risk are found, it is only significant for pre-menopausal women with the disease.[424]

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, and several times that amount is produced globally.[425] BPA is the building block of polycarbonate plastic and is also used in the manufacture of epoxy resins. Significant levels of BPA have been measured in ambient air,[426] house dust[427] and river and drinking water.[428]

BPA is commonly found in the lacquer lining of metal food cans and in some types of plastic food containers, including some baby bottles, water 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.[429] 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 blood samples from developing fetuses as well as the surrounding amniotic fluid,[430] and it has been measured in placental tissue and in umbilical cord blood at birth.[431] CDC researchers also found BPA in 95 percent of about 400 urine samples from a broad national sample of adults.[432]

Several studies using both rat and mouse models have demonstrated that even brief exposures to environmentally-relevant doses of BPA during gestation or around the time of birth lead to changes in mammary tissue structure predictive of later development of tumors. Exposure also increased sensitivity to estrogen at puberty.[433, 434, 435, 436] Recent data demonstrate that early exposure to BPA leads to abnormalities in mammary tissue development that are observable even during gestation.[437] Prenatal exposure of rats to BPA also led to increases in the number of pre-cancerous lesions and in situ tumors (carcinomas[438]), and an increased number of mammary tumors following adulthood exposures to a sub-threshold dose (lower than that needed to induce tumors) of a known carcinogen.[439]

Studies using cultures of human breast cancer cells demonstrate that BPA acts through the same response pathways as natural estrogen (estradiol).[440, 441] BPA can interact weakly with the intracellular estrogen receptor (ER), and it also can alter breast cell responsiveness and induce cell proliferation in vitro and in vivo. It affects cellular functions through interactions with the membrane estrogen receptor.[442, 443] Along with its many other effects on cell growth and proliferation, BPA has been shown to mimic estradiol in causing direct damage to the DNA of cultured human breast cancer cells.[444]

Alkylphenols ◈

Alkylphenols are industrial chemicals used in the production of detergents and other cleaning products, and as anti-oxidants in products made from plastics and rubber. They are also found in personal care products, especially hair products, and as an active component in many spermicides. In the Silent Spring Institute study of contaminants in samples from homes, alkylphenols — especially 4-nonylphenol (4-NP) and its breakdown products — were found in all samples of house air and 80 percent of house dust samples.[457] Substantial concentrations of these chemicals have also been found in wastewater associated with domestic sewers[458] and municipal landfills.[459]

The alkylphenols, including 4-NP, have been shown to mimic the actions of estradiol, mediating their effects through the cellular estrogen receptor (ER).[460] They also bind to the newly described cell membrane ER and mimic cellular signaling

Breathing It All In

Air Pollutant(s)	Description	Sources of Exposure

Polycyclic Aromatic Hydrocarbons (PAHs)	Class of chemicals produced in combustion
	Example: benzo(a)pyrene
		• Outdoor and indoor air pollution
		• Tobacco smoke
		• Coal and coke-burners
		• Auto exhaust (diesel)
		• Diet
		  ○ Smoked and grilled foods
		  ○ Foods contaminated by outdoor air pollution
		• Occupational exposures

Dioxins	Class of chemicals produced in combustion of PVC, PCBs and other chlorinated compounds
	Example: tetra chlorodibenzo-p-dioxin (TCDD)
		• Outdoor air pollution
		• Waste incineration
		• Pulp and paper manufacturing and other industrial processes
		• Diet (indirect, primary exposure)
		  ○ Dietary fat, especially in milk, eggs, fish, meat
		  ○ Foods contaminated by outdoor air pollution
		• Occupational exposures

Organic Solvents	Class of chemicals that include chlorinated and other solvents Examples: toluene, methylene chloride, trichloroethylene, formaldehyde	• Outdoor and indoor air pollution • Waste incineration • Used in manufacture of computer parts • Used in manufacture of cleaning products and some cosmetics • Occupational exposures

Alkylphenols	Industrial chemicals used in manufacturing of consumer products
	Example: 4-nonylphenol
		• Indoor air and dust
		• Personal care products
		  ○ Hair products
		  ○ Spermicides
		• Used in manufacture of cleaning products and detergents
		• Occupational exposures

Vinyl Chloride	Released when PVC is produced. PVC is used extensively in food packaging, cars, toys, credit cards, rainwear and other products.	• Outdoor and indoor air pollution • Tobacco smoke • Air near hazardous waste sites and landfills • Occupational exposures during PVC manufacture
Benzene	High production volume petrochemical	• Outdoor and indoor air pollution • Tobacco smoke • Gasoline fumes • Auto exhaust (diesel) • Industrial burning/combustion • Serious occupational exposures
Ethylene Oxide	Chemical used to sterilize medical equipment and in some cosmetics	• Primarily indoor air pollution • Possibly from cosmetics • Occupational exposures in sterilization facilities or cosmetics manufacturing
Aromatic Amines	Class of chemicals found in the chemical and plastic industries. Combustion byproducts of manufacturing. Types: monocyclic, polycyclic, heterocyclic	• Outdoor or indoor air pollution • Tobacco smoke • Combustion of wood chips or rubber • Formed in production of polyurethane foams, dyes, pesticides and pharmaceuticals • Auto exhaust (diesel) • Diet – grilled meats and fish • Occupational exposures

Breathing It All In (continued)

Air Pollutant(s)	Description	Sources of Exposure
Pesticides	Class of chemicals used residentially or in agriculture to kill plant and animal pests Examples: atrazine, heptachlor, dieldrin, DDT	• Outdoor or indoor air pollution • Dust in households • Diet – non-organic food • Occupational exposures
1,3-Butadiene	Product of internal combustion engines and petroleum refineries	• Outdoor or indoor air pollution • Tobacco smoke • In manufacture of rubber products and some fungicides • Occupational exposures

Sources: Brody JG, Moysich KB, Humblet O, Attfield KR, Beehler GP, Rudel RA (2007). Environmental pollutants and breast cancer: Epidemiologic studies. Cancer. 109 (12 Suppl): 2667-711

Rudel RA, Attfield KA, Schifano JN, Brody JC (2007). Chemicals causing mammary gland tumors in animals signal new directions for epidemiology, chemicals testing, and risk assessment for breast cancer prevention. Cancer. 109 (12 Suppl): 2635-66.

responses usually controlled by estradiol.[461]

Prenatal exposure of rats to 4-NP causes altered development of the mammary gland, as well as changes in steroid receptor populations in several reproductive tissues.[462] A recent study showed that treatment of mice with 4-NP led to an increased synthesis of estriol, a weak natural estrogen, by the livers of the treated animals. When compared with mice treated with equivalent amounts of estradiol, the mice exposed to 4-NP had an increased risk of mammary cancer.[463]

Metals ■ ● ◇

Higher accumulations of iron, nickel, chromium, zinc, cadmium, mercury and lead have been found in cancerous breast biopsies as compared to biopsies taken from women without breast cancer. These metals also have been found in serum samples of women diagnosed with cancer as compared with healthy women.[464, 465]

Laboratory studies have shown that a number of metals including copper, cobalt, nickel, lead, mercury, tin, cadmium and chromium have estrogenic effects on breast cancer cells (MCF-7) cultured in vitro.[466, 467] 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 hormone-regulated cellular processes.[468]

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 in some varieties of nail polish, perfumes, skin moisturizers, flavorings and solvents. Phthalates have been found in indoor air and dust,[469] in human urine and blood samples.[470] Levels are highest in children ages 6 to 11 and in women.[471]

Phthalates are considered to be endocrine disruptors because of their complex effects on several hormonal systems including the estrogen and androgen hormone systems. The endocrine disrupting properties of this class of chemicals have been well established in the male offspring of

mother rats who had been treated with phthalates while pregnant. Abnormalities reported included nipple retention, shortened ano-genital distance and increased cryptorchidism (undescended testes).[472, 473] Exposure of human mothers to phthalates, as measured by chemical analysis of urine samples, has also recently been associated with shortened ano-genital distances in their newborn sons.[474]

Some phthalates including butyl benzyl phthalate (BBP) and di-n-butyl phthalate (DBP) act as weak estrogens in cell culture systems. They can bind to estrogen receptors (ER), induce estrogen-appropriate cellular responses and act additively with estradiol in altering these systems.[475, 476] BBP, DBP and another common phthalate, di-(2-ethylhexyl) phthalate (DEHP) significantly increase cell proliferation in MCF-7 breast cancer cells. In addition, these three phthalates inhibited the anti-tumor action of tamoxifen in MCF-7 breast cancer cells.[477]

In rat studies, phthalates have been shown to disrupt the development and functioning of male and female reproductive systems by interfering with the production of testosterone and estradiol, respectively.[478, 479] Phthalates also bind weakly to the androgen receptor (AR), disrupting the cellular actions ordinarily initiated by the androgens.[480] Those that bind the strongest to the AR, and therefore might be expected to exert the greatest effects through this pathway, include DBP, di-i-butyl phthalate and BBP.[481] The role, if any, this androgenic pathway might play in breast cancer development remains to be explained.[482]

Parabens ◇

Parabens are a group of compounds widely used as anti-microbial preservatives in food, pharmaceuticals and cosmetics products, including underarm deodorants. Parabens are absorbed through intact skin and from the gastrointestinal tract and blood. Measurable concentrations of six different parabens have been identified in biopsy samples from breast tumors.[483] The particular parabens were found in relative concentrations that closely parallel their use in the synthesis of cosmetic products.[484] Parabens have also been found in almost all urine samples examined from a demographically diverse sample of U.S. adults.[485]

Parabens have been shown to be weak estrogen mimickers, binding to the cellular estrogen receptor (ER).[486] They also increase the expression of genes that are usually regulated by estradiol and cause human breast tumor cells (MCF-7 cells) to grow and proliferate in vitro.[487]

Sunscreens (UV Filters) ◇

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 many 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.[488]

In a study of six common sunscreen chemicals, five of them exerted significant estrogenic activity, as measured by the increase in proliferation rates of human breast cancer cells (MCF-7 cells) grown in vitro. These chemicals were 3-(4-methyl benzylidene)-camphor (4-MBC), octyl-methoxycinnamate (OMC), octyl-dimethyl-PABA (OD-PABA), bexophenome-3 (Bp-3) and homosalate (HMS).[489] The results for 4-MBC have been repeated in another laboratory.[490]

A recent laboratory rat study has demonstrated that application of OMC to the skin of the animals enhances the penetration of the endocrine-disrupting herbicide 2,4-D.[491]

A Tale of Two Estrogens: BPA and DES

Bisphenol A (BPA) is one of the most universal chemicals in modern life, found in baby bottles, other food and beverage containers, linings of metal food cans, dental sealants and countless other products. It's also found in air, dust, rivers and estuaries — and in Americans of all ages, including newborns. More than 2 billion pounds of BPA are produced in the United States each year; globally, more than 6 billion pounds are produced. Worldwide, BPA generates an estimated $1 million a day in revenue for corporations such as Bayer, Dow, GE Plastics and Sunoco.

BPA is a result of the 1930s search for cheap synthetic estrogens, compounds designed to keep post-menopausal women "feminine forever" and to promote the rapid growth of cattle and poultry industry profits. Synthesized in 1936,[445] BPA was shunted aside two years later by a more potent synthetic estrogen: diethylstilbestrol (DES), now known to cause cancer and reproductive abnormalities in both males and females.[446]

Though they differ in potency, DES and BPA share striking similarities in their structures, functions and histories. Both chemicals:

- Were developed when the health effects of estrogen were poorly understood. Early animal studies linked both chemicals with increased risk of mammary and other cancers and reproductive abnormalities;
- Entered the food chain: DES as an intentional additive and BPA through food containers and packaging. DES was prescribed for pregnant women to prevent miscarriage (which it failed to do[447]) and BPA is associated with recurrent miscarriage as seen in a recent study from Japan;[448] and
- Were aggressively marketed, despite scientific evidence suggesting the need for caution. BPA is still marketed globally. The Food and Drug Administration (FDA) ignored the animal evidence of DES reproductive toxicity and approved the drug for medical use in humans in 1941, then for use during pregnancy and for use in livestock and chickens in 1947. When male agricultural workers exposed to DES suffered sterility and breast cancer, FDA banned the use of DES in poultry, but not in cattle or in women. Between 1938 and 1971, an estimated 5 to 10 million women in the U.S. were prescribed DES.[449] Use of DES in cattle continued into the 1980s.

In 1970, doctors noted an unprecedented number of rare vaginal cancers in young women whose mothers had taken DES during their pregnancy. Ultimately, DES proved to be a transgenerational carcinogen and a reproductive toxicant, resulting in an FDA alert on the drug. Subsequent research showed an indisputable cause-effect relationship between maternal use of DES and clear cell vaginal carcinoma in daughters. DES also increased the risk of breast cancer in the mothers, and studies now show that increased breast cancer risk extends to DES daughters. Decades of research on DES daughters and sons have shown that animal studies can be useful in predicting effects in people. More information on DES is available at www.cdc.gov/des.

Discarded as an estrogen replacement therapy pharmaceutical, BPA was rediscovered by polymer scientists in the late 1940s and quickly became a mainstay of the plastics industry. It is the building block of polycarbonate plastic and is also used in the manufacture of epoxy resins and other plastics, such as polyester and styrene.

Although never prescribed as a drug or deliberately added to foods, BPA enters the food chain by leaching from plastic packaging or containers as the plastic ages or is heated. Once

in food, BPA moves quickly into people, including placental tissue and umbilical cord blood, where it can disrupt normal prenatal development, even at low levels — parts per billion or parts per trillion.[450]

BPA exposure during critical windows of development has been linked with increased risk of breast, prostate and testicular cancer. It's also linked to birth defects, including neurobehavioral disorders, increased risk of miscarriage, decreased sperm production, early puberty in females, obesity and insulin-resistant diabetes.

One recent study showed that neonatal exposure to low levels of BPA causes uterine fibroids, cystic ovaries and precancerous lesions in female middle-aged mice. These results closely parallel the effects of comparable DES exposure.[451] In women, such effects are major contributors to infertility and the most common reasons for hysterectomy. For evidence connecting BPA and breast cancer see page 46.

Many scientists and the public are increasingly concerned about BPA because of (1) high production volume, (2) widespread human exposure and (3) evidence of reproductive toxicity in laboratory animals. Much of the research indicating health risks of early life exposure to BPA has occurred since 1995 and the accumulated evidence is compelling. However, the chemical is regulated based on research findings prior to 1984. The U.S. Environmental Protection Agency standard for BPA safety, called a reference dose, is 50 micrograms per kilogram of body weight, per day. Government studies indicate that human exposure may be 10 times that high.

Manufacturing Doubt

Manufacturers of BPA responded to concern about health risks by criticizing the evidence as controversial, limited and overblown. They called for more research. This all-too-familiar tactic has enabled many industries to continue profiting from tobacco, lead, asbestos, DES and other toxic products while damaging public health. When media reported early studies of BPA's estrogenic effects on the male reproductive system,[452] the chemical industry attacked, saying their scientists could not replicate the studies. Laboratories hired by chemical companies quickly produced studies that found no harmful effects.

A 2005 analysis of the BPA literature revealed a clear pattern of bias in reporting results: the funding source often determined the findings. Of 115 studies on health effects of BPA, 94 government-funded studies conducted in academic laboratories in Japan, Europe and the United States found adverse effects at low dose exposure. None of the studies funded by industry reported adverse effects.[453]

Leading scientists called for a new assessment of BPA based on mounting evidence of its DES-like effects. The National Toxicology Program (NTP) responded by appointing an advisory committee to assess the evidence and prepare a report. In March 2007, it was revealed that the advisory committee's report had been drafted by a private consulting firm with ties to the chemical industry. NTP fired the firm but accepted the report as unbiased.

When the advisory committee reconvened in August 2007 to review the report, leading BPA researchers testified about errors in the report, failure to consider the full range of evidence and reliance on flawed data from industry. The committee remained largely unconvinced, noting in their summary statement "some concern" only for pregnant women, fetuses, infants and children "that exposure to BPA causes neural and behavioral effects."

Neural and behavioral effects are a significant concern — particularly for women of childbearing age who are the first environment for babies. Four million babies are born each

year in the United States exposed to BPA in their mother's wombs. One in every six children in the U.S. suffers from some type of learning or neurobehavioral disorder, ranging from attention-deficit hyperactivity disorder to autism.[454] This amounts to as many as 640,000 children who are harmed each year — an enormous public health issue and a lifelong problem for children and families.

In a parallel process, a collaboration of 38 internationally recognized scientific experts on BPA and other endocrine disruptors published a more exhaustive analysis of the research on BPA, which included a consensus statement plus five peer-reviewed articles. Unlike the NTP committee, the international collaboration concluded: "The wide range of adverse effects of low doses of BPA in laboratory animals exposed both during development and in adulthood is a great cause for concern with regard to the potential for similar adverse effects in humans. Recent trends in human diseases relate to adverse effects observed in experimental animals exposed to low doses of BPA." [455]

Among the examples of trends they cited:

- Increase in breast and prostate cancer
- Uro-genital abnormalities in male babies
- Decline in semen quality in men
- Early onset of puberty in girls
- Metabolic disorders including insulin-resistant (type 2) diabetes
- Obesity in children and adults
- Neurobehavioral problems such as ADHD

The next step for NTP is to compile the data from the two reports, draft its own report and solicit public comment. Meanwhile, California may seek a Proposition 65 listing of BPA as a reproductive toxicant.

One other country has taken action on BPA. Norway has advised the World Trade Organization of its intention to prohibit BPA and 17 other substances from consumer goods in that country. This prohibition will include clothing, bags and toys but will not apply to food products or food packaging.[456] While this legislation applies only to Norway, it could become the new de facto standard for companies exporting to Europe since few companies will vary a product for one small market.

Regulation of the manufacture and use of BPA in the United States may be years away. Meanwhile, consumers can limit exposure to this chemical through the following measures recommended by the Environmental Working Group:

- Minimize the use of plastics, especially plastic wraps and containers, with the recycling label No. 7, which may contain BPA.
- Use glass baby bottles and dishes.
- Discard old, scratched plastic dishes and containers. Don't wash plastic dishes in the dishwasher using strong detergents, which can speed up wear and tear.
- Avoid canned foods and drinks.

Growth Promoters Used in Food Production (rBST and Zeranol)

Background

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 consumers involuntarily to contaminants that enter our bodies. Research suggests that some of these exposures may increase breast cancer risk.

Consumption of animal products also may hold inherent risks because animal fat can retain pesticides, dioxins and other environmental toxicants consumed by the animal. These lipophilic (fat-seeking) 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. Several studies indicate that these growth enhancers may elevate the risk of breast cancer. Concerns about this and other health risks have led the European Union to ban imports of growth-hormone treated beef, including meat from the United States, since 1989.[492]

Bovine Growth Hormone (rBGH)/ Recombinant Bovine Somatotropin (rBST) ◇

Despite opposition from physicians, scientists and consumer advocacy groups, the Food and Drug Administration in 1993 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.

Although the data are complex with some studies reaching different conclusions, several epidemiological studies have indicated a relationship between dairy consumption and breast cancer risk in pre-menopausal women.[493] In many of these studies the risks associated with dairy consumption was much higher than that found for meat consumption.[494]

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 pre-menopausal 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 post-menopausal women. Three studies reported in 2005 by scientists in Sweden, the United Kingdom[495] and the United States[496] also showed an association between circulating levels of IGF-1 and the risk of breast cancer in pre-menopausal women. These studies confirm earlier research linking elevated levels of IGF-1 with increased breast cancer risk.[497, 498, 499]

Laboratory studies have shown that IGF-1 can regulate the growth and increase the proliferation of breast cancer cells (MCF-7) grown in vitro[500] and decrease the death of mammary tumor cells in laboratory animals.[501]

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.[502]

Zeranol (Ralgro) ◇

One of the most widely used chemicals in the U.S. beef industry is zeranol (Ralgro). Zeranol is a potent nonsteroidal growth promoter that mimics many of the effects of the natural hormone estradiol.

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."[503]

A series of studies examined estrogenic activity in normal breast epithelial cells and breast cancer cells. Abnormal cell growth was significant even at zeranol levels almost 30 times lower than the FDA-established limit in beef.[504] Follow-up work demonstrated that zeranol is comparable to natural estrogen (estradiol) and the synthetic estrogen diethylstilbestrol (DES) in its ability to transform MCF-10A human breast epithelial cells to a pre-cancerous profile in vitro.[505]

Evidence Linking Other Chemicals of Concern to Breast Cancer

Benzene ■ ●

Benzene is one of the highest volume petrochemical solvents currently in production, and global production rates are expected to continue to grow over the next several years. Chemical industries estimate that more than 42 million metric tons (more than 105 billion pounds) of benzene will be produced globally by the year 2010.[506] Exposures to benzene come from inhaling gasoline fumes, automobile exhaust and cigarette smoke (primary and secondary) and from industrial burning. Benzene presents a serious occupational hazard for people exposed through their work in chemical, rubber and shoe manufacturing, and oil and gasoline refining industries. Both the NTP and IARC have designated benzene as a known human carcinogen.

Epidemiological studies of the effects of benzene on breast cancer risk are difficult to conduct, mainly because exposures to benzene occur in conjunction with exposures to other chemicals that are also released in combustion and manufacturing processes. Also, few of the occupational studies focusing on chemical and automotive industries have included women in substantial numbers to draw meaningful conclusions. In one study that did look at relevant occupations among female Chinese workers, the occupations in which elevated risks for breast cancer were found included scientific research workers, medical and public health workers, electrical and electronic engineers, teachers, librarians and accountants. In the same study, looking across professions, benzene exposure was associated with an elevated risk of breast cancer.[507] Results from recent studies examining occupational exposures among enlisted women in the U.S. Army[508] and women in different professions in Israel[509] support these conclusions.

The largest and most convincing study implicating benzene and associated chemicals comes from an occupational study looking at men who have been diagnosed with breast cancer. Men who had worked in professions that involved exposures to gasoline fumes and combustion had significantly increased rates of breast cancer. The effect was most pronounced among men who started at their jobs before the age of 40.[510]

Benzene administration to laboratory mice induces mammary tumors.[511] These animals have more mutations of genes that are responsible for suppressing the development of tumors.[512]

Other Organic 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 (including toluene, methylene chloride and trichloroethylene) have been shown to cause mammary tumors in laboratory animals.[513] Such solvents are also used in other industries, such as manufacturing of cleaning products and cosmetics.[514]

Organic solvents are lipophilic (fat-seeking) and accumulate in the fat tissue of the breast. They are also passed from mother to infant through breast- feeding.[515] Again, the known benefits of breast-feeding outweigh these environmentally caused hazards.

Several epidemiological studies have linked occupational exposures to organic solvents with increases in breast cancer incidence. Two recent studies showed an increased risk of breast cancer among workers exposed to chlorinated organic solvents in semiconductor plants.[516, 517] A Danish study showed that women ages 20 to 55 employed in solvent-using industries (fabricated metal, lumber, furniture, printing, chemical, textile and clothing industries) had double the risk of breast cancer compared to women employed outside these industries.[518] A 1995 U.S. study suggested an increased breast cancer risk associated with occupational exposure to styrene,[519] as well as with several other organic solvents including carbon tetrachloride and formaldehyde.[520] These results were validated by studies in Finland, Sweden and Italy.[521, 522, 523, 524]

Mixtures of organic solvents, similar to what might be seen in an industrial setting, induced dose-dependent increases in mammary tumors when young (pre-pubertal) laboratory mice were exposed to the chemicals.[525] Laboratory studies have shown that organic solvents are direct mutagens and carcinogens. That is, these chemicals and their breakdown products can exert direct effects on genes and cells, influencing the rates of gene mutation and altering cell processes in ways that increase the risk of cancer.[526]

Vinyl Chloride ■ ●

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.

Vinyl chloride was one of the first chemicals designated as a known human carcinogen by the National Toxicology Program (NTP) and IARC.[527] Vinyl chloride has also been linked to increased mortality from breast and liver cancer among workers involved in its manufacture.[528,529] Animals exposed long-term to low levels of airborne vinyl chloride show an increased risk of mammary tumors.[530]

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, with the main route of exposure being through inhalation. The National Toxicology Program classifies 1,3-butadiene as a known human carcinogen.[531] Data from research on animals indicate that females may be more vulnerable to the carcinogenic effects of 1,3-butadiene,[532] 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.[533, 534]

Ethylene Oxide ■ ●

Ethylene oxide is a fumigant used to sterilize surgical instruments and is also used in some cosmetics products.[535] Ethylene oxide is classified as a known human carcinogen and one of 48 chemicals that the National Toxicology Program identifies as mammary carcinogens in animals.

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 to ethylene oxide.[536] Although there are contradictory data in the recent literature, several other reports support the finding that exposure to ethylene oxide is associated with increased risk for breast cancer in women.[537]

Studies in which human breast cells grown in vitro were exposed to low doses of ethylene oxide demonstrated that the chemical exposure resulted in a significant increase in damage to the cells' DNA.[538]

Aromatic Amines ■ ● ◇

Aromatic amines are a class of chemicals found in the plastic and chemical industries, as byproducts of the manufacturing of compounds such as polyurethane foams, dyes, pesticides, pharmaceuticals and semiconductors.[539] 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.[540] There are three types of aromatic amines: monocyclic, polycyclic and heterocyclic.

In a project exploring aromatic amine levels in breast milk of healthy lactating women, three monocyclic amines, including *o*-toluidine, were identified.[541] O-Toluidine is known to cause mammary tumors in rodents.[542, 543] These data demonstrate both that the mother's mammary tissue is being exposed to environmental carcinogens during breastfeeding. Perhaps of greater concern is the concurrent exposure of her newborn child.

Heterocyclic aromatic amines (HAAs) are formed, along with PAHs, when meats or fish are grilled or otherwise cooked at high temperatures. A recent questionnaire study found an association between higher lifetime consumption of grilled meats and fish and increased incidence of post-menopausal breast cancer.[544] Studies of both milk and cells from the ducts of women's breast revealed the presence of DNA adducts in association with HAAs.[545, 546] These DNA adducts are indicators of problems in DNA repair in cells, one of the early hallmarks of tumor development.

Laboratory studies of HAAs in systems using cultured breast cancer cells demonstrate that these chemicals can mimic estrogen, and they also can have direct effects on cell division processes in ways that, if also found in in vivo studies with intact tissues, might enhance the development of tumors.[547]

Evidence Linking Radiation to Breast Cancer

Ionizing Radiation ■ ●

"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."[548]

— Charles E. Land

Overview and Mechanisms

Ionizing radiation is any form of radiation with enough energy to break off electrons from atoms (to ionize the atoms). This radiation can break the chemical bonds in molecules, including DNA molecules, thereby disturbing their normal functioning. X-rays and gamma rays are the only major forms of radiation with sufficient energy to penetrate and damage body tissue below the surface of the skin.

Among the many sources of ionizing radiation are traditional 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.[549]

In 2005, the National Toxicology Program classified X-radiation and gamma radiation as known human carcinogens. There is no such thing as a safe dose of radiation.[550, 551, 552, 553] A 2005 National Research Council report confirms this finding in stating, "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."[554] Radiation damage to genes is cumulative over a lifetime.[555] Repeated low-dose exposures over time may have the same harmful effects as a single high-dose exposure.

Exposure to ionizing radiation is the best- and longest-established environmental cause of human breast cancer in both women and men. Ionizing radiation can increase the risk for breast cancer through a number of different mechanisms, including direct mutagenesis (causing changes in the structure of DNA), genomic instability (increasing the rate of changes in chromosomes, therefore increasing the likelihood of future mutations)[556, 557, 558] and changes in breast cell micro-environments that can lead to damaged regulation of cell-cell interactions within the breast.[559, 560] Ionizing radiation not only affects cells that are directly exposed, but it can also alter the DNA, cell growth and cell-cell interactions of neighboring cells, referred to as the "bystander effect."[561, 562]

Interactions Between Radiation and Other Factors

There are a number of factors that may interact with radiation to increase the potency of its carcinogenic effect. Some of these factors include a woman's age at exposure, genetic profile and possibly estrogen levels. As examples:

- It has been well established in a number of studies of women exposed to military, accidental or medical sources of radiation that children and adolescents who are exposed are more seriously affected in their later risk for breast cancer than are older women.[563]
- Recent genetic data indicate that women with some gene mutations (e.g., *ATM*, *TP53* and *BRCA1/2*) are more likely to develop breast cancer and may be especially susceptible to the cancer-inducing effects of exposures to ionizing radiation.[564, 565]
- Studies using animal and in vitro human breast tumor cell culture models have demonstrated that the effects of radiation on mammary carcinogenesis may be additive with effects of estrogens.[566, 567, 568] This is of particular concern given the widespread exposure to estrogen-mimicking chemicals in our environment and the multiple sources of ionizing radiation.

Evidence Linking Ionizing Radiation and Breast Cancer Risk

The link between radiation exposure and breast cancer has been demonstrated in atomic bomb survivors.[569, 570, 571] Rates of breast cancer were highest among women who were younger than age 20 when the United States dropped atomic bombs on Hiroshima and Nagasaki.[572] In addition, scientists reported a significant association between ionizing radiation exposure and the incidence of male breast cancer in Japanese atomic bomb survivors.[573]

Use of X-rays to examine 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.[574] Decades of research have confirmed the link between radiation and breast cancer in women who were irradiated for many different medical conditions, including tuberculosis,[575] benign breast disease,[576] acute postpartum mastitis,[577] enlarged thymus,[578] skin hemangiomas,[579] scoliosis,[580] Hodgkin's disease,[581, 582, 583, 584, 585, 586, 587, 588] non-Hodgkin's lymphoma,[589] and even treatment for acne.[590] Again, evidence from almost all conditions suggests that exposure to ionizing radiation during childhood and adolescence is particularly dangerous with respect to increased risk for breast cancer later in life.

A recent study of female radiology technologists who had sustained daily exposures to ionizing radiation demonstrated an increased risk of breast cancer for those women who began working during their teens or, independent of age, working in the field before the 1940s, when exposure levels were substantially higher than they have been in more recent decades.[591, 592] And a recent review and analysis of all existing related studies found that women who work as airline flight attendants had increased levels of breast cancer. Factors that could explain this increase may include lifestyle and reproductive histories, as well as increased exposures to cosmic (atmospheric) ionizing radiation.[593]

Medical Radiation: Risks and Benefits

There is credible evidence that medical X-rays (including mammography, fluoroscopy and CT scans) are an important and controllable cause of breast cancer.[594,595] 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. Fortunately, the dose given per X-ray has been drastically reduced over the past several decades and the regulatory oversight of equipment and personnel has increased. In mammography, for example, efforts to reduce the radiation dose to as low as reasonably achievable (ALARA) levels have lowered the radiation dose from an estimated two rads in 1976 to 0.2 rads today, without compromising image quality.[596] Digital mammography can yield doses that are one-third those of conventional mammography.

There is credible evidence that medical X-rays are an important and controllable cause of breast cancer.

Patients who ask about the radiation dose involved in any medical procedure are sometimes dismissed with an answer that the dose 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.[597] 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.

Although there has been a significant decrease in exposures to ionizing radiation from individual X-rays, the introduction of CT scans in the 1970s greatly increased the radiation dose per medical examination. According to the National Cancer Institute, CT scans "comprise about 10 percent of diagnostic radiological procedures in large U.S.

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.

hospitals," but contribute an estimated 65 percent of the effective radiation dose to the public from all medical X-ray examinations.[598]

Some studies suggest that doctors and patients should carefully evaluate the risks and benefits of radiation therapy for survivors of early breast cancer, particularly older women. Women older than age 55 derive less benefit from radiation therapy in terms of reduced rate of local recurrence[599] and may face increased risks of radiation-induced cardiovascular complications,[600] as well as secondary cancers such as leukemias and cancers of the lung, esophagus, stomach and breast.[601, 602] Using SEER data from the National Cancer Institute, researchers showed a 16-fold increased relative risk of angiosarcoma of the breast and chest wall following irradiation to a primary breast cancer.[603]

Non-ionizing Radiation (Electromagnetic Fields)

Overview and Mechanisms

Electromagnetic waves 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. Microwaves, radio waves, radar and radiation produced by electrical transmission are examples of radiation sources that generate electromagnetic fields (EMF). Electric lighting generates electromagnetic fields. Fluorescent lighting and many types of low-voltage lighting produce fields that are particularly high compared to incandescent lighting. In addition, computers and many other types of wired and wireless electronic equipment (e.g., cell phones) all create electromagnetic fields of varying strengths.

IARC has classified EMF as possible human carcinogens based on the scientific literature related to EMF and childhood leukemias. In 1998, a National Institute of Environmental Health Sciences (NIEHS) EMF Working Group recommended that low-frequency EMF, such as those from power lines and electrical appliances, be classified as possible human carcinogens, again primarily based on evidence related to childhood leukemias.[604] However, consensus has been more difficult to reach about the relationship between EMF and breast cancer.

Exposure levels of EMF have increased exponentially in the past two decades due to the widespread use and deployment of wired and wireless technologies, including city-wide Wi-Fi networks in the United States and Europe. Everyone in industrialized countries is exposed to EMF from multiple sources every day, and many of these exposures are involuntary.

Despite rising exposure levels, there has been little U.S. federally funded research on the possible health effects of EMF in nearly a decade. Fortunately, research has continued internationally, and the results are troubling to scientists and the public about possible health effects. In August 2007, an international team of respected scientists released a summary analysis of the science on EMF and potential health concerns, including breast cancer and other cancers as well as neurodegenerative diseases and disorders. Called *The BioInitiative Report* (www.bioinitiative.org), it is based on a review of more than 2,000 studies. It calls for stronger safety standards on EMF exposure to prevent future cancers and other diseases and disorders. This report was endorsed by the European Environmental Agency (www.eea.europa.eu).

Evidence Linking Non-Ionizing Radiation and Breast Cancer Risk

Although not all epidemiological or occupational studies have found significant relationships between exposures to EMF and risk for breast

cancer,[605] many have found these effects. Methodological issues may account for some of the discrepancies, given the relatively small (but still statistically significant, and important in real lives) effects that are found and the ubiquitous nature of background EMF in our daily lives.[606]

A recent population-based case-control study in the United States looked at breast cancer risk in women who were exposed occupationally to low, medium or high levels of EMF in their respective work environments. Although the increases in incidence were low as EMF exposures increased, they were sufficiently robust to lead the authors to conclude that their results, "taken together with previous epidemiological studies, suggest that exposure to EMF in the workplace may be associated with a slight elevation in breast cancer risk."[607]

Recently, a second very large population-based, case-control study from Poland found an increased risk for breast cancer in women working in white-collar jobs such as marketing, advertising, management, engineering (electrical, computer, industrial, etc.), social science and economics. Increased risk was also found in blue collar jobs including machine operators in a variety of settings. No single chemical or other exposure can be linked to the occupations with excess risk, leading the authors to conclude that possible associations of these occupations with EMF deserve further attention.[608]

Norwegian researchers have 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. Pre-menopausal women showed an increased risk of estrogen-receptor-positive tumors and post-menopausal women had an increased risk of estrogen-receptor-negative tumors.[609]

Research on EMF exposure has shown increased mortality from breast cancer in women employed in the telephone industry.[610] Further, pre-menopausal women appear to be at higher risk than post-menopausal women.[611]

In 2004, a Norwegian study of residential and occupational 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 younger than age 50 who were exposed to EMF both at home and at work had a modest increase in risk of breast cancer. [612, 613]

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.[614] 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.

Norwegian researchers have 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.

Although breast cancer is rare in men, numerous studies point to a connection between EMF exposure and male breast cancer.[615, 616, 617, 618, 619] A recent literature review on male breast cancer also identifies exposure to EMF as a risk factor.[620]

EMF can also cause increases in mammary tumors in laboratory animals and in vitro systems in which human breast cell tumors are grown in culture. These live animal effects are found in some strains of animals but not others, indicating that subtle differences in genetic background might make some animals more susceptible to the carcinogenic effects of EMF.[621]

The mechanisms by which EMF can affect health are not completely understood. The most widely studied model is built on the finding that EMF exposure and increased light-at-night (LAN) lower the body's level of melatonin, a hormone secreted by the pineal gland during darkness.[622] Through complex interactions with estrogens and cell signaling pathways,[623] melatonin appears to have anti-cancer properties.[624] In a variety of laboratory animal and in vitro systems, melatonin has inhibited the growth of mammary tumor cells.[625]

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.[626, 627, 628] A recent prospective study indicated that higher melatonin levels were associated with a lower risk of breast cancer.[629]

Although breast cancer is rare in men, numerous studies point to a connection between EMF exposure and male breast cancer.

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.[630, 631, 632]

Moving Forward: Breast Cancer Fund's Policy and Research Recommendations

Building a Movement: The Role of Breast Cancer and Environmental Health Advocates

Since our founding in 1992, the Breast Cancer Fund has mobilized the public to secure the institutional and legislative reforms necessary to identify and eliminate the environmental links to breast cancer. We have proven that working at the local and state level is an effective way to achieve success and to build models that can be replicated in other regions. BCF's education and advocacy efforts are playing an important role in making breast cancer prevention a priority on local, state and national levels for a wide variety of populations, including those who have faced breast cancer, those committed to preventing it and those concerned more generally about environmental health.

Our goal is to bring a deep understanding of environmental health to breast cancer advocates and bring the powerful voice of breast cancer prevention advocates to the environmental health and justice movement.

Moving Forward was written for breast cancer prevention, women's health, environmental health and environmental justice advocates. It is also intended for others interested in developing policy and research agendas at the state and federal levels that call for the identification and elimination of the environmental links to breast cancer. Our goal is to build bridges among these important advocacy communities, bringing a deep understanding of environmental health to breast cancer advocates, and bringing the powerful voices of breast cancer prevention advocates to the environmental health and justice movement.

Toward this end, important organizing is already taking place through the Collaborative on Health and the Environment's (CHE) Consensus Statement on Breast Cancer and the Environment. This consensus statement, signed by nearly 100 organizations and individuals from around the country, acknowledges the growing body of scientific evidence demonstrating that human health and the environment are intimately linked. The statement calls for prevention-oriented public health policies and a precautionary approach to chemical policy that makes protecting human health its top priority. (See www.healthandenvironment.org/working_ groups/br_cancer for more information.)

A national study by Silent Spring Institute found that leaders of grassroots breast cancer advocacy groups want to know how the environment contributes to cancer and strongly support environmental research and precautionary public health policies. Across the country, breast cancer survivors — and others touched by breast cancer — are speaking with the kind of authentic and powerful voices that make elected officials and other high-level policy-makers stop and listen. They have the power to raise awareness — and indignation — throughout the states and inspire action to change the status quo. It is our hope that this guide will serve to educate and inspire breast cancer prevention *and* environmental health advocates everywhere to move legislation through their state capitols, thereby creating a ripple effect of change that will reach the halls of Congress.

How to Use This Advocacy Guide

This guide is not meant to present an exhaustive list of public policy and research initiatives needed to fully eliminate the environmental links to breast cancer. Instead, it is meant to present a menu of different options and ways advocates — and policy-makers — can be active in breast cancer prevention from a policy and research perspective.

Each section in this advocacy guide is introduced by a brief description of a key environmental exposure linked to breast cancer and/or specific tool needed to reduce exposures. These introductory paragraphs are followed by state policy, federal policy and research recommendations.

Federal and State Policy Recommendations are directed toward any governmental body capable of making policy by means of regulation, legislation or executive order including regulatory agencies, state legislatures, the U.S. Congress, governors and the President of the United States. Governmental agencies that have primary jurisdiction over issues related to breast cancer and the environment tend to include state and federal departments of health and environmental protection agencies. However, at the state level, agencies that regulate air, water and pesticides can also implement policy to protect against environmental exposures.

Research Recommendations: Funding for breast cancer research in the U.S. comes from many sources: the federal government through appropriations to agencies such as the National Institutes of Health (NIH) and the Department of Defense (DOD); state-based programs such as the nonprofit California Breast Cancer Research Program; the nonprofit sector, such as through organizations like Susan J. Komen for the Cure and the Avon Foundation; and the public sector, such as from pharmaceutical companies that support university research. Each funding stream represents a pressure point where advocates can push for the breast cancer research that matters to them.

Reduce Exposure to Radiation and Synthetic Chemicals

Reduce Exposure to Radiation

Ionizing Radiation

Ionizing radiation is the best- and longest-established environmental cause of breast cancer. There is no safe dose of radiation, and the genetic damage caused by radiation accumulates over a lifetime. Therefore, multiple exposures to low-dose radiation may cause the same harm as a single high-dose exposure. Radiation exposure in combination with exposure to certain synthetic chemicals — in different doses and during key developmental windows — can magnify the effect of radiation and/or result in greater susceptibility to chemical insults in the future.

Exposure to ionizing radiation occurs during medical and dental X-rays, computed tomography (CT) scans, fluoroscopy and other imaging procedures. Diagnostic and therapeutic radiation are invaluable in the practice of medicine and dentistry today. Yet, not all equipment or procedures are subject to the same standards, even though legislation to establish federal standards, has been introduced in every Congress since 1999. Mammography equipment has a higher quality assurance standard than other radiological equipment as a result of the Mammography Quality Standards Act. Currently seven states do not license radiation technologists and four more only partially license.[633] Because most states only have *recommended* quality assurance (QA) standards — if they have standards at all — many medical and dental offices do not perform the required tests that ensure the standards are maintained.

Moving Forward:

FEDERAL POLICY:

- The highest possible standards should be established at the federal level to achieve consistency among the states. Advocates should support The 2007 Consistency, Accuracy, Responsibility and Excellence in Medical Imaging and Radiation Therapy bill (CARE bill), which requires:

  1. People performing medical imaging and radiation therapy meet federal education and credential standards in order to participate in federal health programs such as Medicare, Medicaid and other programs administered by the Department of Health and Human Services; and

  2. Medical imaging examinations and procedures, as well as radiation therapy treatments for patients covered under these programs, would need to be performed by personnel meeting the federal standards to be eligible for reimbursement.

STATE POLICY:

- States should adopt quality assurance standards for all radiation-emitting equipment that meet or exceed standards currently in place for mammography equipment. State QA standards should require physicians and technologists to use the smallest dose of radiation possible to capture the highest quality image. All states should require licensing of radiation technologists.
- Standards should be established by appropriate state agencies so health care providers can more effectively measure and track their patients' lifetime cumulative exposure to ionizing radiation. Ideally, electronic medical records should include patients' exposure to diagnostic and therapeutic radiation.
- States should mandate the use of educational materials in health care facilities to improve patient and physician awareness of the benefits and risks of radiological procedures. Radiation tracking cards should be provided to patients so they can track their cumulative exposure to ionizing radiation and make more informed decisions about optional procedures.

RESEARCH REQUIRED:

- Research is needed to develop safer, non-invasive technologies for breast cancer screening, diagnosis and treatment.
- Research is needed to better understand the possible cumulative, additive and synergistic effects that could result from combined exposure to toxic chemicals and ionizing radiation.

Non-Ionizing Radiation (Electromagnetic Fields)

Continuous daily exposure to electromagnetic fields (EMF) is a fact of life for everyone living in the industrialized world. EMF is a type of low-intensity non-ionizing radiation that has insufficient energy to break off electrons from their orbits around atoms and ionize (charge) the atoms. EMF includes extremely low frequency radiation (ELF-EMF) from electrical appliances and power lines and radiofrequency (RF) radiation from wireless technologies such as cell phones, cordless phones, personal data assistants, laptops, the towers and antennas that support these technologies and broadcast transmission towers.

Decades of research indicate that exposure to EMF is associated with many adverse health effects including breast cancer (in both men and women) and other cancers, neurodegenerative diseases and impaired immune function. Existing public exposure standards for EMF are inadequate to protect public health because they are based on a short-term (30-minute) thermal effect. In other

words, the assumption is that unless heating of tissue occurs within 30 minutes, no harm can result.

There are no federal guidelines for non-thermal effects or long-term chronic exposure. A growing body of international research challenges that assumption and experts around the globe are debating the need to strengthen the standards based on newer science showing health risks of chronic, widespread low-level exposure. In September 2007, Germany's Federal Office for Radiation Protection advised citizens to avoid Wi-Fi wherever possible because of the risks it may pose to health. In the same month, the European Environmental Agency (EEA) called for immediate action to reduce exposure to radiation from Wi-Fi, mobile phones and their masts[634] based on an international scientific review which concluded that safety limits set for these types of radiation are "thousands of times too lenient."[635] In the U.S. there has been little federally funded research on EMF despite the explosion of wireless technologies, particularly cell phones. Rapid expansion and deployment of wireless technologies are outpacing the policy decisions necessary to protect public health.

Breast Cancer Fund supports *The BioInitiative Report* statement that the scientific evidence is sufficient to warrant regulatory action for extremely low frequency electromagnetic fields (ELF-EMF), and it is substantial enough to warrant preventive actions for radiofrequency (RF) radiation.

Existing government limits do not protect the public from adverse health effects of electromagnetic radiation emanating from devices such as power lines, cell phones, wireless Internet, radar and TV and FM broadcast towers. Most of the existing limits on this form of radiation are 1,000 to 4,000 times too lenient to prudently protect humans from cancers in children and adults, and from Alzheimer's and other neurodegenerative diseases, reproductive problems, immune function disruption, electrohypersensitivity and symptoms such as insomnia, headaches, memory loss, concentration and attention difficulties.

Moving Forward:

FEDERAL POLICY:

- Based on the scientific evidence set forth in *The BioInitiative Report* (www.bioinitiative.org) and a growing body of additional research, exposure limits for electromagnetic radiation should be set at the federal level for:
  1. Extremely low frequency electromagnetic fields (ELF-EMF) including power lines, appliances, interior electric wiring and other devices; and
  2. Long-term and cumulative radiofrequency (RF) radiation from outdoor pulsed sources including cell phone antennas, radar, TV and FM broadcast antennas and wireless Internet antennas; and from indoor sources including cell phones, wireless Internet equipment and radiation that permeates buildings from outdoor sources.[636]
- With the setting of federal limits for non-ionizing radiation, special protections should be required for homes, schools and places where children spend large amounts of time.

RESEARCH REQUIRED:

- Research is needed to quantify and monitor the levels and characteristics of ELF-EMF and RF radiation present in schools, workplaces and residential neighborhoods now and into the future.
- Research is needed to determine the effects of chronic exposure to ELF-EMF on women recovering from breast cancer and other cancers.

Reduce Exposure to Toxic Chemicals

There is consensus around the globe that our failure to adequately assess and regulate chemicals is taking a toll on the health of humans and the environment. Evidence of public and environmental health problems related to chemical exposures continues to grow. With the passage of its new law on chemicals,

REACH (Registration, Evaluation, Authorization and Restriction of Chemicals), the European Union is leading the way on the international stage to protect human health and the environment through the better and earlier identification of the properties of chemical substances.

Current Work at the Federal Level

Although there are 80,000 chemicals registered for commerce in the U.S., with 1,000 new chemicals entering the market each year, little is known about the toxicity of the chemicals the public is exposed to every day. The federal statute intended to regulate chemicals before and after they enter commerce is the Toxic Substances Control Act of 1976 (TSCA).

Studies by the National Academy of Sciences, U.S. Government Accountability Office and U.S. Environmental Protection Agency, among others, have concluded that TSCA does not adequately help the public, industry or government to assess the hazards of chemicals in commerce or control those of greatest concern.[637] Attempts to reform this inadequate chemicals policy are underway in Congress. The most recent and promising was the Kids' Safe Chemical Act of 2005, soon to be reintroduced in the 110th Congress.

Current Work at the State Level

Along with activity in Congress and efforts at the federal level by non-governmental research and advocacy groups, there have been some state efforts to better understand and regulate unsafe chemical exposures, such as Proposition 65 in California. Proposition 65 requires the governor to publish, at least annually, a list of chemicals known to the state to cause cancer or reproductive toxicity. Businesses are required to provide a "clear and reasonable" warning before knowingly and intentionally exposing anyone to a listed chemical.

But while these efforts are a step in the right direction, they are not comprehensive enough to fix the broken chemical regulatory system. More promising are the individuals and organizations working hard at the state level on chemicals policy reform through the State Alliance for Federal Reform of Chemicals Policy (SAFER).

There is consensus around the globe that our failure to adequately assess and regulate chemicals is taking a toll on the health of humans and the environment.

SAFER is a strategic campaign whose long-term vision is to establish a new precautionary federal chemicals policy that is the basis of a clean, green economy by 2020. SAFER is composed of environmental health and justice coalitions in eight states including California, Connecticut, Maine, Massachusetts, Michigan, Minnesota, New York and Washington.

Synthetic chemicals registered for use in U.S. today	**80,000***
Chemicals added to registry each year	**1,000***
Portion of registered chemicals with complete toxicological screening data	**7%****

* Environmental Protection Agency, Office of Pollution Prevention and Toxics (2007). Overview: Office of Pollution Prevention and Toxics Programs.

** Bennett ML, Davis BJ. Identification of Mammary Carcinogens in Rodent Bioassays (2002). Environmental and Molecular Mutagenesis. 39:150-157.

Moving Forward:

FEDERAL POLICY:

- As expressed by the Louisville Charter (www.louisvillecharter.org), a full-scale overhaul of TSCA is needed that (1) requires safer substitutes and solutions, (2) phases out persistent, bio-accumulative or highly toxic chemicals, (3) gives the public and workers the full right-to-know and participate, (4) acts on early warnings, (5) requires comprehensive safety data for all chemicals and (6) takes immediate action to protect communities and workers.
- Federal legislation is needed that requires manufacturers to provide health and safety information to government agencies before releasing a chemical into commerce, instead of presuming a substance is safe until proven dangerous. Comprehensive federal chemical policy reform should protect the most vulnerable (children, women of childbearing age, people with weakened immune systems and the elderly) and those who bear an unequal burden of chemical exposures (workers, fenceline communities, etc.).
- Federal tax incentives are needed to stimulate investments in green chemistry.
- Federal legislation should require chemical manufacturers to pay a fee to register their chemicals to offset the financial burden, similar to the model of the Federal Insecticide, Fungicide, Rodenticide Act/Food Quality Protection Act (FIFRA/FQPA), in which pesticide manufacturers pay a fee to register pesticides. Proceeds could offset the costs of monitoring and data collection to evaluate post-market impacts.

STATE POLICY:

- States should take on the regulatory authority the federal government has been unwilling to accept to protect the public from chemical exposures including, as listed above, the core components of the Louisville Charter.
- States should prioritize protection of the most vulnerable populations by requiring the phase-out of chemicals that harm developing fetuses.
- State policies should require that manufacturers provide comprehensive health and safety data for chemicals; information about where and how chemicals are used in consumer products and industrial processes; and the availability of safer alternatives. This information should be made readily available to the public and should also be made available for data-sharing among states. States should require the labeling of chemicals linked to adverse health effects in consumer products. If health data is not available for a chemical ingredient, labeling should state that the health and safety of that chemical ingredient is unknown and/or cannot be substantiated.
- States should institute producer-take-back rules requiring manufacturers of computers and other products made with toxic materials to take back and reuse or recycle their products to reduce the quantity of waste that goes to landfills, where it can leach into soil and water.
- States should encourage market innovation and reform by mandating the purchase of non-toxic products by all state agencies through their procurement policies.
- States should augment undergraduate and graduate chemistry curricula with green chemistry classes such as coursework in toxicology, exposure assessment, ecology and environmental science.

RESEARCH REQUIRED:

- Pre-market testing of new chemicals and post-market testing of legacy chemicals (such as PCBs, DDT, etc.) are needed to assess the impacts of all chemicals on human health, worker health and environmental health.
- Green chemistry research is required to identify

or create safer alternatives to toxic chemicals used in manufacturing and industrial processes.

Air Contaminants

According to Silent Spring Institute (SSI)'s 2007 comprehensive scientific review of environmental links to breast cancer,[638] 216 chemicals have been associated with increases in mammary gland tumors in animals. Of those, 35 are air pollutants. There is widespread public exposure to many of these chemicals in outside air, offices, homes, restaurants and schools. Another 2007 SSI review of studies of human populations[639] found that the evidence generally supports an association between breast cancer and ubiquitous air pollutants called polycyclic aromatic hydrocarbons (PAHs). And, while human studies are limited in number, evidence also points to an association between breast cancer and two other chemical families of air pollutants: dioxins and organic solvents.

Most of the air pollutants can be found in primary and secondhand tobacco smoke, diesel exhaust and/or in specific occupational settings (see summary of evidence on air pollutants and breast cancer on page 48). According to the California Air Resources Board there are 20 mammary carcinogens in tobacco smoke alone. In 2006, California EPA determined that "overall, the weight of evidence…is consistent with a causal association between [environmental tobacco smoke] exposure and breast cancer in younger, primarily pre-menopausal women."

Moving Forward:

FEDERAL AND STATE POLICY:

- States should adopt environmental (second-hand) tobacco smoke bans in all public locations, including restaurants and bars. There are 26 states/commonwealths plus the District of Columbia with laws in effect that require 100 percent smoke-free workplaces and/or restaurants/bars.[640]
- States should follow California's lead and adopt tough emission standards for off-highway diesel vehicles like bulldozers, airport baggage trucks and ski resort snowcats. Diesel engine exhaust contains, among other toxic substances, PAHs, which rose to the top of the list of breast carcinogens in a 2007 review by the Silent Spring Institute.
- There are many outstanding organizations working on reducing air pollution. Visit their Web sites for other recommendations — both personal and political — for reducing air contaminants like PAHs, tobacco smoke and diesel exhaust:
  - Natural Resources Defense Council, Air Program, www.nrdc.org/air
  - Environmental Defense, Clean Air for Life, www.environmentaldefense.org/
  - American Lung Association Action Network, www.lungaction.org/

RESEARCH REQUIRED:

- Increase the number of chemicals that are monitored in the ambient air. Air toxicants (188 hazardous air pollutants as defined by the EPA) should be tracked in addition to the six criteria pollutants required by the Clean Air Act. This data should be supplemented with personal monitoring (for example, devices used on kids to monitor their exposure to diesel exhaust from school buses) and biomonitoring studies in impacted areas, disproportionately affected communities or health-affected groups.
- Occupational studies that look at workers regularly exposed to air pollutants like PAHs, tobacco smoke, diesel exhaust and organic solvents should be prioritized.

Pesticides

Some pesticides and herbicides have been labeled as human or animal carcinogens and many are found in water supplies as well as in air and dust in homes.

Though banned in the U.S in 1972, dichloro-diphenyl-trichloroethane (DDT) and its metabolite DDE are still found in the body fat of humans and animals, and in human breast milk and placenta. The triazine herbicides — atrazine, simazine and cyanazine — have all been shown to cause mammary cancer in rats. Atrazine, the most studied of the three, is of particular concern for breast cancer because it disrupts — in fact increases — the activity of aromatase, which can lead to more estrogen in the body. Through different mechanisms, three other pesticides — heptachlor, dieldrin and aldrin — have also been shown to increase estrogen levels and/or stimulate growth of breast cancer cells.

Of particular concern is the health of agricultural workers and their families, and communities affected by pesticide drift. Biomonitoring studies of children of agricultural workers revealed that high levels of pesticides can be found in the children's urine soon after application in the fields near their homes. Many pesticides are endocrine disruptors, so this is a concern for children's exposures during susceptible windows of development.

Moving Forward:

FEDERAL POLICY:

- Advocates should pressure the EPA to follow the lead of the EU and ban the use of atrazine in the U.S.
- Advocates should pressure the EPA to ensure that the Endocrine Disruptor Screening Program gets underway as mandated by Congress, and that the EPA screens these chemicals and makes the results readily available to the public without delay.
- Strengthened pre-market health and safety testing and regulation of pesticides should be included in comprehensive chemical policy reform, as discussed on page 68.

STATE POLICY:

- In the absence of federal legislation, states should either ban or label the use of chemicals in home pesticides linked to endocrine disruption, carcinogenesis, central nervous system disruption and reproductive disorders and encourage the use of safer substitutes.
- States and municipalities should ban the use of "cosmetic" pesticides and the use of pesticides in parks. In Canada, support is growing (mostly at the municipal level) for bans on cosmetic — purely aesthetic — use of pesticides, where the weed or pest poses no danger to human health, the environment or property. The cities of San Francisco and Oakland, Calif. have banned the use of pesticides in their parks for years. Efforts like these that aim to end the non-essential uses of pesticides should be supported and ultimately written into state legislation.
- States should ban the use of pesticides on or near school grounds, including day care centers and nurseries.

RESEARCH REQUIRED:

- Moving away from toxic, endocrine disrupting pesticides will require a just transition strategy and viable alternatives. A significant national investment in integrated pest management research is essential and long overdue.
- More research is needed on the cumulative exposures of agricultural workers and their families to first, protect their health and second, gain a greater understanding of the role of pesticides in the development of breast cancer and other diseases.

Consumer Exposures

Each day, consumers use products that contain chemicals untested for impacts on human health and the environment. Consumers have the power to send a clear message to companies that we want safe products. By joining with other consumers

through market-based corporate accountability campaigns such as the Campaign for Safe Cosmetics, they can wield enormous power and expand the market share for safe products. Below we focus on the potential impacts of toxic chemicals on breast cancer; however, reducing human exposure will also keep these chemicals out of our air, waterways, soils and ice caps to reduce exposure for all animals, including humans.

Plastics

Plastics are widely used in consumer products and packaging of all kinds. There are, however, serious risks to human health and the environment from the widespread use of plastics. Most plastics are made from petroleum, a non-renewable resource. Not all plastic is recycled and millions of bottles go to landfills every year, where they will continue to leach chemicals into the environment for many generations. Even worse, many plastic products end up in the ocean where they have formed enormous flotillas of plastic, harming plankton and the entire food chain of fish, turtles and birds that depend on these tiny creatures.

The three plastics that have been shown to leach toxic chemicals when heated, worn or put under pressure are polycarbonate (leaches bisphenol A), polystyrene (leaches styrene) and PVC (leaches phthalates).[641] Bisphenol A is used in the linings of cans, baby bottles, sports water bottles and dental sealants. The evidence about bisphenol A and its many effects on human health is convincing and growing. Studies funded by the chemical industry say it's harmless; non-industry studies show it's a powerful hormone-disruptor linked to breast cancer. (See page 46 to learn more)

Phthalates, another chemical family of concern, are found in many consumer products including rubber ducks, other children's bath toys and teething toys, and are used to soften plastics, especially PVC. Phthalates are endocrine disruptors that increase the risk of early puberty in girls (and therefore, breast cancer) and have been linked to reduced testosterone levels, lowered sperm counts, genital defects in baby boys and testicular cancer in young men.

Moving Forward:

FEDERAL POLICY:

- As highlighted above, the public should pressure the EPA to fully implement the Endocrine Disruptor Screening Program as mandated by Congress to effectively and efficiently screen chemicals for hormonal activity and to make the results readily available to the public without delay.
- Congress should ban the manufacture, distribution and sale of consumer products containing bisphenol A and phthalates.

STATE POLICY:

- In the absence of federal regulation, states should either ban or label the presence of endocrine disrupting chemicals like bisphenol A and phthalates in all consumer products.
- Until then, advocates should support legislation at the state level (like the Toxic Toys Bill of 2007 in California) that reduces children's exposures to endocrine disrupting chemicals in consumer products.

RESEARCH REQUIRED:

- Invest in green chemistry research on bio-based plastics that can be composted after they have been used in consumer products.
- Human studies are needed that look at exposure to endocrine disrupting chemicals — like bisphenol A and phthalates — and breast cancer outcomes. This may require an investment in new methodologies because exposure to these chemicals is so widespread in the population, challenging currently available testing methods. These limited (and expensive) human studies should both inform and be informed by

The Connection Between Plastic and Breast Cancer

Plastic	Breast Cancer Fund Rating	Link to Breast Cancer		Explanation	Source of Exposure in Consumer Products
		Carcinogen By-product of Manufacturing[i, ii]	Hormone Disruptors Can Leach Out[iii]		
#1 PET PETE Polyethylene terephthalate ethylene	OK				Soft drink, juice, water, detergent and cleaning product bottles
#2 HDPE High density polyethylene	OK				Opaque plastic milk and water jugs; bleach, detergent and shampoo bottles; some plastic bags
#3 PVC Polyvinyl chloride	Avoid	X	X	Vinyl chloride and dioxin, both known human carcinogens (NTP and IARC), are formed in manufacturing; dioxin is also a hormone disruptor; hormone disrupting phthalates can leach out of PVC.	Cling wrap; some plastic squeeze bottles; cooking oil, detergent and window cleaner bottles; toys; vinyl shower curtains; wall and floor coverings
#4 LDPE Low density polyethylene	OK				Grocery store bags, most plastic wraps, some bottles
#5 PP Polypropylene	OK				Most reusable food-storage containers; straws; syrup, yogurt and other other clouded plastic containers; some baby bottles
#6 PS Polystyrene	Avoid	X		Styrene can leach from polystyrene, is an animal mammary carcinogen and is possibly carcinogenic to humans (IARC).	Styrofoam food trays, egg cartons, disposable cups and bowls and carryout containers; opaque plastic cutlery
#7 Other Usually polycarbonate	Avoid		X	Hormone-disrupting bisphenol A can leach from polycarbonate under heat and pressure or as plastic ages.	Most plastic baby bottles, 5-gallon water bottles, "sport" water bottles, metal food can liners, clear plastic "sippy" cups, dental sealants, some clear plastic cutlery

Note: Portions of table above based on Smart Plastics Guide: Healthier Food Uses of Plastics, Institute for Agriculture and Trade Policy, www.iatp.org/foodandhealth

i. Silent Spring Institute's Science Review published in Cancer in 2007 includes information on 216 animal mammary gland carcinogens. www.sciencereview.silentspring.org

ii. International Agency for Research on Cancer (IARC) carcinogenic risk classification is based on evaluation of potential tumor development at all sites, not only breast/mammary tissue. Categories include: Known, Probable, Possible and others. The National Toxicology Program (NTP), within the National Institute of Environmental Health Sciences of the National Institutes of Health, provides carcinogenicity ratings based on scientific evidence in both animals and humans. Categories include: Known, Reasonably Anticipated, and others. (Report on Carcinogens, Eleventh Edition; U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program.) Not all chemicals have been rated by IARC or NTP.

iii. To date, neither the NTP nor IARC has classified most endocrine disruptors as carcinogens in humans. List of endocrine disruptors from: Brody JG, Rudel RA (2003). Environmental pollutants and breast cancer. Environmental Health Perspectives 111: 1007-1019.

Atrazine, Frogs and Breast Cancer

Atrazine, a triazine herbicide, has been banned in the European Union since 2005. The U.S. EPA concluded it was an endocrine disruptor in 2000 but that didn't stop farmers from using 77 million pounds of it in the U.S. in 2003.

Sixty percent of Americans are regularly exposed to atrazine, an herbicide that may be negating the positive effects of breast cancer medications.

Atrazine has been shown to cause mammary cancer in lab rats. Recent data suggest that the major mechanism by which atrazine exerts its endocrine disrupting effects is by increasing the activity of the enzyme aromatase. Aromatase facilitates the conversion of testosterone and other androgens to estrogens, including estradiol.

Apparently, this pathway of estrogen production is of great enough importance to the development of breast cancer that a current class of breast cancer drugs aims to block this activity of aromatase. Femara (Letrozole) is one of these drugs. It knocks out aromatase, which in turn reduces estrogen and keeps breast cancer cells from growing initially.

Dr. Tyrone Hayes at the University of California at Berkeley has spent his career examining atrazine and its effect on the growth and development of frogs. He has shown that atrazine chemically castrates and feminizes male amphibians in the wild and in the lab. He suggests that atrazine-induced deformities result from the depletion of androgens and production of estrogens, perhaps after atrazine increases the activity of aromatase.

When Dr. Hayes presents his research, he often tells this story: The maker of atrazine is Syngenta, a multi-national agrichemical corporation. Syngenta was formed in 2000, when another multi-national called Novartis merged their Crop Protection and Seeds businesses with Astra Zeneca's Agrochemicals.[642] What is interesting and very disturbing, he argues, is that Novartis is also the producer of Femara, the breast cancer drug discussed above. And so, Dr. Hayes points out, the very company that produces atrazine (that "turns on" aromatase, thereby increasing estrogen which can lead to breast cancer cell growth) is also producing — and selling at great profit — a medication that has the opposite effect (to "turn off" aromatase).

Sixty percent of Americans are regularly exposed to atrazine, an herbicide that may be negating the positive effects of breast cancer medications. Meanwhile, the company that stands to profit from sales on both sides of the equation is in Switzerland, where luckily, atrazine is banned.

Presentation at Women's Health and the Environment: New Science, New Solutions. *Silent Spring to Silent Night: Hermaphroditic Frogs, Breast Cancer and Pesticides. Keynote address:* Tyrone Hayes, Ph.D., University of California, Berkeley. www.womenshealthpittsburgh.org/podcasts.html

targeted animal studies. Coordination of these two research models is critical to moving the research forward.

Household Cleaning Products

There are thousands of household cleaning products on the market. A quick trip through the grocery store reveals hundreds of products from spot removers and glass cleaners to mold removers and toilet bowl cleaners, among others. Like so many other chemicals in consumer products, household cleaners provide little information on their packaging about risks to the environment and human health. If they do, it's usually an acute health advisory like "use in well ventilated area." There is no mention of possible long-term human health or ecological effects. The government provides very little oversight of these products and yet consumers are exposed to them every day.

Certain occupations are especially vulnerable to the effects of toxic cleaning products. Housekeepers and custodians are heavily exposed to cleaning chemicals and are often not given any information about health effects or safety precautions. What's more, little exposure assessment has been done in these occupations. Critical information needed to inform public health interventions has not been collected.

Moving Forward:

FEDERAL AND STATE POLICY:

- In the absence of federal regulation, states should either ban or require the labeling of chemicals linked to cancer and other long-term health effects in cleaning products so consumers can make informed and safer purchases.

RESEARCH REQUIRED:

- Invest in research in green chemistry to replace toxic chemicals in cleaning products with safe alternatives.
- Occupational research is needed that looks at workers regularly exposed to cleaning products and the possible linkage to breast cancer later in life. Use of biomarkers of exposure and early disease should be explored as soon as possible to shorten the length of the study and allow for occupational health interventions.

Hormones in Meat and Milk

Modern food-production methods have introduced new environmental exposures to carcinogens and endocrine-disrupting compounds. Pesticides on crops, antibiotics in poultry and hormones in cattle, sheep and hogs expose consumers involuntarily to unsafe contaminants every day. Consumption of animal products may hold inherent risks because animal fat can retain pesticides and other environmental toxicants consumed by the animal and research suggests that some of these exposures may increase breast cancer risk.

Since its introduction in 1993, bovine growth hormone (rBGH/rBST) has proven controversial because of its potential carcinogenic effects. Several studies have shown an association between dairy consumption and breast cancer in pre-menopausal women. rBGH has been shown to raise insulin-like growth factor 1(IGF-1) levels in the body; which have, in turn, been associated with an increased risk of breast cancer. Another food additive of concern is zeranol, a growth promoter used in the beef industry that mimics the effects of natural estradiol in the body.

Moving Forward:

FEDERAL AND STATE POLICY:

- In the absence of federal regulation, states should either ban or label the presence of hormones in meat and milk so consumers can make informed and safer purchases.

Household Cleaning Products and Human Health Concerns

Chemicals Found in Cleaning Products	Human Health Concern				Source of Exposure in Cleaning Products
	Carcinogen	Central Nervous System	Reproductive Toxin	Endocrine Disruptor	
Diethanolamine		X			Cleaners, degreasers
Diethylene Glycol Monomethyl Ether			X		Floor finish, cleaner and polish
Diethylene Glycol Monoethyl Ether		X	X		Floor finish, tile and grout cleaner, microwave oven cleaner
Dibutyl Phthalate		X		X	Floor finish, floor shine and hardener
Nonylphenol Ethoxylate				X	Cleaners, degreasers, foaming cleaner, air freshener, spot and stain pretreater, metal polish
Octylphenol Ethoxylate				X	Cleaners, degreasers, surface deodorizer
n-Methyl Pyrolidinone			X		Floor finish, stripper, floor cleaner
Nitrilotriacetic Acid	X NTP Reasonably Anticipated				Carpet care products
Coconut Oil Diethanolamide (Cocamide DEA)		X			Cleaners, degreasers, floor cleaner, metal cleaner and polish
Coconut Oil Diethanolamine		X			Cleaners, degreasers
Triethanolamine		X			Cleaners, degreasers, bleach, floor bleach, floor cleaner, wood cleaner
Tetrachloroethylene	X IARC Probable; NTP Reasonably Anticipated	X			Spray polish, spot remover

Adapted from: "Carcinogens & Reproductive Toxins Found in Cleaning Products," a summary prepared by the Janitorial Products P2 Project, www.wrppn.org.

RESEARCH REQUIRED:

- Exposure studies are needed that measure the presence and levels of synthetic hormones in meat and dairy sold and consumed in the U.S. so the potential for negative health effects can be assessed.
- Research that looks at red meat and dairy consumptions and their possible association with breast cancer should consider — and include in the methodology — the presence of synthetic hormones within these products. Without addressing these additives, it is not clear whether the research findings reflect the dietary nutritional composition of the food — e.g., vitamins, fat content and protein — or the presence of synthetic hormones.

Cosmetics and Personal Care Products

Because the U.S. lacks a pre-market screening program, shampoo, deodorant, make-up, lotions and other products that consumers use every day contain chemicals linked to cancer, birth defects and other serious health problems. Words like natural, safe, and pure on labels have no definition in law and no relationship to the hazard inside the packaging. Major loopholes in federal law allow the $50 billion cosmetics industry to put unlimited amounts of chemicals into personal care products with no required testing, no monitoring of health effects and woefully inadequate labeling requirements.

The EU's 27-country, precedent-setting Cosmetics Directive (76/768/EEC) prohibits the sale of personal care products that contain any of the 1,100 carcinogens, mutagens or reproductive toxins (CMRs) classified as toxicants by the directive. The United States only restricts 10 substances and there is no enforcement of those restrictions. Taken alone, the chemicals in a single consumer product are unlikely to cause harm. But the average American woman uses 12 personal care products a day, resulting in exposure to 126 unique chemicals. The combined exposure from personal care products adds to the personal chemical contamination from other consumer products, food, water, air and soil. As a result, more than 200 chemicals have been detected in people's body fluids and breast milk and in the cord blood of newborn babies. The unregulated use of chemicals in personal care products reflects the larger problem of chemicals in commerce without any functioning government framework to protect public health from harm.

The cosmetics industry claims that small amounts of toxic chemicals don't matter. But toxic chemicals are in many of the personal care products used daily by women and families and these exposures add up. As much as 70 percent of what consumers put on their skin ends up inside their bodies — a huge concern for women of childbearing age. Finally, cosmetics are only one of many sources of daily toxic exposures. For example, the public is exposed to phthalates from many different personal care products, as well as from vinyl shower curtains, vinyl car seats, toys, medical devices and pharmaceuticals.

To find out what's in your products, visit the Environmental Working Group's Skin Deep database at www.cosmeticdatabase.org — the world's largest database of chemicals in cosmetics.

Clearly, the industry needs a makeover. Breast Cancer Fund is working with nine other founding organizations of the Campaign for Safe Cosmetics to make that happen and you can help. Learn more at www.safecosmetics.org

Our government needs a makeover too. We can't just shop our way out of this problem. We need new laws that protect people from hazardous chemicals and encourage development of the safest alternatives.

Very Personal Pollution: Cosmetics Ingredients of Concern for Breast Cancer

Many of the so-called "health and beauty" products consumers use every day — including shampoos, deodorant, face cream and makeup — contain chemicals linked to breast cancer and other cancers, birth defects, reproductive problems and learning disabilities. These include industrial chemicals like benzene, ethylene oxide and formaldehyde, for example, and xenoestrogens and other endocrine disrupting compounds such as phthalates and nonylphenol. You won't always see them on the product label, even if you can read the teensy type. Some of the worst ones hide under the word "fragrance." And those are just the toxicants that have been identified.

The cosmetics industry is self-regulated in the United States [643] — another case of the fox minding the hen house. The U.S. Food and Drug Administration (FDA) has no authority to require pre-market testing as it does with drugs, so cosmetics are among the least-regulated products on the market. The FDA allows companies to put unlimited amounts of almost any chemical into cosmetics and only 11 percent of chemicals in cosmetics have been tested for their effects on human health and the environment. Additionally, no federal government agency monitors truth in cosmetic advertising, so words like "organic" and "natural" can also be misleading.

Europe has stronger regulations and companies are already making safer products for sale in European markets. The European Union has banned more than 1,100 chemicals from cosmetics because they cause cancer or reproductive harm. In the U.S., only 10 chemicals have been banned. Many toxic chemicals banned from cosmetics in Europe are still used in products in the U.S.;

Some cosmetics companies already know how to make safer products but many of the big companies refuse to change because they are under no pressure to do so.

Moving Forward:

FEDERAL POLICY:

Federal legislation is needed that:

- Requires pre-market health and safety testing of all cosmetics and personal care products;
- Institutes mandatory recalls of cosmetics containing ingredients that have not been proven safe through scientific testing and/or do not bear appropriate labels warning consumers that the product ingredients have not been tested for safety;
- Restricts the use of ingredients that contain any toxic impurity or that may combine with other ingredients to form harmful impurities;
- Requires all Internet vendors to display a conspicuous list of ingredients in cosmetic products sold on their Web sites;
- Requires labeling of the constituent ingredients of fragrance;
- Requires labeling of nanomaterials in cosmetics and personal care products;
- Requires cosmetics manufacturers to make all existing safety data available to government agencies and to consumers;
- Requires investment in green chemistry solutions to replace toxic chemicals used in cosmetics with safe alternatives; and
- Requires testing of personal care products for their estrogenic activity — especially products used by and on children.

STATE POLICY:

- States should require all companies selling cosmetic and personal care products in the state to provide certification that their formulations meet the standards of the EU Cosmetics Directive 76/768/EEC and are free of chemicals that are known or strongly suspected of causing cancer, mutation or birth defects.

The Connection Between Cosmetics and Breast Cancer

Chemical	Carcinogenic		Disrupt Hormones	Source of Exposure in Cosmetics
	Animal Mammary Gland Carcinogen[i]	Human Carcinogenic Risk Classification[ii]	Disrupts Endocrine System/ Estrogenic[iii]	
Benzene	X	IARC Known; NTP Known		Nail polish and nail polish remover
Bisphenol A			X	Cosmetic containers/packaging
1,3-Butadiene	X	IARC Probable; NTP Known		Rubber sponges for applying cosmetics
1,4-Dioxane	X	IARC Possible; NTP Reasonably Anticipated		Petroleum-derived contaminant formed in manufacture of shampoos, body wash, children's bath products and other sudsing cosmetics
Ethylene Oxide	X	IARC Known; NTP Known		Fragrance
Musks, synthetic (xylene, ketone, ambrette, moskene, tibetene)			X	Fragrance
N-Nitrosamines like n-nitrosodi-n-butylamine		IARC Possible; NTP Reasonably Anticipated		Chemical reactions occur over time in the product to produce nitrosamines, usually found in creams, lotions, shampoos and conditioners.
Nonylphenol			X	Lotions and a wide range of other products
Parabens (butyl-, ethyl-, methyl-, propyl-)			X	Antifungal agent, preservative and antimicrobial used in creams, lotions, ointments and other cosmetics
Petrolatum (**polycyclic aromatic hydrocarbons**, PAHs, are common contaminants)	X	IARC Possible; NTP Reasonably Anticipated	X	PAHs are petrolatum contaminants; found in petroleum jelly, lipsticks, baby lotions and oils; found in 1 of every 14 personal care products.
Phthalates (di-n-butyl- (DBP), di (2-ethylhexyl)- (DEHP))			X	Nail polish, fragrance
Placental extract (**progesterone** main constituent)	X	NTP Reasonably Anticipated	X	Hair conditioners, shampoos and other grooming aids, particularly marketed to women of color
1,2-Propylene Oxide	X	IARC Possible; NTP Reasonably Anticipated		Fragrance
Titanium Dioxide (**dioxin** is a by-product of manufacturing and a contaminant)		IARC Known; NTP Known	X	Sunscreens and mineral make-up; use of titanium dioxide nanoparticles a possible threat to human health
Triclosan (**dioxin** is a by-product of manufacturing and a contaminant)		IARC Known; NTP Known	X	Antibacterial used in soaps, toothpaste, mouthwash and other personal care products
Urethane (ethyl carbamate)	X	IARC Possible; NTP Reasonably Anticipated		Hair care products (mousses, gels, sprays), sunscreens, nail polish, mascara, foundation

Note: 1,4-dioxane, PAHs, dioxin and n-nitrosamines will not appear on product labels because they are contaminants and formed in manufacturing or through chemical reactions in the product.

i. Silent Spring Institute's Science Review published in *Cancer* in 2007 includes information on 216 animal mammary gland carcinogens. www.sciencereview.silentspring.org.

ii. International Agency for Research on Cancer (IARC) carcinogenic risk classification is based on evaluation of potential tumor development at all sites, not only breast/mammary tissue. Categories include: Known, Probable, Possible and others. The National Toxicology Program (NTP), within the National Institute of Environmental Health Sciences of the National Institutes of Health, provides carcinogenicity ratings based on scientific evidence in both animals and humans. Categories include: Known, Reasonably Anticipated and others. (Report on Carcinogens, Eleventh Edition; U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program.) Not all chemicals have been rated by IARC or NTP.

iii. To date, neither the NTP nor IARC have classified most endocrine disruptors as carcinogens in humans. List of endocrine disruptors from: Brody JG, Rudel RA (2003). Environmental pollutants and breast cancer. Environmental Health Perspectives 111: 1007-1019.

- States should require all companies selling cosmetics and personal care products in the state to submit to their Department of Health a list of chemicals used in the manufacture of products distributed in the state that are flagged by authoritative scientific bodies as being associated with cancer, endocrine disruption, birth defects or other health hazards, persistence in the environment or bioaccumulation.
- States should require all companies selling cosmetics and personal care products in the state to have on file with the state department of health a substitution plan that includes a timeline and plan for substituting chemicals of concern with safe alternatives.
- States should require all companies selling cosmetics and personal care products in the state to list fully all ingredients on the label, including components of fragrance and other mixtures and nanomaterials; and list fully all ingredients on the company's Web site if Internet sales of their products to that state are taking place.

RESEARCH REQUIRED:

- Currently only 11 percent of the ingredients used in cosmetic products have been tested for safety. Research is needed to increase this number to 100 percent.
- Green chemistry solutions are needed to replace toxic chemicals used in cosmetics with safe alternatives.
- Personal care products should be tested for their estrogenic activity — especially products used by and on children.

Occupational Exposures

Although women make up nearly half the paid workforce in the United States, relatively few studies have been conducted 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 or title, rather than by specific exposures, making the findings difficult to interpret. Women in the U.S. have two places of work: home and the paid workplace. Each place has its unique set of exposures to chemicals and non-ionizing radiation, further complicating exposure assessment.

The evidence that does exist shows increased risk of breast cancer among two broad categories:

(1) Those who work with toxic chemicals, such as chemists, dental hygienists, paper mill workers and microelectronics workers, and

(2) Professionals in higher socioeconomic groups such as school teachers, social workers, physicians and journalists.

There are other occupational groups with increased risk of breast cancer whose work involves chronic exposure to specific chemicals, higher than average levels of non-ionizing radiation, and in some cases, ionizing radiation as well.

Moving Forward:

FEDERAL POLICY:

Federal occupational health policy should require that:

- Workers be fully informed of the risks involved in performing their jobs, including chronic exposures to chemicals and radiation; and
- Workers receive maximum protection (personal protective equipment and culturally appropriate training in its use as well as environmental controls) to reduce or eliminate occupational exposures that can contribute to breast cancer.

STATE POLICY:

- States should fund community-based biomonitoring studies that include occupational groups as one of the early communities of focus.

Although women make up nearly half the paid workforce in the United States, relatively few studies have been conducted to identify occupational exposures associated with breast cancer.

Understanding — and more accurately measuring — the exposures and resulting health outcomes of workers in occupations with increased risk of breast cancer is essential to protecting workers' health and could contribute significantly to our broader understanding of environmental exposures and breast cancer.

RESEARCH REQUIRED:

- Methodologies need to reflect real world exposures. For example, chronic low-dose exposures to mixtures of chemicals must be considered as well as high-dose acute exposures. For women who have two workplaces, exposures at home and in the paid workplace to chemicals and non-ionizing radiation, for example, must be considered as well as their potential interaction with other risk factors.
- Occupational exposure assessment needs to consider non-traditional occupations and work hours. Occupational health scientists need new methodologies to account for the fact that women may move in and out of jobs throughout their lives and work long hours one day and short shifts another.

Occupations Associated With Increased Risk of Breast Cancer[644, 645, 646, 647, 648, 649, 650]

- Aircraft and automotive workers
- Barbers and hairdressers
- Chemists and chemical industry workers
- Clinical laboratory technologists
- 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
- Furniture and woodworking industry 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
- Rubber and plastics industry workers
- Social workers
- Telephone workers

Tools and Research Needed to Strengthen the Evidence and Reduce Exposures

Build Better Tools

There are several scientific tools (also used extensively in policy development) that are needed to reduce exposure to the radiation and chemical exposures discussed above. These tools — statistics, biomonitoring, health tracking — help scientists, policy-makers and the public understand breast cancer more clearly. Statistics can pinpoint who the disease is hitting hardest and how these rates are changing over time. Biomonitoring measures "pollution in people," helping to connect chemicals in the environment to disease by measuring the burden of toxicants in the body. Health tracking uses biomonitoring, chemical release, geographic exposure and health outcome data to explore and document connections between the environment and our health.

Statistics on Breast Cancer in All Populations

We need statistics to help identify trends in breast cancer incidence and mortality. These statistics are necessary to evaluate current programs, design new prevention and treatment plans and measure our progress in eradicating the disease. There is general agreement that the incidence of breast cancer in the United States has risen in past decades; however, precise statistics on the actual incidence of breast cancer and the rate of change in various populations is difficult to establish due to our slow, fragmented and under-funded state cancer registries system and the absence of a single national cancer tracking system.

Both the National Cancer Institute (NCI) and the Centers for Disease Control and Prevention (CDC) separately fund cancer registries. National estimates of incidence and mortality are projected from NCI's Surveillance, Epidemiology and End Results Program (SEER) data. According to the SEER Web site, this population is "comparable to the general U.S. population with regard to measures of poverty and education" but "somewhat more urban and has a higher proportion of foreign-born persons." SEER sites are concentrated on coastal cities, omitting much of the South and Midwest regions.

Cancer tracking has not kept pace with the increasing diversity of the U.S. population. In Asian Pacific Islanders (API), for example, collecting and reporting aggregate breast cancer rates tends to obscure those API groups with high incidence and/or mortality rates, perpetuating the myth that breast cancer incidence and mortality are low among all API women. Disaggregating the data on California API women showed substantial increases in breast cancer incidence among Japanese, South Asian, Chinese and Korean women.[651]

As discussed in the Framework section of this report on page 26, most research studies only look at women with invasive breast cancer. However, between 1980 and 2001, with increased use of mammography, diagnoses of ductal carcinoma in situ (DCIS) have increased sevenfold. Mainstream cancer organizations such as the American Cancer Society do not always include in situ breast cancer incidence rates in their breast cancer models and statistics, thereby giving a skewed picture of breast cancer in the U.S. These numbers deserve more than a footnote. They represent real women whose DCIS is treated the same as invasive breast cancer, with surgery and possibly radiation and/or chemotherapy.

Finally, under our current system, cancer reporting is a slow process subject to error due to delays. The 2003 cancer incidence and mortality statistics were reported in 2007. According to the NCI, it takes "four to 16 years for 99 percent of the cancer cases

to be reported."[652] There is much that needs to be done to mend our fragmented national and state breast cancer registries. Reliable statistics are essential to measuring progress toward our goal of eradicating breast cancer.

Moving Forward:

FEDERAL AND STATE POLICY:

- BCF supports the recommendation of Trust for America's Health (TFAH) that national standards be created to strengthen states' public accountability and enforce their performance standards in cancer tracking. If the North American Association of Central Cancer Registries (NAACCR) and the CDC's National Program of Cancer Registries (NPCR) fail to provide leadership on these issues, Congress should mandate that NPCR set these standards for all registries receiving federal support.
- BCF supports the recommendation of Trust for America's Health (TFAH) that Congress should direct the Institute of Medicine to conduct a study on the federal management of cancer registries and make recommendations that will guide development of a single cancer tracking system in the U.S.
- State and federal registries should be adequately funded to achieve steady improvement in data quality and timeliness.

Biomonitoring

Over the past 30 years, there have been great improvements in environmental pollution measurement. Simultaneously, medical advances have led to better detection and understanding of disease. But between the environment and human health there are still big gaps in our understanding. How do chemical exposures affect human health? One way to help answer this question is to measure the levels of toxic chemicals in people through a process called biomonitoring.

History of Cancer Registries

Some states have tracked cancer since the 1930s and 1940s. Other states, particularly in the South, had no registries until Congress passed the Cancer Registries Amendment Act in 1992.

1935

First central cancer registry in the U.S. (Connecticut)

1946

Second central cancer registry in the U.S. (California)

1973

NCI's SEER Program establishes first national cancer registry

1992

Congress establishes National Program of Cancer Registries

1993

State laws make cancer a reportable disease

2002

NCI and CDC produce the first combined annual federal report of cancer statistics

Agencies That Track Cancer Data

Agency or Organization	Program Funded	What It Does	% of U.S. Population Represented
National Cancer Institute (NCI)	Surveillance, Epidemiology and End Results Program (SEER)	Collects and reports data from 18 sites in U.S. www.seer.cancer.gov/registries	26
Centers for Disease Control and Prevention (CDC)	National Program of Cancer Registries (NPCR)	Supports central cancer registries in 45 states, 3 territories and the District of Columbia	96
NCI and CDC in collaboration with the North American Association of Central Cancer Registries (NAACCR)	NCI, CDC and NAACCR combined program	Since 2002, have published combined annual national cancer statistics; www.cdc.gov/cancer/npcr/uscs/	93

Biomonitoring, short for "biological monitoring," involves testing biological samples — such as urine or blood — for the presence of industrial compounds, pollutants and other chemicals in a person's body. Biomonitoring can generate data crucial to better understanding chemical exposures and their relationship to increasing rates of breast cancer, asthma, birth defects, autism and other diseases. Biomonitoring can also help scientists, medical professionals and community members identify communities disproportionately affected by chemical exposures, support efforts to improve environmental and health regulations, and help set priorities for legislative and regulatory action to protect public health.

Nationally the Centers for Disease Control and Prevention (CDC) supports state and local public health information campaigns about blood lead levels in children. The National Health and Nutrition Examination Survey (NHANES), an ongoing population-based survey carried out by the National Center for Health Statistics, also monitors chemical levels in blood and urine, which are published every two years in the CDC's National Report on Human Exposure to Environmental Chemicals. The most recent report, released in 2005, measured and analyzed 148 chemicals in the blood and urine of almost 8,000 individuals throughout the United States. Aggregated nationally, the data does not tell states and local communities about their specific chemical body burdens. A third NHANES report is expected to be released in 2008.

Moving Forward:

FEDERAL POLICY:

- The CDC should expand its biomonitoring grants program to support states that have existing state programs with the goal of augmenting these programs in FY'08 and creating new programs in upcoming years. Such funds could be used to help states expand lab capacity; conduct subpopulation studies; conduct representative analyses of routinely collected blood, cord blood and other biospecimens; develop protocols for conducting biomonitoring of sensitive subpopulations such as children; and support biomonitoring field operations such as participant enrollment, sample collection, data analysis, report generation and results communications. This work should be coordinated with EPA's efforts to identify and monitor ambient air and other sources of toxic chemical releases.

- The CDC's state grants program should make funds available to state biomonitoring programs to develop methods for identifying sources and routes of exposure for biomonitored chemicals; and support the creation of model exposure questionnaires; and support the collection of relevant household and other environmental samples and development of new methodologies to identify exposure sources.
- Federal funding should support the creation of regional biomonitoring labs to share costs, resources and the develop analytical testing methods.

STATE POLICY:

- States should fund community-based studies that couple chemical monitoring data and biomonitoring of individuals within a geographic area, occupation or disproportionately affected community (e.g., high disease rates and fenceline communities). Biomonitoring can then help assess effectiveness of chemical exposure reduction efforts within disproportionately affected communities.
- Biomonitoring studies at the state level should include occupational groups. Understanding — and more accurately and directly measuring — the exposures and resulting health outcomes of workers in occupations with increased risk of breast cancer is essential to protecting workers' health and could contribute significantly to our broader understanding of environmental exposures and breast cancer.
- To better understand early-life exposures and how they contribute to later-life disease, states should fund biomonitoring studies that examine cord blood, placenta, meconium (newborn's first bowel movement) and other appropriate biospecimens.

Health Tracking

With funding from Congress in 2002, the CDC created the National Environmental Public Health Tracking Program. The program defines health tracking as "the ongoing collection, integration, analysis, and interpretation of data about… environmental hazards, exposure to environmental hazards, and health effects potentially related to exposure to environmental hazards." Once analyzed, this information (which includes biomonitoring data, discussed previously) can be used by local, state and federal agencies to better prevent disease and protect health. Health tracking programs integrate multiple databases such as biomonitoring data, chemical release data, geographic distribution patterns of exposure and health outcome data.

Health tracking is "the ongoing collection, integration, analysis, and interpretation of data about… environmental hazards exposure to environmental hazards, and health effects potentially related to exposure to environmental hazards."

The National Environmental Public Health Tracking Program has given grants to states to build their health tracking programs. The CDC awarded planning grants to 27 states and implementation grants to 16 states. Prior to these investments, however, most states had no tracking system to assess many of the exposures and health conditions that may be related to environmental hazards. Because health databases, registries and monitoring systems are not coordinated and/or linked and because some hazards and chronic diseases are not tracked at all, it is difficult to carry out key public health functions.[653] For example, for breast cancer, it is difficult to determine if there is an unusually high rate of the disease in a certain community or population. It is also difficult to determine which environmental hazards communities are exposed to and how they compare to other communities. Making the

connections between environmental exposures and disease is an enormous challenge without comprehensive health tracking systems.

Moving Forward:

FEDERAL POLICY:

- Congress should appropriate funds to build state infrastructure, which could include state laboratories capable of performing biomonitoring of human samples for an array of contaminants; initiating state 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.

Health tracking programs integrate multiple databases such as biomonitoring data, chemical release data and geographic distribution patterns of exposure and health outcome data.

- The CDC should be directed to make funding available to state environmental health tracking programs to develop replicable models for disease, hazard and exposure data-sharing at the local, state and national levels that incorporate data confidentiality protections.
- Advocates should continue to push for enactment of the Coordinated Environmental Public Health Network Act of 2007 (S 2082/ HR 3643), introduced by House Speaker Nancy Pelosi and Senator Hillary Clinton, which expands and strengthens the nationwide health tracking network. For updates on federal health tracking visit Trust for America's Health at www.tfah.org.
- The CDC should be further directed to include non-governmental organizations representing health-affected constituencies, environmental health and environmental justice in their advisory groups.

STATE POLICY:

- With CDC support, states should strengthen the coordination between health and environment agencies of health tracking programs.

Invest in New Science

As outlined in the Framework section of this report, there are several important themes that emerge from a review of the state of the evidence on the environmental links to breast cancer. These and two other emerging areas of research are ripe for further scientific exploration.

Low Dose Exposures

Over the past decade, science has demonstrated that very low-level exposures to some chemicals can have a larger effect on health than very high levels of exposure. In the past, scientists relied on thresholds, or the dose or exposure below which no deleterious effect is expected to occur, to set safe limits of exposure. But today, scientists are moving away from assuming there is a threshold of safety and are instead assuming that there is no threshold and testing to see if there is one. This huge change in toxicology moves the focus away from the "dose makes the poison" rationale of years past. It has become clear that even in very small doses, some chemicals can disrupt the endocrine system and in some cases combine with naturally occurring hormones like estrogen to exacerbate natural biological processes. This is a concern because excess exposure to estradiol (naturally occurring estrogen) is a risk factor for breast cancer.

Mixtures

In our daily lives, the public is exposed to a wide variety of chemicals in the air we breathe the food we eat, the water we drink and in the products we use. Increasingly, scientists are trying to study the effects of mixtures of chemicals and radiation on

breast cancer risk. In addition to sorting out the complexities of additive and synergistic effects of multiple chemicals, they must also consider different mechanisms of action like gene mutation and hormone disruption.

Timing of Exposure and Later-Life Breast Cancer

Mammary cells are more susceptible to the carcinogenic effects of hormones, chemicals and radiation from the prenatal period through puberty, and from adolescence, and on until the first full-term pregnancy.[654] Changes in the fetal environment, accompanied by increased exposures to synthetic chemicals that act like estrogen, can lead to higher incidence of breast cancer in adulthood. Evidence also suggests exposures during puberty — a key period of breast development — may have an especially large impact on later-life breast cancer risk.

Early Puberty and Later-Life Breast Cancer

Girls today get their first periods, on average, a few months earlier than did girls 40 years ago, but they get their breasts one to two years earlier.[655] This is a concern because early puberty is a known risk factor for breast cancer. How early puberty increases breast cancer risk is not completely clear but there are some clues. Early puberty is associated with an increased exposure to estrogen, and early puberty expands the window of vulnerability for breast cancer development between first menstruation and first pregnancy.

Moving Forward:

FEDERAL POLICY:

- The federal government should support large studies that follow girls from conception to adulthood like the National Children's Study (NCS) mandated by Congress in 2000, which will follow 20,000 children from conception to adulthood. Securing Congressional funding over the next five years of the NCS will be critical because during this time recruitment will be in full swing and prenatal and early life baseline measurements will take place.
- In 2007, there are two active federal-level efforts to build the science connecting the environment and breast cancer: the NIEHS-funded Breast Cancer and Environment Research Centers (BCERC) exploring early puberty and connections to later-life breast cancer, and the Breast Cancer and Environmental Research Act (BCERA), proposed federal legislation that provides a framework and strategy for generating an international research agenda on breast cancer and the environment. Even when combined, both of these efforts represent a small portion of the federal funding needed for this important scientific inquiry. For more information visit www.nbcc.org for BCERA and www.bcerc.org for BCERC.
- The EPA's Endocrine Disruptor Screening Program, mandated by Congress, is eight years behind schedule and not one chemical has been screened to date. Advocates should keep the pressure on Congress and the EPA to ensure this important work gets done in a timely and fully transparent manner.

STATE POLICY:

- States should use the California Breast Cancer Research Program as a model of innovative state research programs. The CBCRP is a research program created by a ballot initiative and funded by a cigarette tax that created a special $18 million statewide initiative focused on the effects of the environment on breast cancer. The program also stresses the applicability of research to policy solutions and emphasizes stakeholder involvement so that advocates, clinicians, researchers, policy makers and the general public can help direct research funding. For more information, visit www.cbcrp.org.
- In the absence of comprehensive chemicals policy reform, states should ban phthalates and

bisphenol A from all products marketed to children and pregnant women — toys, including baby bottles, bedding, water bottles and other products — to protect children from early-life exposures that may contribute to later-life breast cancer.

RESEARCH REQUIRED:

- Methodological research is needed on early biomarkers of disease, so the public does not need to wait decades for expensive long-term human studies to show results. Similarly, animal studies should be used strategically with human studies to move more quickly toward understanding mechanisms of breast cancer initiation and promotion.
- As highlighted by the Silent Spring Institute report on breast carcinogens,[656] human epidemiological studies that look at breast carcinogens are limited in number. More studies of human populations that include biomarkers of exposure and disease are needed so that scientists can begin to see associations in a shorter time period without waiting decades for results. Mammary carcinogens should be prioritized for study based on the size of the population exposed to them.

Mammary cells are more susceptible to the carcinogenic effects of hormones, chemicals and radiation from the prenatal period through puberty and adolescence and on until the first full-term pregnancy.

- We need more human epidemiology studies that look specifically at endocrine disruptors and mammary carcinogens to which women are exposed every day like diesel exhaust, phthalates, PFOS/PFOA, bisphenol A and others.
- Methodological research challenges in areas like mixtures, occupational exposure assessment and key windows of susceptibility require serious and ongoing investment and commitment from agencies and funding institutions.
- Risk characterization methodologies need to account for the complexities of multifactorial disease, low-dose exposures and disproportionately susceptible populations.
- To better understand and address the early puberty phenomenon, research is needed to understand the mechanisms behind the initiation of puberty, the distinct roles of hormones and enzymes and the impact of chemical exposure during pregnancy among other important areas of study.[657]

Nanotechnology

Nanomaterials can be extremely toxic. Due to their extremely small size and structure, they can be inhaled, ingested and absorbed into the body, enter the blood stream, penetrate cells and even interfere with critical DNA processes. Of course, these characteristics are also what make them so valuable. See page 88 for more information on nanomaterials.

Early in its development, the cosmetics industry embraced this new technology, adding nanomaterials to many products that consumers use every day such as sunscreen and some high-end luxury products like anti-aging creams and lotions. Consumers have a right to know if the cosmetics and personal care products they use contain untested nanomaterial ingredients. Manufacturers and retailers should take a precautionary approach to the use or sale of products with nano-sized particles until these materials have been fully tested for their impact on the public, workers and environmental health.

Consumers have a right to know if the cosmetics and personal care products they use contain untested nanomaterial ingredients.

Moving Forward:

FEDERAL POLICY:

To protect workers, consumers and the environment from the known and unknown consequences of nanomaterials, the FDA should be directed to:

- Require the manufacturers of products to conduct comprehensive pre-market testing of products formulated with nanomaterial ingredients for their impact on public health, worker health and environmental health;
- Prohibit the unsafe or untested use or sale of nanomaterial ingredients in consumer products;
- Create a publicly accessible database on the environmental, human health and worker safety impacts of nanomaterial ingredients; and
- Require manufacturers to label all products they manufacture or sell that contain nanomaterial ingredients.

RESEARCH REQUIRED:

- Research on the health effects of nanomaterials needs to go hand-in-hand with the huge body of research underway exploring its possible applications. The public needs to know the short- and long-term health impact of nanotechnology on public, worker and environmental health before we unleash and build this untested technology into our everyday lives.

Nanotechnology: Friend or Foe?

Nanotechnology has been called the "next industrial revolution." It involves the manipulation of materials and the creation of tiny structures and systems that exist at the scale of atoms and molecules. (To put things in perspective, a nanometer is one-billionth of a meter — to cover the width of a human hair you would have to line up 80,000 nanometers.) This manipulation changes the physical properties of materials. Opaque materials can become transparent, for example, and chemically stable materials can be made reactive.

The good news is that these physical changes may lead to medical advances, more durable products, new ways to clean up pollution, increased fuel cell efficiency and, market research suggests, perhaps billions of dollars in profits. This fact is not lost on Fortune 500 companies, virtually all of which have invested in nanotechnologies, according to news reports.

Hundreds of consumer products, including cosmetics and personal care products, stain-resistant clothing, food storage containers and computers, now include nanomaterials, according to one academic report. A 2006 report by Friends of the Earth found that at least 116 personal care products containing nanoingredients — defined as smaller than 100 nanometers — are on the market.[658]

Scientists at Rice University's Center for Biological and Environmental Nanotechnology are using nanoparticles in new cancer detection and treatment, allowing them to target and destroy only cancerous cells. But as news of nanotechnology's promise emerges, there are also concerns about health and environmental risks.

Nanomaterials can be extremely toxic. Due to their size and structure, they can be inhaled, ingested and absorbed into the body, enter the blood stream, penetrate cells and even interfere

with critical DNA processes. According to the Natural Resources Defense Council, nanoparticles have caused inflammation and pre-cancerous lesions, and have damaged brain cells in animal studies.[659]

Scientists at the New Jersey Institute of Technology found that high levels of nano-alumina oxide stunt the growth of five plant species including corn and soybeans. In March 2006, six people were hospitalized for pulmonary edema in Germany after they used a product called Magic Nano, a protective sealant for glass and ceramics. Almost 80 others who used the spray reported breathing problems and coughing. The product was pulled from the market two days after its introduction.[660] Government is struggling to catch up with this new science, where tiny nanomaterials slip through the cracks of environmental and health regulations.

Many advocacy and public policy groups are pushing for a new approach and are pressuring the FDA to regulate products containing nanoparticles. The Project on Emerging Nanotechnologies at the Woodrow Wilson International Center for Scholars is calling for increased federal agency leadership and coordination as well as increased funding for targeted research.[661] The Campaign for Safe Cosmetics has drafted a position statement on nanotechnology that calls for "a precautionary approach to the use or sale of products with nano-size particles until these materials have been fully tested for their impact on human health, environmental health and worker health."

Appendices

Appendix 1:

List of IARC Accepted, Possible or Probable Carcinogens Related to Breast/Mammary Cancer

(Rudel et al, 2007) See key on page 93.

IARC	Mam List	Chemical	Category
1	P,N,C	benzene	Industrial Chemical
1	P,I,N	ethylene oxide	Industrial Chemical
1	P,I,N,C	vinyl chloride (PVC)	Industrial Chemical
1	P,I,N,C	4-aminobiphenyl	Dye
1	P,I,N	benzidine	Dye
1	P,C	chloroambucil	Pharmaceutical
1	N,C	cyclophosphamide	Pharmaceutical
1	I,N,C	thiotepa	Pharmaceutical
1	P,I,N,C	diethylstilbestrol	Hormone
1	I,C	estrogens, steroidal	Hormone
1	I,C	estrogens, nonsteroidal	Hormone
1	I,C	estrogen therapy, postmenopausal	Hormone
1	I,C	estrogen-progestogen menopausal therapy	Hormone
1	I,C	estrogen-progestogen oral contraceptives	Hormone
1	I,N	wood dust	Natural Product
2A	P,I,N,C	ethylene dibromide (1,2-dibromoethane)	Industrial Chemical
2A	P,N,C	1,3-butadiene	Industrial Chemical
2A	P,I,N,C	4,4'-methylene-bis(2-chloroaniline)	Industrial Chemical
2A	P,I,N,C	acrylamide	Industrial Chemical
2A	P,I,N,C	glycidol	Industrial Chemical
2A	I,N	indium phosphide	Industrial Chemical
2A	P,I,N	ortho-toluidine	Industrial Chemical
2A	P,I,N,C	vinyl fluoride	Industrial Chemical
2A	P,I,N,C	1,2,3-trichloropropane	Chlorinated Solvent
2A	N,C	benzo[a]pyrene	Product of Combustion
2A	N	dibenz[a,h]anthracene	Product of Combustion
2A	P,I,N,C	IQ	Product of Combustion
2A	P	chlordane	Pesticide
2A	P,I,N,C	benzidine base dyes: Direct Black 38	Dye

Appendix 1 (cont'd)

2A	P	azacitidine	Pharmaceutical
2A	I,N,C	adriamycin	Pharmaceutical
2A	P	phenacetin	Pharmaceutical
2A	P,I,N,C	procarbazine hydrochloride	Pharmaceutical
2A	I,N	androgenic (anabolic) steroids	Hormone
2A	N,C	n-nitroso-n-methylurea	Research Chemical
2B	P,I	1,2-propylene oxide	Industrial Chemical
2B	P,I,C	1,4-dioxane	Industrial Chemical
2B	P,I,N,C	2,2-bis(bromomethyl)propane-1,3-diol	Industrial Chemical
2B	I,N,C	2,3-dibromopropan-1-ol	Industrial Chemical
2B	P,N,C	2,4-diaminotoluene	Industrial Chemical
2B	P,I,N,C	2,4-dinitrotoluene	Industrial Chemical
2B	N,C	2-methylaziridine	Industrial Chemical
2B	P,I,N,C	5-nitroacenaphthene	Industrial Chemical
2B	P,I,N,C	acrylonitrile	Industrial Chemical
2B	P,I,C	AF-2(2-furyl)-3-(5-nitro-2-furyl) acrylamide	Industrial Chemical
2B	P,I,N,C	chloroprene	Industrial Chemical
2B	I	hydrazine	Industrial Chemical
2B	P,N,C	nitrobenzene	Industrial Chemical
2B	P,I,N,C	nitromethane	Industrial Chemical
2B	N	n-nitroso-di-n-butylamine	Industrial Chemical
2B	N	ortho-aminoazotoluene	Industrial Chemical
2B	P,I,N,C	1,3-propane sultone	Industrial Chemical
2B	P,I,C	styrene	Industrial Chemical
2B	N,C	ethyl carbamate (urethane)	Industrial Chemical
2B	P,I,N,C	1,2-dichloroethane	Chlorinated Solvent
2B	P,I,N	carbon tetrachloride	Chlorinated Solvent
2B	P,I,N,C	dichoromethane (methylene chloride)	Chlorinated Solvent
2B	I,N,C	1,8-dinitropyrene	Product of Combustion
2B	P,I,N,C	1-nitropyrene	Product of Combustion
2B	I	2-nitrofluorene	Product of Combustion
2B	C	Trp-P-2 (3-amino-1-methyl-5h-pyrido[4,3-b]indole)	Product of Combustion
2B	I,N,C	4-nitropyrene	Product of Combustion
2B	N	6-nitrochrysene	Product of Combustion
2B	C	dibenzo[a,e]pyrene (dibenzo[def,p] chrysene)	Product of Combustion
2B	I,N,C	isoprene	Product of Combustion
2B	I,N,C	MeIQ (2-amino-3,4-dimethylimidazo[4,5-f]-quinoline)	Product of Combustion

Appendix I (cont'd)

2B	I,N,C	PhIP (2-Amino-1-methyl-6-phenylimidazo[4,5-b]-pyridine)	Product of Combustion
2B	P	chlordane	Pesticide
2B	P,I,N,C	1,2-dibromo-3-chloropropane	Pesticide
2B	N,C	dichlorvos	Pesticide
2B	P,I,C	2-(2-formylhydrazino)-4-(5-nitro-2-furyl)thiazole (nifurthiazole)	Pesticide
2B	P,I,N,C	sulfallate	Pesticide
2B	P,I,N,C	3,3'-dichlorobenzidine	Dye
2B	N	3,3'-dimethoxybenzidine	Dye
2B	N	3,3'-dimethylbenzidine	Dye
2B	P,I	4,4'-methylene-bis(2-methylaniline)	Dye
2B	N	C.I. Acid Red 114	Dye
2B	N,C	C.I. Basic Red 9	Dye
2B	P,I,C	FD & C Violet No. 1	Dye
2B	I,C	n,n'-diacetylbenzidine	Dye
2B	P,I,C	3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone (MX)	Drinking Water Disinfectant
2B	P,I,C	1-[(5-nitrofurfurylidene0amino]-2-imidazolidnone	Pharmaceutical
2B	P,I,C	2-amino-5-(5-nitro-2-furyl)-1,3,4-thiadiazole	Pharmaceutical
2B	I	5-morpholinomethyl)-3-[(nitrofurfurylidene)amino]-2-oxazolidinone	Pharmaceutical
2B	I	amsacrine	Pharmaceutical
2B	P,I,N	dacarbazine	Pharmaceutical
2B	I,C	daunomycin	Pharmaceutical
2B	P	griseofulvin	Pharmaceutical
2B	I,C	merphalan	Pharmaceutical
2B	P,I,N,C	metronidazole	Pharmaceutical
2B	C	mitomycin-c	Pharmaceutical
2B	P,I,C	n-[4-(5-nitro-2-furyl)-2-thiazolyl] acetamide	Pharmaceutical
2B	I,C	niridazole	Pharmaceutical
2B	I	trans-2-[(dimethylamino) methylimino]-5-[2-(5-nitro-2-furyl) -vinyl]-1,3,4-oxadiazole	Pharmaceutical
2B	I,C	uracil mustard	Pharmaceutical
2B	P,N,C	ochratoxin A	Natural Product
2B	N	ethyl methanesulfonate	Research Chemical

IARC (International Agency for Research on Cancer) carcinogenic risk classification, based on evaluation of potential tumor development at all sites, not only breast/mammary tissue: Group 1 – This chemical is carcinogenic to humans; Group 2A – This chemical is probably carcinogenic to humans; Group 2B – This agent is possibly carcinogenic to humans.[662]

MamList: Identifies the source from which scientists at the Silent Spring Institute have identified the chemical as causing mammary tumors in animal models: P – Carcinogenicity Potency Database;[663] I –IARC Monographs;[664] N – National Toxicology Program technical reports or the 11th Report on Carcinogens (NTP 2002);[665, 666] C – National Library of Medicine Chemical Carcinogen Research Information System.[667]

Appendix 2:

List of Endocrine Disrupting Compounds

(Brody et al., 2003)

Compound	Exposures/Uses
Pesticides	
Atrazine	Selective herbicide
Chlordane	Insecticide (ticks and mites), veterinary pharmaceutical
Chlorpyrifos	Insecticide (ticks and mites)
Cypermethrin	Insecticide
2,4-Dichlorophenoxyacetic acid	Herbicide
DDT (and associated compounds)	Contact insecticide
Dieldrin, aldrin, endrin	Insecticide
Lindane	Insecticide
Malathion	Insecticide
Methoxychlor	Insecticide, veterinary pharmaceutical
Pentachlorophenol	Insecticide (termites), wood preservative
Permethrin, sumithrin	Insecticide
Toxaphene	Insecticide
Tributyl tin (chloride)	Biocide, rodent repellent
Vinclozolin	Agricultural fungicide
Persistent non-pesticide organochlorines and PAHs	
PAHs	Compounds in industrial air pollutants, smoke from cola or coke-burners, tobacco tar, some foods
Polybrominated biphenyls	Flame retardant
Polybrominated diphenyl ethers	Flame retardant
PCBs (Aroclor 1254)	Production of electrical capacitors and transformers and other electrical equipment; carbonless copy paper
Dioxins and furans	Byproduct of incineration, paper manufacturing, production of chlorine aromatics; impurity in some herbicides
Phenols and alkylphenols	
Bisphenol A	Polycarbonate and polyester-styrene resins
4-tert-Butylphenol	Intermediate in manufacturing of varnish and laquer resins, soap antioxidant

Appendix 2 (cont'd)

Nonylphenol polyethoxylate, 4-nonylphenol, 4-octylphenol	Surfactant, detergent, defoaming agent, some pesticides, degradation product of alkylphenol, ethoxylated antioxidant in some plastics
o-Phenylphenol	Disinfectant fungicide, rubber production
Phthalates	
bis(2-Ethylhexyl) phthalate, butyl benzyl phthalate	Plasticizer for polyvinyl chloride (PVC) polymers
Di-n-butyl phthalate, diethyl phthalate	Personal care products including nail polish, perfume, hair spray; plasticizers, inks, adhesives
Parabens	
Butyl-, ethyl-, methyl- and propyl-parabens	Pharmaceutical antifungal agent, preservative in foods, antimicrobial in creams, lotions, ointments and other cosmetics
Other Organics	
Amsonic acid	Used in manufacturing of dyes, bleaching agents, optical brighteners, whitening agents
Styrene	Used in manufacturing of plastics, synthetic rubber, resins; insulator
Vinyl acetate	Used in production of wide range of polymers, paints, food packaging
Metals	
Cadmium, lead	Batteries, plastic stabilizers, pigments
Mercury	Thermometers, dentistry, pharmaceuticals, anti-fouling paints
Phytoestrogens	
Genestein, coumestrol, zearalenone	Soy, grains, grain molds

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Endnotes

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