



STATE OF THE EVIDENCE:

THE CONNECTION BETWEEN BREAST CANCER AND THE ENVIRONMENT

by Janet Gray, Ph.D.



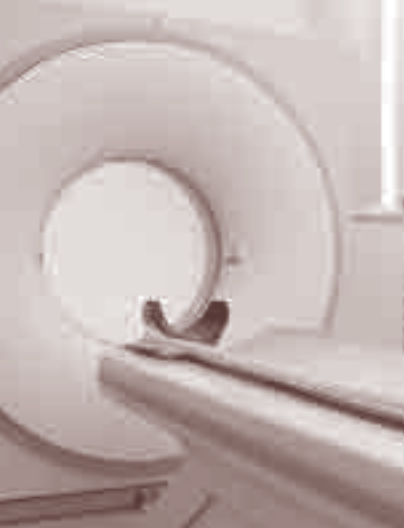
PREVENTION STARTS HERE.

Sixth Edition 2010

FROM SCIENCE TO ACTION

by Janet Nudelman, M.A., and Connie Engel, Ph.D.





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Preface

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Maintaining the high scientific integrity that is its hallmark, the 2010 document also presents a new, more in-depth section devoted to explaining how policymakers and advocates can translate this scientific information into action at the state and federal levels.

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State of the Evidence: The Connection Between Breast Cancer and the Environment 2010 is the sixth edition of the Breast Cancer Fund's signature report examining the scientific evidence linking exposures to environmental chemicals and radiation with breast cancer. In this edition, the evidence is placed in a larger conceptual context, with a substantial discussion of framing themes and methodological issues. The report concludes with an exploration of the policy initiatives required to make breast cancer prevention a public health priority, and presents advice on what individuals can do to reduce their risk.

The latest *State of the Evidence* has a new focus on vulnerable populations, while keeping steady emphasis on several main themes seen in the last edition. These themes include the importance of examining factors such as (a) timing of exposures, especially at early stages of an individual's development; (b) low-dose exposures at environmentally significant levels, again especially in early development; (c) real-life mixtures of exposures; and (d) the complexity of interactions between environmental and other risk factors for breast cancer. The

document reflects the recent burst of scientific research on these issues, incorporating information from more than 250 new research articles. New evidence is cited in almost all categories of exposures covered here, as well as in the framing, methodology and policy sections.

Maintaining the high scientific integrity that is its hallmark, the 2010 document also presents a new, more in-depth section devoted to explaining how policymakers and advocates can translate this scientific information into action at the state and federal levels. This second section, titled "From Science to Action," provides practical, straightforward information aimed at summarizing the concerns about environmental links to breast cancer and motivating personal and political action. It is intended to serve as a tool for policymakers and advocates in the areas of breast cancer prevention, women's health, environmental health and environmental justice.

Each of the six subsections of "From Science to Action" highlights the key sources of unsafe chemical exposures in a certain category, describes populations disproportionately affected by such exposures, and offers a description

Preface *(continued from previous page)*

...with *State of the Evidence 2010* we continue our tradition of providing an invaluable scientific resource for our partners and allies...

of the current regulations as well as related policy changes to reduce exposure. Each section also includes personal tips for reducing risk and a summary table of exposures for that category.

Before writing this sixth edition, the Breast Cancer Fund engaged an independent consultant to survey readers about the use, value, credibility and clarity of the previous one, *State of the Evidence 2008*, and to elicit suggestions for the upcoming report. Scientists, legislative staff, environmental health advocates, educators, and women living with breast cancer, along with members of their communities, all gave enthusiastic ratings to the overall value, scientific integrity and clarity of the document. For this edition, they suggested ways to better connect the scientific information with issues relevant to women and their families on a day-to-day basis, and ways to make *State of the Evidence 2010* more accessible through the Breast Cancer Fund's Web site.

The new document also reflects responses from scientific colleagues following publication of the fifth edition in the *International Journal of Occupational and Environmental Health*, an international peer-reviewed journal.

We have listened carefully to all of this feedback and believe that with *State of the Evidence 2010* we continue our tradition of providing an invaluable scientific resource for our partners and allies, while also making the material more accessible, both as a hardcopy manuscript and through its translation on the Web and in ancillary materials. As part of this effort, this spring we launched the Breast Cancer Fund's dynamic new Web site. We invite you to visit www.breastcancerfund.org, where you can easily access the information contained in this document, find more tips for prevention, advocate for change and engage with the Breast Cancer Fund community.

In sum, we believe *State of the Evidence 2010* builds on the strengths of past editions, pushing the project to new levels of scientific sophistication, clarity and accessibility. It also expands the connections between this information and the personal, community and policy initiatives that form the core of the Breast Cancer Fund's programmatic focus.

I thank you for being part of our conversation and invite you to stay engaged with the work of the Breast Cancer Fund and our important mission: *To identify and eliminate the environmental and other preventable causes of breast cancer.*

Janet Gray, Ph.D.
Poughkeepsie, New York

July 2010

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STATE OF THE EVIDENCE:

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Framework of the Scientific Review



With this broad lens for understanding the scientific literature examining environmental causes of breast cancer, we provide the groundwork for economic and political changes that can lower the future incidence of breast cancer for our children and grandchildren.

I. Introduction

In *State of the Evidence: 2010*, the Breast Cancer Fund examines the continually expanding and increasingly compelling data linking radiation and various chemicals in our environment to the current high rates of breast cancer. We acknowledge the importance of many widely understood risk factors for breast cancer, including primary genetic mutations; reproductive history; and lifestyle factors, such as weight gain, alcohol consumption and lack of physical exercise (Dumitrescu, 2007). Yet we begin with an understanding that, in total, these factors do not address a considerable portion of the risk for the disease (Kruk, 2006). A substantial body of scientific evidence indicates that exposures to common chemicals and radiation, singly and in combination, also contribute to the unacceptably high incidence of breast cancer. This report focuses on these environmental issues.

In examining the role of environmental chemicals and radiation in affecting the development of breast cancer, we embed our analysis in a model of causation that articulates complexity. We explore interactions

among various environmental chemicals and radiation as well as between these environmental exposures and genetic, reproductive history and lifestyle factors. This model also addresses the need to take into account the different times in a person's life when particular factors may exert stronger effects in influencing later development of disease.

With this broad lens for understanding the scientific literature examining environmental causes of breast cancer, we provide the groundwork for economic and political changes that can lower the future incidence of breast cancer for our children and grandchildren. Although this report focuses on connections between the environment and breast cancer, we also join the collective effort to turn the tide on a number of other diseases. Unfortunately, the environmental exposures we discuss are implicated not only in the rising incidence of breast cancer, but also in a number of other cancers, asthma, and several reproductive, neurodegenerative and learning disorders (Barlow, 2007; Kamel, 2004; Kleinerman, 2006; Landrigan, 2005; Perera, 2005). We therefore join in collaboration with other individuals and organizations

striving to educate and advocate for change based on the scientific literature in the broad field of environmental health.

A. What we mean by “environment”

The term “environment” may encompass 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, we focus on people’s exposures to environmental chemicals, including many of those found in personal care products, household products, plastics, food, air and water, as well as several sources of radiation, including medical radiation and electromagnetic waves. Although we may have control over our personal use of some of these chemicals, exposures to many of these factors are not voluntary. On a daily basis, we are all exposed to many of these agents in the air we breathe, the water we drink, the grounds we walk and play on, the toys and other products we handle, and the substances we put on our bodies. Often we are not even aware of these exposures.

Limiting this report to the complex scientific materials on environmental chemicals, radiation and breast cancer, we will not discuss in detail the literatures emphasizing possible relationships between breast cancer risk and diet, stress and obesity (Michels, 2007), except as these factors interact with environmental toxicants and radiation in affecting the incidence of the disease. We will, however, consider pesticides, herbicides, hormones and chemicals that leach from packaging materials

into foods, thereby increasing people’s total exposures to synthetic chemical compounds that have been implicated in increased risk for breast cancer. We will not examine the science underlying our understanding of the relevance of reproductive history in predicting risk for the disease, except as it informs our understanding of mechanisms by which environmental factors may be exerting their effects, and of the critical role played by timing of exposures in influencing changes in risk for developing breast cancer.

B. What we mean by “risk”

Toxicologists and regulatory agencies use the term “risk assessment” to refer to the formal process of examining potentially adverse health effects that may be posed by chemicals or other factors in the environment (NRC, 2009). This information is used to inform decisions that may be made to help protect our air, water and land, and to support food, drug and consumer product safety regulation. In formal risk assessment, there are four stages: (1) *Hazard assessment* is the determination, based on scientific data, as to whether or not a chemical or other environmental source is causally linked to adverse health effects. With regard to agents that might be linked to cancer, the U.S. National Toxicology Program (NTP) rates substances as “known human carcinogens,” “reasonably anticipated to be human carcinogens” and “other” (NTP, 2009). The World Health Organization’s International Agency for Research on Cancer (IARC) uses slightly different categories: “carcinogenic to humans,” “probably carcinogenic,” “possibly carcinogenic,” “unclassifiable” and “probably not carcinogenic” (IARC,

2009). (2) *Dose-response assessment* examines the relationship between the amount or dose of a substance to which individuals are exposed and specific outcomes. As we will see, determination of dose-response relationships is one of the most critical issues in understanding the effects of many environmental toxicants and their effects on breast cancer incidence. (3) *Exposure assessment* evaluates how much of the environmental factor people are actually exposed to, recognizing differences in home, work, school and recreational profiles of different subsets of people. (4) Finally, *risk characterization* integrates the data from the first three steps and draws conclusions about whether or not formal procedures should be created to protect people from the target substance.

The term “risk” is used by environmental health scientists to reflect the principles of the more formal assessment outlined above, but without linkage necessarily to specific regulatory deliberations. Throughout this report, we use the term “increased risk” to refer to an enhanced likelihood of diagnosis of breast cancer, resulting from exposure(s) to particular environmental chemicals and/or radiation. Where data address these issues, we are mindful to discuss issues of dose (as well as timing and other clarifying characteristics) of exposures and conditions under which people are more or less likely to be subjected to these exposures. We will address these issues of timing and dose at more conceptual levels later in this framework section.

C. What we mean by “breast cancer”: One disease or many?

As is true in so much of the public and scientific conversation, in this report we often discuss breast cancer as if it were a single disease. In fact, there are several different presentations and increasing sophistication in the way some scientific studies differentiate among subtypes or classifications of breast cancer. 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, with the result that tumors tend to be larger and more aggressive at the time of diagnosis (Love, 2005). Another type of breast cancer, inflammatory breast cancer, is a relatively rare (1 to 6 percent of cases in the United States) 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 (Daewood, 2007).

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. Most research studies only look at women with invasive breast cancer. The non-invasive form of breast cancer, or, for some, “pre-cancer,” is found in diagnoses of ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS), where there is the appearance of abnormal cells contained within the walls of the structures of the breast. Whereas invasive metastatic cancer is often life threatening, at the time of diagnosis, DCIS (or LCIS) is not. A diagnosis of carcinoma in



situ is associated with a fourfold increase in risk for later diagnosis of invasive breast cancer (Warnberg, 2000), although at present clinicians cannot predict with reliability which women this will affect (Peterson, 2009). Some research studies examine both in situ and invasive forms of breast disease, although they almost always are careful to separate the data from the two categories.

For research purposes, breast cancers also often are distinguished by the woman's age 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 medical records. Menopausal status is of note because it marks the gradual but important downward shift in secretion of estrogens in the body. Total exposures to estrogens, estrogen mimickers and endocrine-system disruptors — from any

of a number of sources — have been associated with increased risk for breast cancer later in life (Russo, 2008).

Based on a number of biological markers (genes or proteins found in cells that have been associated with mechanisms underlying breast cancer), a new set of breast cancer classifications has been established: basal, HER-2 over-expression, luminal A, luminal B and unclassified (Perou, 2000; Sorlie, 2003). The basal subtype is also called “triple negative” cancer, because the cells are negative for three common markers: estrogen receptors (ER), progesterone receptors (PR), and Human Epidermal Growth Factor Receptor-2 (HER-2). Although the basal subtype is only found in about 15 percent of breast cancer diagnoses, it has been shown to be aggressive, unresponsive to treatment and ultimately indicative of a poor prognosis (Perou, 2000). As the name suggests, HER-2 over-expression tumors have extra copies of the HER-2 gene

Globally, breast cancer affects more women than any other type of cancer and is the leading cause of cancer-related deaths among women.

and over-produce the resulting growth-enhancing protein. These tumors tend to grow quickly, but they are treatable with targeted drugs like herceptin. Luminal A and B subtypes are both estrogen-receptor-positive (ER+) and low grade, with Luminal A tumors growing very slowly and Luminal B tumors growing more quickly. Luminal A tumors have the best prognosis.

Finally, it is important to acknowledge that at least 1 percent of all diagnoses of breast cancer are in men (Onami, 2010). 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 coming into play (Ying, 2005). Among the environmental issues that have been linked to male breast cancer are occupational exposures to gasoline and vehicle combustion, polyaromatic hydrocarbons (PAHs), electromagnetic fields (EMFs) and some industrial solvents (Hansen, 2000; Palli, 2004; Weiss, 2005; Ying, 2005). Nevertheless, almost all of the scientific research has been directed toward an understanding of breast cancer and its underlying causes in women or female animals, and therefore this will be the main focus of this report. Where specific data exist from men or male laboratory animals, they will be included within the larger discussion. We hope that, ultimately, a better understanding of the complex causes underlying female

breast cancer will also illuminate the factors influencing its development in males.

II. Breast Cancer and the Environment: Background

A. Breast cancer statistics: A brief introduction

Globally, breast cancer affects more women than any other type of cancer and is the leading cause of cancer-related deaths among women (Hortobagyi, 2008). In the United States, cancer of the breast results in the highest mortality rates of any cancers in women between the ages of 20 and 59. The median age of death from breast cancer is 68 (Horner, 2009). Although mortality rates from breast cancer increase as women age, the elderly are more likely to succumb to lung cancer than breast cancer (Jemal, 2009).

Based on trends from 1996 to 2006, the American Cancer Society predicted that in 2009, some 40,170 U.S. women would die of breast cancer and 192,370 would be diagnosed with the disease (ACS, 2009).

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 data were established, through the end of the 20th century (Jatoi, 2005). Between 1973 and 1998, breast cancer incidence rates in the

United States increased by more than 40 percent (NCI, 2001). Today, a woman's lifetime risk of breast cancer is 1 in 8 and, as of January 1, 2006 (the most recent time point for which data have been released), more than 2.5 million U.S. women were living following a diagnosis of breast cancer (Horner, 2009). Despite these current high rates, the most recent incidence data (2006) indicate a significant decline over the past several years in both breast cancer incidence and mortality in the United States (Horner, 2009), although this effect may only be relevant for women over 50 with a particular subtype (estrogen receptor positive or ER+) of the disease (CDC, 2007; Glass, 2007; Ravdin, 2007). The most widely discussed explanation for this decrease is the sharp decline in use of post-menopausal hormone replacement therapy (HRT) over the past decade and especially following the announcement in 2002 of the association of HRT use with increased risk for breast cancer (Ravdin, 2007; Robbins, 2007).

Rates of diagnosis of ductal carcinoma in situ (DCIS) increased four- to fivefold in the 1980s and 1990s, in large part because of the increased use of mammographic screening, a technology capable of detecting these smaller, non-invasive forms of cancer. Over the past decade, rates of in situ breast cancer have decreased for women over 50, while they continue to increase in younger women (Horner, 2009).

This snapshot of recent statistics for breast cancer incidence and mortality does not do justice to the complexity and variability underlying these numbers. In Section III, we will tease out in more nuanced fashion many of the

issues regarding more vulnerable populations and some of the factors that are associated with this enhanced vulnerability.

B. Migration studies

Women who move from countries with lower 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 4 to 7 times lower, experience an 80 percent increase in risk after living in the United States for a decade or longer (Stanford, 1995; Zeigler, 1993). A generation later, the risk for their daughters approaches that of U.S.-born women. Hispanic women born in the United States have a significantly higher rate of breast cancer than do immigrant Hispanic women. But the longer the period of time these Hispanic women spend in the United States, the greater their risk for breast cancer. This is especially true for women who immigrated before the age of 20 (John, 2005). 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 (Hemminki, 2002).

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 due to nutritional content, contaminants or food additives, or a combination of these factors. Immigration may also affect reproductive behavior, such as the use of oral contraceptives and when or if a woman decides to have children. In addition to

changing an immigrant's social support structures, moving to a more industrialized society may also increase exposure to environmental pollutants that have been implicated in increased risk of breast cancer (Andreeva, 2007).

An increasingly compelling body of evidence from both human and animal models (see below) indicates that exposures of fetuses, young children and adolescents to radiation and environmental chemicals put them at considerably higher risk for later breast cancer diagnosis (Birnbaum, 2003). These data are consistent with the contributory role of environmental exposures, especially at young ages, in the later incidence rate of breast cancer in women who have immigrated to relatively industrialized areas from regions of the world with lower risks of breast cancer.

C. Environmental chemicals in our bodies

Many social and lifestyle changes have occurred in the decades following World War II, a period during which breast cancer rates increased dramatically. In addition, and strikingly, the increasing incidence of breast cancer over these decades paralleled the proliferation of synthetic chemicals. Approximately 85,000 synthetic chemicals are registered today in the United States, and it is estimated that 1,000 or more new chemicals are synthesized each year (EPA, 2007). 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 (Bennett, 2002). 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 (Rudel 2007). Many of these chemicals persist in the environment (Rudel, 2003), accumulate in body fat and may remain in breast tissue for decades (Nickerson, 2006; Siddiqui, 2005).

Studies by the Centers for Disease Control and Prevention (CDC) of chemical body burdens show that all Americans carry many contaminants in our bodies, and that women have higher levels of many of these chemicals than do men (CDC, 2009). Some of the 212 contaminants that the CDC found in people's blood and urine — including chemicals used in common fuels, solvents and other industrial substances and practices — have been linked to mammary tumors in animals (Rudel, 2007).

Many of these same chemicals have recently been detected in young girls (age 6 to 8 years) living in New York, Ohio and California (Wolff, 2007). Data from the Breast Cancer and the Environment Research Centers (BCERC) indicate that levels of many persistent chemicals vary by geographical location and racial/ethnic heritage, with levels of several chemicals being higher in blood samples of California girls than in those of girls from Ohio. Across research sites, higher levels of the flame retardant PBDEs were found in black girls than in Hispanic and white girls, while the opposite relationship was found for PCBs (Windham, 2010).

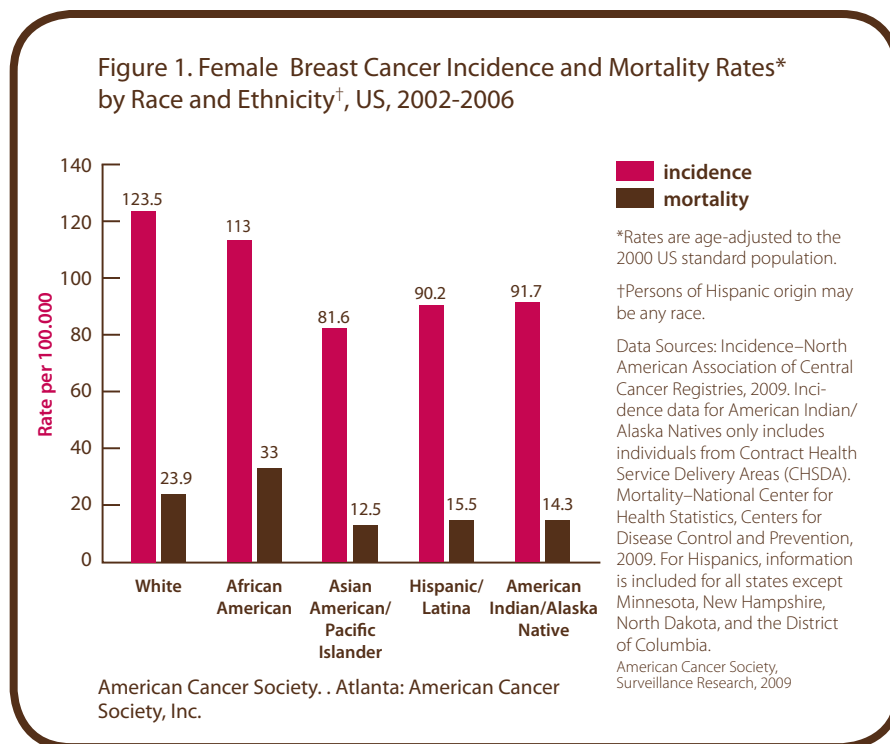
In biological samples from pregnant women and mothers who have recently given birth, some of these chemicals are found in maternal blood, placental samples

and breast milk, indicating that maternal burdens of environmental contaminants are being passed on to their young during pregnancy and breast-feeding (Anderson, 2000; Chen, 2006; Padmanabhan, 2008; Shen, 2007). The Environmental Working Group has published two reports examining the presence of toxic chemicals in the cord bloods from white (EWG, 2005) and minority (EWG, 2009) children at the time of their births. Although sample sizes for these studies were small, individual blood samples were tested for scores of chemicals. Blood samples contained multiple chemicals, with one infant's cord blood testing positive for 191 individual toxic chemicals (EWG, 2009). These data are of great concern given the growing number of studies demonstrating that chemical exposures during the prenatal period through adolescence have profound lifelong impacts on breast tissue development and susceptibility to cancer later in life — an issue that we will discuss throughout this report.

III. Vulnerable Populations

A. Race and ethnicity

Note: In this report we have chosen to use the terms for various racial and ethnic groups that have been used by the authors of the particular papers we are citing. We recognize the complexity, and perhaps inappropriateness, of using simple names to categorize richly different groups of people who are clustered together somewhat arbitrarily because of their biological, social or cultural histories. Yet we also believe it is important to cite and discuss the growing scientific literature demonstrating disparities in exposures and responses to



exposures across different racially and ethnically designated groups.

As cancer incidence data have become more nuanced over the past decade, it is clear that the incidence of breast cancer varies considerably by a number of factors, including age and ethnicity. In the United States for the time period 2002–2006, white women had the highest overall annual incidence rate for the disease (123.5 cases per 100,000 women), followed by African American (113.0 per 100,000), American Indian/Alaska Native (91.7 per 100,000), Hispanic/Latina (90.2 per 100,000), and Asian American/Pacific Islander (81.6 per 100,000) women. (See Figure 1.) Within these racial and ethnic data, there are other distinct patterns. For example, the great majority of women diagnosed with breast cancer are 45 years old or older, and a higher rate of the disease is found in white women as compared to African American women for all ages after 45 (ACS, 2009). Yet there

is a higher breast cancer incidence rate for African American than white women younger than 45 (Horner, 2009).

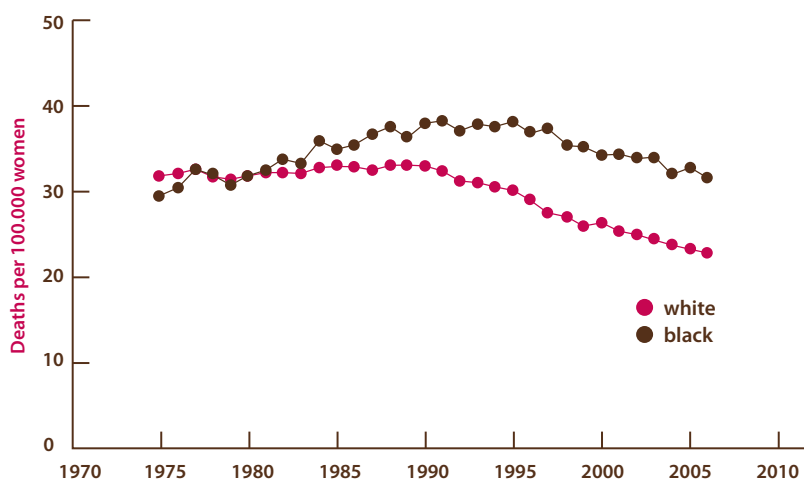
Most important, younger women in general, and younger African American women in particular, are more likely to present with the triple negative subtype of the disease, a diagnosis that is both more aggressive and associated with a higher mortality (Bowen, 2006; Jones, 2004). Published data from the Carolina Breast Cancer Study 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 (Carey, 2006). Like young black women, Latinas are also disproportionately affected by aggressive triple-negative tumors (Bauer, 2007).

Throughout the 1990s, the incidence of inflammatory breast cancer (IBC), a rare type that affects primarily pre-menopausal women, increased in both black and white women (Hance, 2005). 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.

Globally, more than 1.15 million women were diagnosed with breast cancer in 2002 (Parkin, 2005, 2006). 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, breast cancer is the most commonly diagnosed cancer in women (Parkin, 2006). In northern Africa, as in many regions that are either developing or in transition, breast cancer rates are escalating sharply (Althuis, 2005; Parkin, 2006). 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.

With regard to mortality, across racial and ethnic groups in the United States, death rates from breast cancer have decreased over the few years since their peak in the mid- to late 1990s (Horner, 2009). Despite this apparent good news, significant racial/ethnic disparities have remained consistent over the last several decades. In the United States, black women have the highest breast cancer mortality rates (33.0 deaths per 100,000

Figure 2. Mortality Rates for White and Black Women in the United States Between 1975 and 2006 (Horner, 2009)



women) of any racial/ethnic group. Asian American women have the lowest mortality rates (12.5 deaths per 100,000), with white (23.9 deaths per 100,000), Hispanic (15.5 deaths per 100,000) and American Indian/Native American (17.6 deaths per 100,000) women having intermediate rates (ACS, 2009).

Mortality rates by racial groups have been recorded for the full three decades since 1975 only for blacks and whites in the United States. At any age, black women are more likely to die from breast cancer than are white women. While mortality rates for both groups have decreased over the past couple of years, the decrease has been much less for black women, and the disparity between mortality rates for white and black women has grown over the two decades since the mid-1980s, when they were comparable (Horner, 2009; Figure 2).

Understanding differences in vulnerability across geographic areas, racial/ethnic groupings and

ages is a daunting task, made even more complicated by the changing trends across time. Yet many studies are examining these variables, trying to tease apart possible genetic, lifestyle, reproductive history and, increasingly, environmental factors that contribute to enhanced vulnerability to a diagnosis of or death from breast cancer. Most important, many studies are now examining the interactions of many of these factors. 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 like race/ethnicity, body mass, reproductive history and social factors might make some women more susceptible to the carcinogenic effects of the organochlorine pesticides (Millikan, 2000). Other studies have supported the concept that particular risk factors

may exert different effects on women of different racial/ethnic backgrounds. For example, early age at first birth and having four or more children before age 45 appear to increase risk of breast cancer in younger black women, while in white women early childbearing reduces breast cancer risk (Palmer, 2003). Recent data indicate that pregnancy is associated with higher levels of circulating insulin-like growth factor-1 (IGF-1) and that IGF-1 levels are elevated in black women as compared to either white or Hispanic women (Arslan, 2006). Although certainly not the only factor involved in breast cancer development, IGF-1 is a hormone that has been associated with increased risk of breast cancer (Laban, 2003). Although black women report using oral contraceptives less frequently than do white women (Bruner Huber, 2009; Saxena, 2006), studies indicate that use of oral contraceptives may increase the risk of breast cancer in black women, in association with elevated levels of IGF-1. While oral contraceptive use suppresses levels of IGF-1 in white women, long-term use is also associated with increased risk of breast cancer (Jernstrom, 2001). This suggests that effects of oral contraceptives on increased risk for breast cancer may be mediated in part through different pathways in women of different racial/ethnic heritage.

Racial and ethnic minorities often are exposed to disproportionately high levels and varieties of environmental pollutants in the United States (Brulle, 2006). We also now know that there are racial/ethnic differences in the body burden of different environmental chemicals that have been associated with increased risk for breast cancer.

According to CDC scientists, blacks have higher body burden levels than whites or Mexican Americans of many chemicals, including PCBs, mercury, lead, PAHs, dioxin and phthalates. Mexican Americans have higher levels of the pesticides DDT/DDE, lindane and 2,4,5-TCP (CDC, 2009).

Where scientific studies address differences in susceptibility to the effects of specific environmental risk factors that are associated with racial or ethnic backgrounds, we will try to explore those complexities. This will be important both for understanding the interactions of these many different factors at a scientific level, and for informing decisions about policy to minimize exposures, especially for vulnerable populations.

B. Accidental, occupational and home exposures

Understanding racial/ethnic variations in susceptibility to risk factors for breast cancer is, of course, further complicated by many other variables, including neighborhood, home and workplace environments and occupational exposures to chemicals and radiation, as well as proximity to accidental and unregulated releases of chemical toxicants from primarily industrial sources.

Exposures to carcinogens from catastrophic events, such as the detonation of atomic bombs in Japan; the accidental releases of radiation in Chernobyl, Russia, and of dioxin in Seveso, Italy; all provide demonstration of the devastating long-term effects of very high-dose and chronic exposures to environmental toxicants. In all cases, younger women's exposures were more influential in determining

later increased risk for breast cancer, and results only became apparent two to three decades after the initial exposure (Land, 2003; Pesatori, 2009; Pukkala, 2006).

Although women make up nearly half the workforce in the United States, relatively few studies have been conducted to identify occupational exposures associated with breast cancer. Most occupational research on women reports risk by job type or title, rather than by specific exposures, which makes it difficult to draw direct connections between particular environmental factors and health outcomes (Brody, 2007). Many women actually have two places of work: their homes and the paid workplace. Each site has its unique set of exposures to chemicals and non-ionizing radiation, further complicating exposure assessment. However, traditional occupational exposure studies focus on exposures only in the paid workplace.

The relationship between toxic exposures in the workplace and later diagnosis of breast cancer has been difficult to establish in large part because, until recently, occupational studies have not included women in sufficient numbers to evaluate relationships between environments and female-specific cancers like breast cancer (Thompson, 2005). The evidence that does exist shows increased risk for breast cancer in two broad categories: (a) those who work with toxic chemicals (especially organic solvents) and ionizing radiation, such as chemists, dental hygienists and radiology technicians (Bhatti, 2007; Sigurdson, 2003; Simon, 2006) and agricultural (Brophy, 2006), paper mill, textile, auto and microelectronics workers (Bernstein, 2002;

Nail Salon Workers: Occupational Health and Environmental Justice



The nail salon industry is one of the fastest-growing sectors in the United States, with more than 300,000 licensed nail salon workers in California alone. Almost all salon workers are women, and 60 to 80 percent are immigrants from Vietnam. Because more than half of these workers are women of childbearing age (CHNSC, 2010a), chemical exposures in the workplace could have implications for the health of both workers and their children. Many salons are poorly ventilated (Quach, 2008), and workers are exposed chronically to chemicals that have been linked to increased risk for breast cancer and a number of other diseases.

Chemicals that workers in nail salons are commonly exposed to include dibutyl phthalate (DBP), formaldehyde and toluene (EPA, 2007b; Kwapniewski, 2008; Tsigonia, 2009). Such exposure can lead to nausea, dizziness and respiratory and muscular problems, as well as neuropsychological disorders (LoSasso, 2002, Quach, 2008). The health effects of many other chemicals used in nail products are unknown; because cosmetics are not regulated in the United States, only about 13 percent of the more than 10,500 chemicals found in cosmetics and nail products have been fully tested for their impact on health (EWG, 2010). In addition, current regulations do not require professional-use

products to list ingredients, making it difficult for workers to track their own exposures.

A recent study found that urinary levels of DBP metabolites were twice as high in nail salon workers as in the general public (Hines, 2009). DBP is an endocrine-disrupting compound that has been linked in laboratory studies to reproductive abnormalities and to altered growth and proliferation of mammary cells.

An ongoing study funded by the California Breast Cancer Research Program at the Cancer Prevention Institute of California, in collaboration with Asian Health Services, is examining whether nail salon workers have a higher risk of developing breast cancer because of chemical exposures in the workplace (CPIC, 2010).

Understanding possible links between salon workers' occupational exposures and health risks, including breast cancer, is a critical occupational health and environmental justice issue: What is the real price of beauty, and who is paying it?

Some practical suggestions from the California Healthy Nail Salon Collaborative

For nail salon workers: (1) Wear nitrile gloves while working to decrease exposures to dangerous chemicals including DBP; (2) wear an N95 face mask when buffing or filing nails; (3) open windows before work starts to increase ventilation and decrease exposures to chemicals, especially formaldehyde, that may have built up overnight; (4) wear long-sleeved shirts to protect skin; (5) wash hands, arms and face after each customer; and (6) keep all nail polish bottles closed when not in use. For consumers: Buy only nail polish that does not contain the "toxic trio" — toluene, formaldehyde and DBP (CHNSC, 2010b).

Shaham, 2006; Thompson, 2005); and (b) professionals in higher socioeconomic groups, such as schoolteachers, librarians, social workers and journalists (Teitelbaum, 2003; Zheng, 2002). At least in the case of agricultural jobs, there is evidence that workers may take home significant amounts of pesticides on their shoes and clothing, adding prolonged and expanded exposures to themselves and their families (Curwin, 2005).

With expanded use of bio-monitoring to measure actual levels of chemicals in women's bodies, we expect that clearer results will emerge concerning the exposures experienced by women in particular job settings and their future risk of breast cancer and other diseases. But these studies will always be complicated if comparisons are made between people working within industries and those who share residences in the surrounding community, especially if the work site is a source of local pollution for all in the area (Brody, 2007). And, in ways similar to what we have seen before, women with different ethnic and racial backgrounds, genetic profiles and/or lifestyle histories may have different sensitivities to occupational exposures. For example, a new study examining radiation effects on breast cancer incidence in radiologic technicians has demonstrated that there may be interactions between genetic background — especially with genes related to the body's ability to synthesize and metabolize estrogen — and susceptibility to the risk-enhancing effects of occupational radiation (Sigurdson, 2009).

In the home, effects of environmental pollution are often more chronic and more difficult to monitor.

Given the time lag between years of early exposures and later effects on cancer risk, these data can be difficult to collect in a meaningful way. Yet new studies are taking advantage of records kept by state agencies (Bonner, 2005), and evidence about home exposures is now being gleaned by evaluating air and dust samples (Rudel, 2003, 2009a; Zota, 2008). It is hoped that, together, these data will provide a more detailed profile of individual people's environmental toxicant exposure profiles, allowing for better correlations between exposures and health outcomes, including diagnosis of breast cancer.

C. Timing of exposures

More than two decades of research on laboratory animals, wildlife and isolated cell systems has 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, an effect that makes research into environmental risks and disease even more challenging (Calabrese, 2004). 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 (Fenton, 2006). Issues of timing reflect the fact that mammary cells are more susceptible to the detrimental effects of hormones, chemicals and radiation during early stages of development, from the prenatal period through puberty and adolescence, and on until a woman's first full-term pregnancy (Russo, 2001).

1. 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 (Herbst, 1970). An estimated 5 to 10 million American women and fetuses were exposed to DES between 1947 and 1970 (Guisti, 1995). Prenatal exposures to DES led to structural abnormalities in the daughters' reproductive tracts, leading to later infertility and increased vaginal and cervical cancer rates (Li, 2003). Evidence over the past decades indicates that both for the mothers who took the drug and for their daughters who were exposed prenatally, exposure to DES is also associated with an increased risk for breast cancer (Colton, 1993; Titus-Ernstoff, 2001; Troisi, 2007).

Over the past several decades, numerous studies have shown that increased prenatal exposures to endogenous (naturally occurring) maternal estrogens increase risk for breast cancer (Park, 2008). Recent data also indicate that changes in the fetal environment, possibly including increased exposures to synthetic estrogens or estrogen-mimicking chemicals, may lead to higher incidence of breast cancer in adulthood (Park, 2008; *cf* Troisi, 2003). These studies look at indirect markers of fetal estrogen exposure, mainly infant birth weight. Higher birth weight is associated both with increased maternal estrogens during pregnancy and risk of breast cancer, especially pre-menopausal cancer, in later life (Hilakivi-Clarke, 2006), although the exact relationship is unclear.

A long-term study of Dutch women living in a period of severe famine

during 1944–45 showed that famine during pregnancy, especially during the first trimester, led to a several-fold increase in breast cancer rates in daughters (Roseboom, 2006). 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.

It is exceedingly difficult to separate fetal exposures to environmental chemicals and radiation from sustained exposures over a lifetime. One may be able to look back on medical records and determine what prescription drugs a mother might have taken during pregnancy, and therefore what pharmaceutical agents her daughter might have been exposed to during prenatal development. But such clearly recorded information does not exist regarding the multiple exposures in the real world, and rarely are exposures limited so neatly to one particular period of development. Whether exposed briefly or for longer durations, people are unlikely to have accurate knowledge about exposures 30 to 60 years later when breast cancer is diagnosed. This makes it very difficult to study the effects on breast cancer risk of prenatal, neonatal and early-childhood exposures to environmental chemicals and radiation, at least using traditional epidemiological tools to assess exposures.

There is one human study that has more directly examined the connection between environmental exposures around the time of birth and later development of breast cancer. A study from western New York examined air-monitoring records from 1959 to 1997 to establish polycyclic

aromatic hydrocarbon (PAH) levels in residential areas. 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 a number of hormone-mediated systems (Kemp, 2006; Santodonato, 1997). This case-control study of 3,200 women (ages 35 to 79) showed that exposures to high levels of PAHs at the time of birth were associated with an increased risk of post-menopausal breast cancer decades later (Bonner, 2005).

Data from animal studies support the conclusion that prenatal exposures to environmental chemicals can increase the later risk for breast cancer (Soto, 2008b). Bisphenol A (BPA) is a chemical found widely in food packaging and containers as well as in many other commonly used products. National studies by the CDC have demonstrated that more than 90 percent of U.S. adults and children over the age of six have measurable levels of BPA in their urine, demonstrating how ubiquitous the chemical is and how prevalent it is within our bodies (Calafat 2005, 2009). Other studies have shown BPA to be present in maternal and cord blood as well as placental tissues, indicating that developing human fetuses are also exposed to this common synthetic chemical (EWG, 2009; Ikezuki, 2002; Schonfelder, 2002). 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 (Muñoz-de-Toro, 2005; Wadia, 2007).

These results demonstrate that alterations of perinatally exposed animals' mammary gland structure 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, a common technique used in many laboratory studies (Soto, 2008a). According to Markey and colleagues (2001), these findings "strengthen the hypothesis that in utero exposure to environmental estrogens may predispose the developing fetus to mammary gland carcinogenesis in adulthood."

Most important, prenatal exposures of mice to BPA led to the appearance in mammary glands of preneoplastic (intraductal hyperplasias) and neoplastic (carcinoma in situ) lesions that were visible at the onset of puberty (Murray, 2007a). Following brief post-pubertal exposure to a known carcinogen, adult animals that had also been exposed prenatally to low doses of BPA developed more pre-cancerous and cancerous abnormalities in their mammary tissues (Durando, 2007). Similarly, laboratory studies have shown that prenatal exposures to either the dioxin TCDD (Brown, 1998; Fenton, 2002; Jenkins, 2007) or a breakdown product of the commonly used herbicide atrazine (Enoch, 2007) alter subsequent mammary gland development in

Early Puberty and Breast Cancer



Over the past two decades, the age at which girls begin breast development (known as thelarche) has decreased by a year or more in both the United States and Europe. During the same time period, the age of first menstruation (menarche) has decreased by several months (Euling, 2008; Toppari, 2010). What does it mean that childhoods have been shortened for girls today? This troubling trend has been associated not only with a wide variety of medical, social and psychological problems in adolescent girls (Steingraber, 2007) but also with the development of later-life breast cancer (Anderson, 2007; Clavel-Chapelon, 2002; Shatakumar, 2007b).

The nuanced and complex series of structural changes that occur during pubertal breast maturation is regulated by estrogens, which orchestrate the sequence and timing of breast development. Numerous chemicals that we use in our daily lives are endocrine-disrupting compounds that can mimic or alter the activity of many hormones, including estrogens. Exposures to

these common environmental toxicants may be responsible in large part for the falling age of breast development in young girls (Hiatt, 2009; Toppari, 2010; Bourguignon, 2010).

Some studies examining exposure during infancy and very early childhood to hormone-disrupting compounds such as PCBs and DDT/DDE have reported effects on the age of puberty, including breast development (Den Hond, 2009). Early breast development in girls (Colon, 2000) and gynecomastia (male breast enlargement) in boys (Durmaz, 2010) have also been associated with increased body burdens of estrogenic phthalates — compounds that are found in many plastics and personal care products. A recent study from the Breast Cancer and Environment Research Centers (BCERC) initiative of the National Institute of Environmental Health Sciences (NIEHS) finds evidence of these developmental effects of phthalates, especially those commonly used in personal care products and fragrances (Wolff, 2010).

Environmental chemicals that alter the body's naturally occurring hormones probably interact with genetic, dietary and other lifestyle factors in determining the age of breast development. Reducing exposures to common endocrine-disrupting compounds may help reverse the trend of decreasing age at breast development. This would help mitigate the medical and social issues faced by girls who go through early puberty and would help protect them against later development of breast cancer.

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.

2. Childhood and adolescent exposures

In addition to direct effects on risk for breast cancer, numerous environmental chemicals, including many discussed in this report, have been shown to alter reproductive

system function, including the age of puberty. Early puberty is a known risk factor for breast cancer (Anderson, 2007; Clavel-Chapelon, 2002; Shatakumar, 2007b). The average age of menarche (first period) has been decreasing significantly over the past several decades, and the trend is more pronounced for young girls of racial and ethnic minorities (Steingraber,

2007). The pre-pubertal reproductive system, including brain and breast tissue, is exquisitely sensitive to even low levels of estrogens, with premature breast development being associated with slightly elevated levels of circulating estrogens (Aksglaede, 2006). Given that many environmental chemicals interfere with, and sometimes mimic, our natural hormones, including estrogens, one possible mechanism underlying the advancement of puberty over the past several decades may be exposures to endocrine-disrupting chemicals (Aksglaede, 2006; Steingraber, 2007).

In 2003 the National Cancer Institute (NCI) established the Breast Cancer and the Environment Research Centers (BCERC), a network of collaborations across the United States charged with examining the impact of pre-pubertal exposures to environmental chemicals on pubertal timing and development in young girls, as well as development of mammary tumors in young rodents (BCERC, 2010). As these data continue to be published over the next few years, we hope to get a clearer understanding of the links between environmental exposures, their timing in childhood and puberty, and later risk for breast cancer.

More direct connections between exposures to environmental chemicals during childhood and adolescence on later risk for breast cancer have been examined in only a few studies. For example, one recent study demonstrated 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 in women

under the age of 50 (Cohn, 2007). The connection between breast cancer and exposures to radiation in childhood or adolescence is clearer (Boice, 2001; Preston, 2002). In women, links between radiation exposure and breast cancer have been confirmed in atomic bomb survivors (Land, 2003; Pierce, 1996; Tokunaga, 1994). Rates of breast cancer were highest among women in Hiroshima and Nagasaki who were under 20 when the United States dropped the atomic bombs (Land, 2003). Following the 1986 accidental radiation contamination in Chernobyl, 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 (Pukkala, 2006). It 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.

Regular treatment of teenage and young adult women with medical radiation has also led to an increased incidence of breast cancer. 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 (Morin-Doody, 2000).

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 (Clemons, 2000;

Schellong, 1998). Girls and adolescents treated with radiation to combat non-Hodgkin's lymphoma have a similar increase in rates of breast cancer several decades later (Tward, 2006). For women who had repeated fluoroscopic exposures while being treated for tuberculosis as young girls, larger doses and younger age at the time of radiation exposure were both associated with higher incidence of breast cancer in adulthood (Howe, 1996). When women who had been treated with radiation for enlarged thymus glands during infancy were compared with their non-treated sisters for the incidence of breast cancer decades later, a 3.6-fold increase in incidence of breast cancer cases was found among the women who had received early X-ray treatments (Hildreth, 1989). A recent study demonstrated that women who were exposed to dental X-rays during early childhood (starting before age 10) without the consistent use of protective lead aprons had almost a doubled risk of later diagnosis of breast cancer, compared with those who had used appropriate protection (Ma, 2008).

3. Pregnancy and lactation

Regardless of racial/ethnic background, full-term pregnancy and lactation confer significant long-term protection against a diagnosis of post-menopausal breast cancer. This protective effect reflects the full maturation of the mammary cells of the breast, resulting in lower proliferation rates and decreased sensitivity to hormonal and other chemical factors (Russo, 2008). First pregnancies earlier in adulthood are more effective in offering protection especially for post-menopausal breast cancer, and higher numbers of births over a woman's reproductive life are



also associated with a decreased later risk for developing the disease (Kauppila, 2009). These data are complicated by the results cited earlier, showing racial differences in the effects of multiple childbirths on pre-menopausal breast cancer incidence. Having a greater number of children is associated with an increased risk for black women, while increased childbirth and lactation confer protection for both pre-menopausal and post-menopausal breast cancer for white women (Palmer, 2003; Stuebe, 2009).

On the other hand, high hormone levels during pregnancy and lactation, and the rapid proliferation of mammary cells during these periods, have been linked with what is termed “pregnancy-associated breast cancer,” meaning cancer that is diagnosed during pregnancy (relatively rare) or during the first several months of breast-feeding (Kauppila, 2009). This transient increase in risk may last for several

years following delivery, before the longer-term protective effects are realized (Lyons, 2009). Pregnancy-associated cancers have been shown to be more aggressive than similarly staged tumors detected later in life (Mathelin, 2008), and the enhanced postpartum risk is exacerbated by older age at first pregnancy and carrying mutations in the so-called primary breast cancer genes (BRCA1 and BRCA2) (Lyons, 2009). Although no epidemiological data address this point, at least one rodent study has demonstrated that exposure to the environmental chemical dioxin (TCDD) significantly impaired differentiation and maturation of mammary tissue (Vorderstrasse, 2004), a known risk factor for breast cancer. The possibility that exposure to environmental toxicants is contributing to the increased rates of pregnancy-associated breast cancer observed over the past few decades (Andersson, 2009) needs to be explored in more depth.

IV. Complexity of Breast Cancer Causation

A. Mixtures and interactions

Scientists increasingly recognize that to understand the risks underlying a particular disease, they need to focus on the “lived experiences of local populations” or individuals at risk (Koppe, 2006). This means not only understanding possible effects of single types of exposures, but also looking at interactions between substances to which we are exposed and the social and biological contexts in which those exposures occur.

Numerous animal studies indicate that the kinds of mixtures to which an animal (including, by extension, a woman) is exposed are significant in determining ultimate risk (Kortenkamp, 2006). Only a relatively few combinations and doses of chemicals have been tested. This is perhaps not surprising: One estimate predicts that it would require 166 million experiments to test all combinations of three out of the 1,000 most common synthetic chemicals currently in use (Koppe, 2006). While only a few of those studies have actually been conducted, several indicate either additive (to illustrate, $2 + 3 = 5$) or synergistic ($2 + 3 > 5$) effects of mixtures of low levels of chemicals in a number of systems that are relevant to exploring risk for breast cancer. 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.



Over the past several years, methods have been established and validated for examining the effects of large numbers of chemical exposures on mammary cell proliferation and gene activation. The E-screen assay uses estrogen-receptor-positive human breast cancer tumor cells (MCF-7 cells) that are dependent on estrogens for cell growth and proliferation (Soto, 1995), and single studies can examine the effects of scores of chemicals at multiple doses, alone and in combination (Silva, 2007a; van Meeuwen, 2007). One 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 (Rajapakse, 2002). Similarly, and at levels found in our environment, the ubiquitous plastic component BPA significantly increased the effects of estradiol (Rajapakse, 2001; Wadia, 2007).

These results show that even at low concentrations, environmental chemicals may exacerbate some of the biological effects of natural estrogens. For example, in a variety of different types of experimental systems, two different weakly estrogenic pesticides — dieldrin and toxophene — showed either additive (Ramamoorthy, 2001) or synergistic (Arnold, 1996) 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 fish model that, like human breast tissue, is sensitive to estradiol and related estrogenic compounds (Xie, 2005). 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, a suds producer and a chemical disperser (4-n-octylphenol and 4-nonylphenol). Clear additive

effects across the four chemicals were observed (Foster, 2004).

Interactions between factors involved in breast cancer risk go beyond mixtures of chemicals. In a study of mammary tissue development, mixtures of chemicals commonly found in the environment made rat mammary tissue more susceptible to exposures to dietary compounds with estrogenic properties after birth. These profound tissue abnormalities have been associated with mammary tumors (Foster, 2004). Similarly, pretreatment of young rats with a low dose of radiation resulted in earlier occurrence and increased frequency of mutated mammary tumors after subsequent exposure to a known chemical carcinogen (Imaoka, 2005, 2009).

A number of 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 occur solely in primary breast cancer genes 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 (Hoyer, 2002; Laden, 2002; Olivier, 2001).

B. New models for thinking about dose-response relationships

Although it has long been understood that many of our body's natural chemical signals, including hormones and neurotransmitters, may exert nonlinear effects, the challenge to linear toxicology models has only been made in the past several years (Hoffman, 2009; NRC, 2009). Increasingly scientists are learning that many environmental toxicants, including especially the class of chemicals called endocrine-disrupting compounds (EDCs), can exert devastating effects at infinitesimally small levels of exposures, especially during early critical windows of vulnerability (Diamanti-Kandarakis, 2009; Fenton, 2006). And, most important, the effects of these toxicants are not linear but sometimes follow U-shaped (or inverted U-shaped) curves in a similar fashion to the effects observed in tissues that respond to naturally occurring hormones, such as estradiol (Vandenberg, 2006). Thus, very low doses may exert more severe effects than moderate doses. As we will see in this report, prenatal and early-life exposures to very low, environmentally relevant doses of EDCs have been implicated in later risk for developing breast cancer as well as a number of other diseases.

These results require the dismissal of linear approaches to toxicological assessment. And they require the continued intensive study of the effects of low-dose exposures to chemicals, especially during critical periods of development from the prenatal stages through adulthood (Calabrese, 2006). Finally, studies also need to reflect an evaluation of background exposures to environmental toxicants as well

as of processes underlying disease progression and factors associated with the biological and social worlds of vulnerable populations (NRC, 2009).

C. Changes in cell processes: Genetic, epigenetic and tissue organizational effects

We understand clearly now that various factors, whether related to environmental, genetic, lifestyle or reproductive histories, all interact to create the particular risk profile for an individual. Even the term “gene-related” can involve a variety of processes, always being expressed in the larger context in which the individual develops and lives. Genes function within cells, interacting in complex ways with hundreds of neighboring cells, all communicating closely with one another and influencing each other's structure and function.

1. Primary breast cancer susceptibility genes

It is estimated that somewhere between 5 and 10 percent of all female breast cancers are the result of mutations in the primary nucleotide sequences of genes inherited from one's parents. The most common and best studied of these so-call germ-line mutations are *BRCA1* and *BRCA2*, both of which belong to the broad class of “tumor suppressor genes.” So, for example, among the various functions that *BRCA1* regulates are those related to DNA repair, chromatin remodeling and cell-cycle checkpoint control (Oldenberg, 2007).

Inheritance of a mutated form of either of the BRCA genes, or of other less common tumor-suppressor genes that have been associated with breast cancer, is

associated with a significantly increased risk for breast cancer. Yet not all women (or men) with BRCA mutations develop breast cancer. One factor that may influence ultimate risk may be the site where the mutation lies on the actual gene (Bradbury, 2007; del Valle, 2009). Other factors, like early exposure to environmental chemicals and/or radiation, may also influence later expression of genetic irregularities (King, 2003).

2. Lower penetrance genes (polygenic model)

In addition to these primary mutations in tumor-suppressor genes, recent scientific evidence indicates that structural alterations in other genes, such as those involved in hormone synthesis and breakdown, may increase the susceptibility for later development of breast cancer. Other genes may work in concert to affect regulation of cell-cycle and DNA repair processes. Mutations in one or more of those genes may alter susceptibility to other genetic, lifestyle, hormonal or environmental challenges (Bradbury, 2007; Conde, 2009; Silva, 2009). Increasingly, data are demonstrating that the complexity of individual genetic profiles may help explain some of the differential sensitivity to environmental as well as hormonal and lifestyle factors when it comes to predicting risk for later disease (Ghoussani, 2009).

3. Mutagenesis

One way in which many agents affect development of breast cancer is by causing mutations, or changes in the sequence of base nucleotides in the DNA, through deletions, replications or substitutions of original base pairs. These mutations are then replicated during regular

cell-division processes. When the mutations are in genes that regulate cell proliferation or aspects of tumor suppression, they can contribute to the development of cancer.

4. Epigenetics

In addition to classical gene mutations, data from the past several years have demonstrated another mechanism by which alterations in genes can influence susceptibility to diseases, including breast cancer. This second mechanism, called epigenetics, refers to a change in the timing or frequency of expression of a gene, rather than changes in the genetic code or base sequences (Dworkin, 2009). The most common epigenetic changes are in the rate of methylation of DNA or changes in DNA-associated histone proteins. In both cases, the result is a change in the rate (either activation or repression) of transcription (expression) of an associated gene (Chiam, 2009). These epigenetic changes tend to be fairly small, but potentially cumulative, over an individual's lifetime (Baccarelli, 2009) and may, therefore, exert important effects on disease initiation.

A number of environmental toxicants, including heavy metals, several organic solvents and endocrine-disrupting compounds, have been shown to lead to

epigenetic changes in gene activity. All of these substances are also implicated in an increased risk for breast cancer. Of particular importance is the growing evidence from human and especially animal studies that epigenetic changes very early in life can have profound effects on physical development and susceptibility to onset of breast cancer much later in life (Chiam, 2009). Critically, some epigenetic changes may be transmitted to future generations (Skinner, 2010).

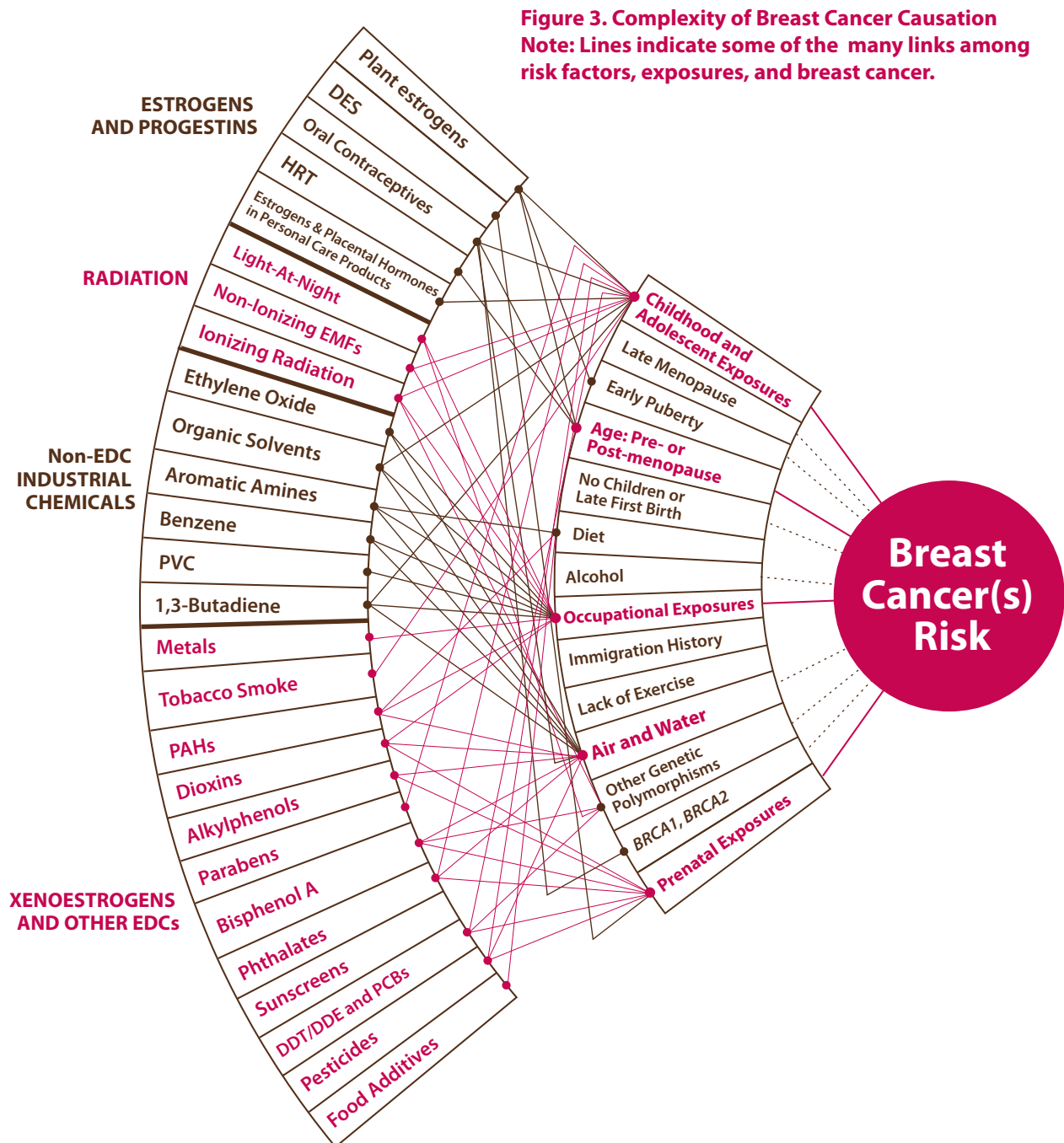
5. Tissue Organization Field Theory (TOFT) of carcinogenesis

The evidence for epigenetic changes underlying non-inherited cancers, including breast cancer, has contributed to the emergence of a new model of the processes mediating the development of cancer. (Soto, 2004, 2008a). Rather than thinking about cancer development only as an accumulation of increasingly serious DNA mutations, Tissue Organization Field Theory builds on a more ecological view of cellular functioning and tissue organization. TOFT begins by recognizing that cell proliferation is the default state for cells, with processes and chemical signals critically regulating the rate of proliferation, and also that cells work in constant interaction with neighboring cells in the various tissues within an organ (Soto, 2004).

Perturbations of the chemical and/or biomechanical signals between cells and their microenvironment, or disruption of cell-cell interactions, potentially caused by environmental chemicals or radiation, may underlie the development of cancer in affected tissues.

D. A “simple” model for thinking about the links between environmental toxicants and breast cancer

We need to think of breast cancer causation as a complex web of often interconnected factors taken together, each exerting both direct and interactive effects on cellular and extracellular processes in mammary tissue. Even as we turn to the evidence implicating particular environmental exposures to increased risks for developing breast cancer, the results need ultimately to be understood in the larger context of the developmental, social and personal contexts in which each individual lives. (See Figure 3.)



State of the Methodology



More commonly, women, adolescents, young girls and even fetuses are exposed unknowingly to multiple chemicals at lower doses. This makes it difficult for researchers to compare exposure histories ... for women who develop or do not develop breast cancer.

I. Introduction

A substantial scientific literature has developed that implicates 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 inform our understanding of risk for the disease on a broader level. Scientists are exploring the relationship between breast cancer and environmental exposure using a combination of approaches, including human epidemiological and biomonitoring studies as well as experimental laboratory research studies in animals (in vivo) and in cell cultures (in vitro). New methods and technologies in each of these approaches have enhanced our understanding of breast tissue's vulnerabilities to exposures to a wide range of environmental chemicals and radiation. Together, they have provided compelling evidence that exposures to a number of environmental agents contribute to an increased risk of breast cancer.

II. Human Studies

A. Epidemiological studies

Epidemiological studies explore the relationships between environmental exposures and incidence of breast cancer in women (and occasionally men), describing historical, social and/or environmental conditions under which the disease occurs in particular groups. These studies are often critical starting points for developing hypotheses and, ultimately, for thinking about effects of exposures on incidence of disease in people. Epidemiological studies can also provide powerful tests of specific hypotheses, and several studies can be combined statistically to afford more precise estimates of cause-effect relationships.

Well-recorded and high-level exposures to environmental chemicals or radiation following military campaigns or industrial accidents constitute unusual but important sources of data, demonstrating relationships between these exposures and changes in rates of diseases such as breast cancer. Examples include the radiation exposure following the atomic bomb detonations in Japan (Land, 2003); the accidental release of radiation in Chernobyl, Russia (Pukkala, 2006); the

accidental release of dioxin in Seveso, Italy (Pesatori, 2009); or cases of substantial and sustained occupational exposures to industrial chemicals or radiation (Bhatti, 2007; Brophy, 2006; Sigurdson, 2003; Simon, 2006; Teitelbaum, 2003; Zheng, 2002). These exposures have been associated with increased incidence of later breast cancer, especially for women exposed at younger ages.

More commonly, women, adolescents, young girls and even fetuses are exposed unknowingly to multiple chemicals at lower doses. This makes it difficult for researchers to compare exposure histories — in terms of what, when and how much — for women who develop or do not develop breast cancer. In addition, many of the chemicals of concern may influence factors like timing of puberty or menopause, and, in turn, pubertal or menopausal status might influence susceptibility to the effects of environmental factors (Eskenazi, 2005; Steingraber, 2007). The challenges of exploring these relationships in our mobile, industrial society require the use of a variety of complementary approaches to examine human environmental exposures and development of breast cancer. These approaches run the gamut and include enhanced measurement of present and past exposures in our environment; more detailed measurement of chemical contaminants in the body at different times over the life span; development of community-based studies finding intersections between these approaches; and new information from genomic studies that examine predisposing vulnerabilities to disease progression in different groups and individuals.

B. Chemical exposures: Air and dust measurements

Chemical exposure profiles in our homes, schools and workplaces have changed greatly over the past several decades (Weschler, 2009). During the middle decades of the past century, levels of many pesticides and solvents increased significantly. Following regulatory action banning or limiting production and use of some of these substances, exposures levels decreased, often substantially. Other chemicals, including many that did not exist 50 years ago — including many plasticizers, flame retardants and other common additives to products we use daily — have recently increased in usage and presence in our environment.

Measuring indoor levels of chemicals allows for a significant snapshot of our daily exposure profiles. Chemical concentrations tend to be higher indoors and to degrade more slowly (Goyal, 2009; Rudel, 2003, 2009a). Levels of several volatile chemicals and particulate matter (associated with the presence of many chemicals) have been shown to be higher in schools and homes than outside, with levels particularly high in homes (Fromme, 2008; Kotzias, 2009). Exposures to chemical pollutants in our homes, our schools and outdoors may vary by season or even by day of the week (e.g., weekend vs. weekday), reflecting differences in ventilation and in agricultural, traffic, cleaning and professional/recreational activities (Goyal, 2009; Perrone, 2010; Verschaeve, 2007; Zimmerman, 2008). Analyses of air and dust samples in homes have revealed significant levels of many compounds, including phthalates, alkylphenols, pesticides, flame retardants and many other

endocrine-disrupting compounds (EDCs) (Rudel 2003, 2009a). Most of these chemicals are found in commonly used consumer products, yet few of these substances have been thoroughly analyzed for their health effects in humans (Diamanti-Kandarakis, 2009).

Measurement of indoor air and especially dust may be particularly salient for understanding the environment to which young children are exposed (Hwang, 2008). This is critical information, as we know that early life exposures have profound effects on development of many diseases, including breast cancer, but also asthma and several neurodevelopmental disorders (Kamel, 2004; Landrigan, 2005; Perrera, 2005; Wigle, 2008). And we know that exposures of children to toxicants in the home may lead to a higher body burden of those chemicals as compared to that of adults, because of the differences in children's ventilation rates, metabolism of toxicants, hand-to-mouth behaviors and constant contact with floors and other surfaces (Ginsberg, 2008).

C. Chemical exposures: GIS mapping

Geographic Information Systems (GIS) are an important technology in epidemiological research. GIS studies allow for the complex spatial mapping of many environmental, demographic, historical and health-related variables. These studies result in detailed individual and community information that can be used to correlate exposures that occur differently across geographic space and time with later development of diseases, including breast cancer (Graves, 2008).

Scientists at the Silent Spring Institute in Massachusetts are using GIS mapping to overlay extensive historical exposure records, local chemical contamination profiles, and detailed questionnaire information about chemical usage and personal health histories on Cape Cod. This has led to the creation of the Cape Cod Breast Cancer and Environment Atlas as well as to the publication of a number of studies exploring these complex relationships (Brody, 2004; McKelvey, 2004; Rudel, 2003).

Another example of the use of GIS is a recent study examining disparities in survival rates among women living with breast cancer in association with demographic factors (race/ethnicity and socioeconomic status) along with profiles of tumor grades, medical treatment and screening histories. Several clusters of longer- or shorter-than-expected survival ages were identified (e.g., a cluster of shorter-than-expected survival in the Detroit metropolitan area), suggesting a starting point for

looking at environmental and other factors that might be influencing mortality rates in these areas (Schootman, 2008).

D. Biomonitoring

An important development is the increased resolution and use of biomonitoring techniques to analyze the types and concentrations of chemicals and their breakdown products (metabolites) in our bodies, recognizing that many of the chemicals of concern, or their metabolites, accumulate in our bodies. These chemicals can be measured in people's blood, urine, hair and saliva (Angerer, 2006). Several of the chemicals of greatest concern in this report, the endocrine-disrupting compounds (EDCs), are lipophilic, or fat-seeking, and may be found in fat tissue, including the extensive fat tissue found in breasts, as well as in the milk of lactating mothers (Anderson, 2000; Shen 2007).

Monitoring excretion (urine samples), circulation (blood samples) or salivary levels of chemicals can

be fairly straightforward and can be done reliably and repeated 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 is impractical and risky and would pose ethical concerns. Nevertheless, fat and biopsy 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 (Siddiqui, 2005). Reliable measurement of chemicals in placental tissue or cord blood at the time of birth, or meconium and breast milk after delivery, can give non-invasive information about fetal and perinatal exposures to chemicals at critical times in a child's development (Shen, 2007).

One important trade-off that must be considered in current biomonitoring studies is the choice between measuring single or limited numbers of chemicals in large numbers of samples or obtaining richer profiles of body burdens of environmental chemicals in smaller samples. The recent publication by the U.S. Centers for Disease Control and Prevention (CDC) of the *Fourth National Report on Human Exposure to Environmental Chemicals* (CDC, 2009) measured 212 different chemicals from the blood and urine samples of approximately 2,400 adults participating in the National Health and Nutritional Examination Survey (NHANES). It presents data on chemicals, one at a time, related to the proportion of individuals with detectable levels of particular chemicals and the ranges of the levels detected.

At the other extreme, for example, is the small study run by the



Environmental Working Group (EWG) examining umbilical cord blood from 10 minority infants at the time of birth. In addition to group profiles of exposures to particular chemicals, EWG was able to look at the fuller profile for each individual child. One cord sample contained detectable levels of 191 chemicals, indicating the importance for scientists to be studying effects of early exposures not only to potential toxicants, but also to mixtures of chemicals (EWG, 2009).

Although biomonitoring data are excellent indicators of people's exposures to various environmental compounds, the data do not necessarily identify the sources or the duration of exposure (Morello-Frosch, 2009). Nevertheless, aggregate exposure levels have been useful in identifying links between body burdens of environmental chemicals and disease development. 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 (Fernandez, 2007; Ibarluzea, 2004).

E. Genome-wide association studies: Acquired susceptibility

In addition to helping researchers understand the role of the primary breast cancer genes, *BRCA1* and *BRCA2*, new technologies allow molecular epidemiologists to scan broadly across the full genome (using genome-wide association studies, GWAS) to find possible variations that are associated with

disease states, including breast cancer (NHGRI, 2010). Although the contributions of individual genetic variants are often fairly weak, the robustness of the methods for detecting associations with particular variants has led to great increases in the number of studies looking at these factors. Of particular interest will be the contribution of these gene-scanning approaches to understanding the variability of sensitivity to environmental factors that is found in individuals and populations with different vulnerabilities to developing breast cancer (Dumeaux, 2008; Vineis, 2009).

F. Community-based participatory research

The increased use of exposure assessment, biomonitoring and genetic-susceptibility information by environmental epidemiologists and activist groups alike, has provided important opportunities for citizen involvement in raising scientific questions and for personal and civic responses to the resulting exposure data (Altman, 2008; Brody, 2009; Morello-Frosch, 2009). These approaches have presented opportunities for scientists and community members to cooperate in all aspects of the design and reporting of study results. They have also created an obligation to provide individual sampling results to those study participants who want them (e.g., Altman 2008). Reporting individual and aggregate data to study participants allows for enhanced opportunities for individual action and collective advocacy to reduce exposures. This approach can be contrary to a more traditional clinical ethics model in which individual results are not shared with participants when the clinical or public health

significance of exposures are not well understood (Morello-Frosch, 2009).

Major research institutions, including the National Institute of Environmental Health Sciences (NIEHS) and the Breast Cancer and the Environment Research Centers (BCERC), now routinely include breast cancer advocates along with scientists and clinicians in the full implementation of large-scale research projects. Additionally, the California Breast Cancer Research Program's (CBCRP) special research initiative on environment and disparities includes not only basic science but also community-directed research projects aimed at better understanding factors underlying enhanced vulnerability for breast cancer diagnoses. All aspects of the CBCRP granting process include community partners and advocates. It is hoped that this multidisciplinary approach will continue to encourage dialogue between the various stakeholders interested in better understanding the connections and debates related to environmental risks and breast cancer.

Of course, not all research in the field is completed using epidemiological or human-based studies. A more detailed understanding of underlying mechanisms by which various environmental exposures may influence breast cancer susceptibility comes from experimental research including animal (usually rat or mouse) models, cell culture (e.g., tumor or pre-tumor cells grown in Petri dishes) studies, and gene-array systems.



III. Experimental Studies: Animal (In Vivo) Studies

Use of animal, most commonly 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 important in learning about risks underlying mammary cancers within the context of otherwise healthy, biologically intact mammals. Rodents are particularly susceptible to chemically induced cancers, making them a good system for studying the cellular and intercellular processes involved in the initiation and progression of mammary tumors (Kim, 2004b, 2010). Their shorter life span and comparable profile of development make mice and rats good models for studying the effects of early exposure to environmental toxicants on susceptibility to tumor development.

Since human breast cancer is a complex and heterogeneous disease, the variety of rodent models for

mammary cancer can provide important information about specific aspects of the human disease (Medina, 2007). Rat and mouse models of mammary development have proven critical to our understanding of complex changes in breast tissue over the human life span, which is essential for examining the effects of chemical and radiation exposures at different critical periods of mammary tissue development. A recent convening of 75 mammary-gland biologists, toxicologists, pathologists, epidemiologists, risk assessors and regulators concluded in consensus, "Given what we know about human, rat and mouse mammary tissue development progression, the rat and mouse are adequate surrogates for human breast development" (Rudel, 2009b).

Rodent models have been critical in understanding some of the complexity of tumor development (Balmain, 2000), with growing evidence that cancer cannot be explained solely by an accumulation of genetic mutations in the tissue, but instead that changes in the

development of and interactions between different cell types (e.g., epithelial and stromal cells) may predispose the organism to cancer (Maffini 2005; Sonnenschein, 2000). This shift in focus toward examining the more complex biological context in which cancer develops has been essential to our understanding of the ways that environmental factors affect molecular, subcellular and tissue organizational systems, and lead to greater breast cancer susceptibility. Animal models have also been important in profiling changes in gene expression associated with development of breast cancer (Chan, 2005; Drost, 2009; Shoushtari, 2007) as well as some of the interactions between genetic and environmental factors in altering risk for breast cancer (Zarbl, 2007).

Limitations of animal models include the fact that rodents have considerably shorter life spans 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 (Kim, 2004b).

In recent years, there has also been considerable debate over whether injection of chemicals (such as BPA) into rodents appropriately mirrors human exposures, which tend to occur mainly through diet, inhalation or absorption through the skin. These debates have often been more political than scientific (Borrell, 2010). In the case of BPA, a chemical for which there is considerable regulatory action pending, the National Institute of

Environmental Health Sciences (NIEHS) is funding a large set of studies in which direct comparisons of oral and injected exposures will be made (NIEHS, 2009).

Another controversy related to the use of rodents for testing human health effects of exposure to endocrine-disrupting compounds (EDCs), including risk of breast cancer, comes from recognition that not all rodents are equally sensitive to the hormone-disrupting effects of EDCs. Strains of rats with low estrogen-receptor levels are relatively nonresponsive to EDCs like BPA in terms of later effects on reproductive and developmental processes (Gray, 2010; Ryan, 2009; vom Saal, 2010). Ultimately, understanding the variability in sensitivities to exposures across species, strains and individuals will be critical in understanding the nuanced mechanisms by which environmental exposures affect risk for people with differing vulnerabilities.

Regardless of positions on particular points, most agree that rodents 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.

IV. Experimental Studies: Cell Culture (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 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) profiles; for example, some cell lines are estrogen receptor positive (ER+) and progesterone-receptor positive (PR+), while others are receptor negative (Lacroix, 2004). 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.

The MCF-7 human breast tumor cell line is dependent on estrogenic stimulation for cell proliferation. This in vitro cell system has been critical in the characterization of many environmental chemicals as EDCs affecting estrogenic pathways. Among the many chemicals identified as being estrogenic using this system are alkylphenols, phthalates, BPA and several pesticides (Soto, 2006).

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 (Dewan, 2006; Heneweir, 2005).

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 replicated. These cell studies are run in the absence of normal feedback from all of 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 (Nelson, 2006).

V. Genomic Studies

The past decade has seen an explosion of research centered on the changes in specific gene activity. This new field of “genomics” began with the deciphering of the code of the human and mouse DNA sequences, as well as the sequences of hundreds of other mammalian and nonmammalian species. Toxicogenomics is the new research field that allows scientists to identify and describe the changes in specific gene activities in the presence of different exposures, and to then study the relationships between these genetic changes and health outcomes (Jayapal, 2010; Zarbl, 2009). Recent technical developments allow for screening of gene expression in clinically derived tissues, whether from experimental animal models or from cell systems treated with various environmental chemicals.

DNA array technology allows for the screening of literally thousands of genes and their products at the same time. This is an extraordinarily powerful descriptive tool that allows scientists to develop hypotheses about changes in cell activity at the

gene-expression level and about the interactions between numerous factors, without needing to rely on large numbers of clinical or animal samples. The sheer quantity of data requires investigators to make choices about which genes and gene products to focus on — a decision process that may vary greatly from lab to lab, especially since there is considerable redundancy in gene regulation of critical cell pathways implicated in breast cancer.

Using molecular profiling and genomic approaches in studying breast cancer has underscored the complexity of the disease, with different genomic profiles arising, depending on breast cell type (e.g., stromal vs. epithelial) and tumor characteristics like size of tumor, node involvement, receptor status and menstrual or estrous cycle phase (Sims, 2009). Nevertheless, genomic approaches are now being used to study changes in breast tissue over the course of cancer development with the hope of better understanding the process of carcinogenesis, the factors responsible for inducing that process, and possible interventions (Rennstam, 2006).

Most important, new applications of this genomics approach are being developed to study the effects of low-dose exposures to environmental toxicants on gene expression through both traditional transcription studies and examination of epigenetic processes that have been implicated in lifetime accrual of added risk for cancer development (Vineis, 2009). These strategies can examine multiple mixtures of environmental factors as they affect cells with different genetic and epigenetic histories.

The ultimate goal will be to combine genomic technologies and epidemiological studies so that we can understand how changes in gene expression over a life span are related to different genetic, reproductive and lifestyle factors as well as to exposures to environmental toxicants (Lund, 2008). A first attempt at this sort of ambitious study is the “Norwegian Woman and Cancer” (NOWAC) post-genome cohort study. Part of a larger national study, it involves following about 50,000 women born between 1943 and 1957. They have answered extensive medical, reproductive history and lifestyle questionnaires and given blood samples that can be used for extensive gene-expression profiling analysis. Should a participant be diagnosed with breast cancer, blood samples and tumor biopsy tissues will be analyzed using similar gene expression assays and compared with samples from healthy women (Dumeaux, 2008).

As we now turn to the evidence supporting the conclusion that exposures to environmental chemicals and radiation contribute to the current high incidence of breast cancer, it will be important to remember the issues of complexity raised in the framework section as well as the strengths and weaknesses of different research strategies explored in the State of the Methodology section. It is also important to recognize the strength of the aggregate body of evidence examining various environmental exposures and their links to breast cancer. The data are simply too powerful, as a whole, to be ignored.

Evidence Linking Environmental Factors and Breast Cancer



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In the sections below, we address many of the chemicals and radiation sources for which there is solid (though at times contested) evidence in the peer-reviewed scientific literature that exposures are linked to increased risk for breast cancer.

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I. Introduction

In the sections below, we address many of the chemicals and radiation sources for which there is solid (though at times contested) evidence in the peer-reviewed scientific literature that exposures are linked to increased risk for breast cancer. 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 substances’

ratings 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. 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. Not all chemicals have been rated by the IARC or NTP.

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

Institution	Rating Category
I: International Agency for Research on Cancer (IARC)	K: Known Pr: Probable Po: Possible
N: National Toxicology Program (NTP)	K: Known R: Reasonably anticipated
	EDC: Endocrine-disrupting compound

Table 1: Summary of IARC and NTP Ratings		IARC			NTP		Endocrine-Disrupting Compound
Compounds Linked to Breast Cancer		Known	Probable	Possible	Known	Reasonably Anticipated	
Hormones: Pharmaceutical and Personal Care Products							
Hormone replacement therapy (HRT) and oral contraceptives		○			○		
Diethylstilbestrol (DES)		○			○		
Estrogens and placental hormones in personal care products		○			○		
Xenoestrogens and Other Endocrine-Disrupting Compounds (EDCs)							
Bisphenol A (BPA)							○
Phthalates							○
Parabens							○
Alkylphenols							○
Polycyclic aromatic hydrocarbons (PAHs)			○			○	○
Pesticides and herbicides							
Triazine herbicides: Atrazine							○
Heptachlor				○			○
Dieldrin and aldrin							○
Other pesticides							○
Polybrominated diphenyl ether (PBDE) fire retardants							○
Dioxins		○			○		○
Persistent organochlorines							
DDT/DDE				○	○		○
PCBs			○			○	○
Aromatic amines			○			○	○
Sunscreens (UV filters)							○
Tobacco smoke: Active and passive exposures		○			○		○
Metals		○			○		○
Hormones in Food: Natural and Additive							
Phytoestrogens							○
Zeranol (Ralgro)							○
Recombinant bovine somatotropin (rBST)							○
Non-Endocrine Disrupting Industrial Chemicals							
Benzene		○			○		
Organic solvents other than benzene			○			○	
Vinyl chloride		○			○		
1, 3-butadiene			○		○		
Ethylene oxide		○			○		

II. Hormones: Pharmaceutical and Personal Care Products

A. 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 (Russo, 2004), and it is believed that many environmental chemicals exert their carcinogenic effects, at least in part, by mimicking or disrupting hormone-regulated pathways, especially estrogenic ones.

Breast cancer in men also implicates estrogen as a contributing factor. Although breast cancer is relatively rare in men, those who develop the disease have higher than normal levels of estrogen, originating from secretions of the testes and adrenal glands (de Los Santos, 2000; Nordman, 2008).

Hormones like estradiol and progesterone are lipophilic, or fat-seeking. This means that they can accumulate in fatty tissues of the body. Breasts are composed primarily of fat and therefore are repositories 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 (Honma, 2007), and its activity is positively correlated with the amount of estrogen receptors (ER) found in breast cancer cells (Miki, 2007).

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 (IARC, 1987a), 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 (NTP, 2002).

These classifications confirm scientific evidence that has been collected since the 1930s linking estrogens with increased cancer risk (Krieger, 2005). Data now show that when a woman's natural estrogens are supplemented by oral contraceptives and/or HRT, her risk of breast cancer increases (CGHFBC, 1996, 1997). 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 (Lund, 2007). The effect may be most pronounced for

pre-menopausal women who have taken both oral contraceptives and hormone therapy (Shantakumar, 2007a).

Pharmacological treatments for infertility also are composed of substances that mimic or block natural hormones, depending on the particular drug combination. Many infertility treatments include taking natural or synthetic gonadotropins, hormones that are involved directly in inducing ovulation, and also in the regulation of ovarian release of estrogens and progestins. Other infertility treatments include synthetic selective estrogen receptor modulators (SERMs) like clomiphene. These drugs work by altering signals to the brain and pituitary, causing the pituitary to release higher levels of natural gonadotropins (Homberg, 2002). Although studies indicate a link between clomiphene and breast cancer, in general the links between infertility treatments and the disease are less strong than for other types of hormone treatments.

On the other hand, the clearest evidence that a synthetic hormone can increase risk for cancer decades later comes from the tragic experience with the pharmaceutical drug diethylstilbestrol (DES). Women who were exposed to DES during their pregnancies and their daughters who were exposed prenatally have increased rates of breast cancer.

B. Hormone replacement therapy (HRT)

Between 1995 and 2000, several epidemiological studies indicated that use of combined estrogen-progestin HRT treatments led to an increase in invasive breast

cancer (Colditz, 1995; Magnusson, 1999; Ross 2000; Schairer, 2000). In 2002, a study designed to explore the benefits and risks of combined estrogen (conjugated equine estrogens) plus progestin (medroxyprogesterone acetate) HRT in post-menopausal women was halted three and half years before the intended end of the study period. This project, called the Women's Health Initiative (WHI), enrolled more than 16,600 healthy women ages 50 to 79. The study was designed as a large randomized control trial, a method considered to be the most rigorous approach to studying clinical responses in human populations (Sibbald, 1998). Half the women took the combined estrogen-progestin HRT, while the other half took a placebo, and a number of health and disease outcomes were monitored. The WHI study was halted early because researchers observed 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 (Rossouw, 2002). More recent analyses clarify that the increased risk of breast cancer in the WHI study is found in women taking the combined estrogen-progestin formula, but not in those women taking estrogen-only HRT supplements (Anderson, 2004).

Since the initial results of the WHI study were published, other large studies have supported its major conclusions. 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 (Holmberg, 2004).

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 (MWSC, 2003). 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).

Other recent 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 (Biglia, 2005; Borquist, 2007; Reeves, 2006) but also of cancers with low proliferation rates (mitotic indices) and favorable prognostic outcome (Reeves, 2006; Schuetz, 2007).

A follow-up study of the women in the WHI trial three years after all participants stopped taking either the HRT or placebo treatments demonstrated increases in invasive cancers of all sorts (grouped together) in women who had been in the HRT arm of the trial. While breast cancer rates remained elevated in this group, a trend over time toward rates similar to those found in the placebo group made these effects nonsignificant (Heiss, 2008). These data suggest that the increased risk for breast cancer that accompanies use of HRT is reversible within a fairly short period following discontinuation of the treatment. This finding is consistent with the rapid drop in post-menopausal breast cancer incidence rates since 2002, a decrease that has been attributed



to the precipitous drop in HRT prescriptions following the release of the data from these large studies (Verkooijen, 2009).

C. Oral contraceptives

Numerous studies have shown an increased risk of breast cancer in women using oral contraceptives (Althuis, 2003; Dai, 2009; Delort, 2007; Kumle, 2002). 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 and took them for longer periods of time (Pasanisi, 2009; Rosenberg, 2009). Several studies have shown that women with *BRCA1* or *BRCA2* mutations (Haile, 2006; Narod, 2002; Pasanisi, 2009; cf. Figueiredo, 2010), as well as women with family histories of breast or ovarian cancer (Haile, 2006; Narod, 2002; cf. Gaffield, 2009), have an increased susceptibility to the risk-inducing effects of oral contraceptive exposures. The data with *BRCA* carriers support the hypothesis that increases in the penetrance (proportion of women carrying the mutation in which the deleterious effects are expressed) of the mutation are related to exposures to environmental toxicants (King, 2003), especially those that mimic or interfere with natural estrogens.

As with HRT, current use of oral contraceptives has been associated with an increase in breast tumors originating in the lobular tissue (Newcomer, 2003), as well as with the ER– (no or low estrogen-receptor) profile of the disease (Althuis, 2003). Use of oral contraceptives for 10 years or longer has also recently been associated with a diagnosis of comedo DCIS

(Phillips, 2009), the most aggressive form of DCIS, which is sometimes confused with early forms of invasive breast cancer (Pervez, 2007).

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 ER+. Despite these group differences, use of oral contraceptives in the past five years is associated with significant increases in breast cancer incidence in both groups. The effect was magnified for women of both groups when oral contraceptive 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 following prolonged oral contraceptive use (Sweeney, 2007).

Post-menopausal women who used oral contraceptives for eight or more years but have discontinued use for at least a decade show no significant increase in breast cancer rates (CGHFBC, 1996; Vessey, 2006).

D. Infertility treatment drugs

Despite the substantial evidence linking HRT and oral contraceptive use with increased incidence of breast cancer, neither the condition of subfertility nor the use of infertility-treatment (or ovulation-stimulation) drugs appears to have a clear link to the disease (Gauthier, 2004; Klip, 2000; Orgeas, 2009). This is true also when the study involves infertile women who are also *BRCA* carriers (Kotsopoulos, 2008). Where the link has been

found, it has been for women who have been treated with high doses of clomiphene citrate.

Two studies found increased risk of breast cancer for women who had been treated for ovarian infertility with drugs including gonadotropins or clomiphene citrate. However, the results were significant only when the incidence of breast cancer was compared with the general population of women, but not with the more appropriate control of women with ovarian infertility who have not been treated with fertility drugs (Brinton, 2004; dos Santos Silva, 2009). Two other studies, however, have found small but statistically significant increases in breast cancer rates in women taking clomiphene citrate compared with rates for infertile women taking no infertility treatment (Calderon-Margalit, 2009; Lerner-Geva, 2006). Looking at a smaller subgroup of women whose infertility was not ovarian in origin and who underwent multiple treatments with high doses of clomiphene citrate, research showed this group to have a substantially increased risk of later developing breast cancer (Orgeas, 2009).

E. Diethylstilbestrol (DES) [I-K, N-K]

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 (Bibbo, 1977; Herbst, 1971). Research indicates that DES exposure is also associated with an increased risk of breast cancer in the women who took it during the 1950s (Colton, 1993; Titus-Ernstoff, 2001).

In a follow-up study of daughters who were exposed prenatally to DES, a nearly twofold increase in breast cancer risk was observed in women older than age 40. An even greater effect was found for women over the age of 50, although relatively few of the daughters had yet reached that age at the time of the study (Palmer, 2006; Troisi, 2007).

Recent studies examining the mechanisms by which DES might be exerting its carcinogenic effects indicate that the compound activates the same subcellular pathways that estradiol does, both by altering cellular metabolism and interaction with DNA (Saeed, 2009) and by increasing the rate of breast-cell proliferation (Larson, 2006).

F. Hormones in personal care products [I-K, N-K]

Placental extracts, probably with high concentrations of progesterone (Rudel, 2007) and estrogenic chemicals (Tiworthy, 1998), 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 on infants and children may also be linked to precocious puberty or early sexual maturation (Li, 2002; Tiworthy 1998, 2003). Early puberty is a risk factor for breast cancer later in life (Hsieh, 1990). Scientists have proposed



that use of these products might be contributing to the increased incidence of breast cancer, especially among young African American women (Donovan, 2007).

Hormones, especially estrogens, are also regularly added to topical anti-aging creams, because of their effectiveness in raising collagen count, as well as skin hydration. Together, these two factors are thought to decrease wrinkling of the skin (Draelos, 2005), but they can also increase women's total lifetime exposure to estrogen.

III. Endocrine-Disrupting Compounds (EDCs)

A. Background

In this section we discuss the links between breast cancer risk and a wide variety of chemicals that have been developed for reasons that are entirely independent of their effects on hormonal systems but nevertheless interact with endocrine (hormonal) processes. These include chemicals that were or are synthesized for their properties as plastic additives, industrial solvents, pesticides and herbicides or are chemical byproducts of combustion or industrial manufacturing of

commonly used products. These chemicals can mimic or otherwise alter the activities of the natural hormones, especially estrogens. These so-called xenoestrogens (meaning stranger or foreign estrogen) are members of a larger class of synthetic chemicals known as “endocrine-disrupting compounds” or EDCs. EDCs 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) and thyroid hormones. Therefore the term “endocrine disruptor” is used to reflect the wide range of effects these compounds may have on the endocrine system.

The effects of EDCs, including xenoestrogens, on reproduction and development have been well established in a number of wildlife species (Guillette, 2008; Oehlmann, 2009). A growing body of evidence links many of these chemicals to reproductive, metabolic and neurologic dysfunctions as well as cancer in animal models and humans (Diamanti-Kandarakis, 2009).

To date, neither the NTP nor the IARC has classified most endocrine disruptors as human carcinogens. 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. However, new leaders at the EPA, FDA and National Institute of Environmental Health Sciences (NIEHS) are arguing for rigorous scientific analysis of existing data and support for needed studies now and in the near future to ensure enhanced science-based policy and regulatory decisions. Of primary importance for all three agencies is deeper understanding of the health effects of exposures to EDCs.

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 (Brody, 2007; Diamanti-Kandarakis, 2009; Rudel, 2007). Scientists have proposed that the primary mechanism by which these chemicals may exert effects on breast cancer risk involves mimicking or disrupting estrogen

or other endocrine pathways (Davis, 1993), linking the processes by which the EDCs may exert effects on breast cancer risk to the ways in which hormones may influence the disease.

1. 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 leached substance as p-nonyl-phenol, an additive commonly used in plastics, which behaves like a natural estrogen (Soto, 1991). This landmark discovery generated widespread interest in what we now call xenoestrogens — 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 (Soto, 1994). 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 (CEC, 2004).

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 a link between exposure to synthetic estrogens in the environment and increased risk of breast cancer (Brody, 1998). Longer residence on Cape Cod is associated with increased risk of breast cancer; women who lived 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 (McKelvey, 2004).

In examining the environments in which the women lived and worked, researchers found synthetic estrogens in septic tank contents, groundwater contaminated by wastewater, and some private wells (Rudel, 1998). 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 (Rudel, 2003). More broadly, the Center for Disease Control and Prevention (CDC) has just released the *Fourth National Report on Human Exposures to Environmental Chemicals* (CDC, 2009). The report describes the presence of 212 chemicals found in a representative sample of people across the United States; included in

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.

the report are findings of substantial levels of many of the EDCs we will be discussing.

In the following sections we address in more detail several of the most common EDCs along with some of the evidence linking them to breast cancer.

B. Bisphenol A (BPA) [EDC]

Bisphenol A (BPA) has been associated with increased risk for cardiovascular disease, miscarriages, breast and prostate cancer, reproductive dysfunction, metabolic dysfunction and diabetes, and neurological and behavioral disorders (Braun, 2009; Lang, 2008; Li, 2009; Sugiura-Ogasawara, 2005).

BPA is one of the most common chemicals to which we are exposed in everyday life. It is the building block of polycarbonate plastic and is also used in the manufacture of epoxy resins. According to Environment Canada (the Canadian equivalent of the EPA), more than 4 billion kilograms (4.4 million tons) of the chemical were produced globally in 2006, and more than 1 billion kilograms (1.1 million tons) were produced in the United States in 2007 (CEPA, 2009).

Present in many common household products, BPA is also commonly found in the epoxy lining of metal food cans and in polycarbonate plastic food containers, including some baby bottles, microwave ovenware and eating utensils. Because BPA is an unstable polymer and is also lipophilic (fat-seeking), it can leach into infant formula and other food products, especially when heated (Brotons, 1995). Once in food, BPA can move quickly into people—a particular concern for women of childbearing age and young children. Two recent

studies have explored the effects of increased ingestion of food and drink packaged in EDC-containing sources. Both found rapid (within a few days to a week) increases in BPA levels in urine and/or blood samples taken from subjects who intentionally increased their intake of common foods and drinks packaged in BPA-containing products (Carwile, 2009; Smith, 2009).

Clearance rates for BPA are quite rapid, with a urinary half-life in the order of hours to days. A recent study of samples taken from fasting people indicate that sources other than foods may also be responsible for the pervasive exposure to BPA, as levels of the chemical did not decrease as rapidly as would have been predicted were food the only source of contamination (Stahlhut, 2009). Significant levels of BPA have also been measured in ambient air (Matsumoto, 2005), house dust (Rudel, 2003), and river and drinking water (Rodriguez-Mozaz, 2005) samples.

CDC researchers have measured BPA in 93 percent of about 400 urine samples from a broad national sample of adults (Calafat, 2005).

BPA has been found in blood (Padmanabhan, 2008) and urine (Ye, 2009a) of pregnant women, and in breast milk soon after women gave birth (Kuroto-Niwa, 2006). BPA has also been found in blood samples from developing fetuses as well as the surrounding amniotic fluid (Ikezuki, 2002), and it has been measured in placental tissue and umbilical cord blood at birth (EWG, 2009; Schonfelder, 2002) as well as in the urine of premature infants housed in neonatal ICUs (Calafat, 2009).

That BPA is found so extensively in people, from prenatal to adult ages, is particularly impressive given the relatively short half-life of the chemical.

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 (Maffini, 2006; Markey, 2001; Muñoz-de-Toro, 2005). Exposure also increased sensitivity to estrogen at puberty (Wadia, 2007). Recent data demonstrate



that early exposure to BPA leads to abnormalities in mammary tissue development that are observable even during gestation and are maintained into adulthood (Vandenberg, 2007; 2008).

Interestingly, some of the long-term effects of neonatal exposure to BPA may be dose dependent, with low- and high-dose exposures resulting in different timing and profiles of changes in mammary gland gene expression. In one study, low-dose exposures had the most profound effect on rat mammary glands during the period just prior to animals reaching reproductive maturity, while higher doses had more delayed effects, altering gene expression in mammary tissues from mature adults (Moral, 2008).

Prenatal exposure of rats to BPA results in increases in the number of pre-cancerous lesions and in situ tumors (carcinomas) (Murray, 2007a), as well as increased number of mammary tumors following adulthood exposures to subthreshold doses (lower than that needed to induce tumors) of known carcinogens (Durando, 2007; Jenkins, 2009).

Studies using cultures of human breast cancer cells demonstrate that BPA acts through the same response pathways as the natural estrogen estradiol (Rivas, 2002; Welshons, 2006). BPA can interact weakly with the intracellular estrogen receptor (ER), and it can also alter breast cell responsiveness and induce cell proliferation in vitro and in vivo. It affects cellular functions through interactions with the membrane estrogen receptor (Watson, 2005; Wozniak, 2005). 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 (Iso, 2006).

In the presence of BPA, cells from the non-cancerous breast of women diagnosed with breast cancer had a gene-response profile associated with the development of highly aggressive tumors (Dairkee, 2008). Two new studies indicate that BPA reduces the efficacy of common chemotherapy agents (cisplatin, doxorubicin and vinblastin) in their actions against proliferating breast cancer cells when tested in cell systems (LaPensee, 2009; 2010). Thus, not only does early exposure to BPA lead to an increased risk for development of breast tumors, but exposure to BPA during chemotherapy treatment for breast cancer may make the treatment less effective.

C. Phthalates [EDC]

Phthalates are a group of endocrine-disrupting chemicals commonly used to render plastics soft and flexible. They are found in a wide variety of common products including plastics (e.g., children's toys), cosmetics, pharmaceuticals, baby care products, building materials, modeling clay, automobiles, cleaning materials and insecticides. Phthalates are readily absorbed through the skin (Janjua, 2008) and can also enter the body through ingestion, inhalation or medical injection procedures (Schettler, 2005).

Phthalates have been found in indoor air and dust (Rudel, 2001) and in human urine and blood samples (Kato, 2003). National data collected by the CDC show that levels are highest in children ages 6 to 11 and in women, and

that blacks have higher levels of phthalates than do whites (CDC, 2005). Phthalates have also been detected in human breast milk and urine (Hines, 2009; Meeker, 2009). Phthalates cross the human placenta, exposing fetuses to the hazards associated with exposure to an important class of EDCs during this critical period of development (Wittassek, 2009). Young infants are also exposed to high levels of phthalates, with measurable levels of seven different phthalates being found in infants born between 2000 and 2005 (Sathyanarayana, 2008).

Phthalates are considered to be endocrine disruptors because of their complex effects on several hormonal systems including the estrogen and androgen hormone systems. 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 (Jobling, 1995; Kang, 2005). Phthalates also bind weakly to the androgen receptor (AR), disrupting the cellular actions ordinarily initiated by the androgens (Borch, 2006). Those that bind most strongly to the AR, and therefore might be expected to exert the greatest effects through this pathway, include DBP, di-i-butyl phthalate (DiBP) and butyl benzyl phthalate (BBP) (Fang, 2003).

The endocrine-disrupting properties of this class of chemicals have been well established in the offspring of mother rats who had been treated with phthalates while pregnant. 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 (Jiang, 2007; Lovekamp-Swan, 2003). Abnormalities in male offspring exposed prenatally included nipple retention, shortened anogenital distance and increased cryptorchidism (undescended testes) (Foster, 2005; Latini, 2006). Exposure of human mothers to phthalates, as measured by analysis of their urine samples, has also been associated with shortened anogenital distances in their newborn sons — a measure of feminization of external genitalia (Swan, 2005).

A recent case-control study examined phthalate levels in apparently healthy girls who went through thelarche (breast development) before the age of 8, as compared with girls who underwent precocious puberty because of abnormalities in their neuroendocrine systems and with girls who were progressing through puberty at normal ages. Increased levels of monomethyl phthalate (MMP) were associated with early thelarche group, but not either of the comparison groups (Chou, 2009). Early breast development in otherwise healthy girls is associated with an increased risk for breast cancer (Steingraber, 2007).

Exposure of very young rats to BBP resulted in increased cellular proliferation in the terminal end buds of mammary tissue. BBP-induced changes in mammary cell gene expression profile were consistent with abnormalities in cellular differentiation and cell-cell communication (Moral, 2007).

In *in vitro* cell systems, 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 (Kim, 2004a). In another cell study, exposure of normal human breast epithelial cells to DBP resulted in changes in gene expression in pathways related to a number of systems, including immune responses, cell cycle regulation and antioxidant status of the cell (Gwinn, 2007).

D. Parabens [EDC]

Parabens are a group of compounds widely used as antimicrobial preservatives in food, pharmaceutical 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 (Darbre, 2004). The particular parabens were found in relative concentrations that closely

parallel their use in the synthesis of cosmetic products (Rastogi, 1995). Parabens have also been found in almost all urine samples examined from a demographically diverse sample of U.S. adults (Ye, 2006a).

Parabens are estrogen mimickers, with the potency of the agonistic response being related to the chemical structure (Darbre, 2008). They can bind to the cellular estrogen receptor (Routledge, 1998). They also increase the expression of many genes that are usually regulated by estradiol and cause human breast tumor cells (MCF-7 cells) to grow and proliferate *in vitro* (Byford, 2002; Pugazhendhi, 2007). Nevertheless, parabens as a class do not fully mimic estradiol in the changes in cellular gene expression nor are the effects of all parabens identical (Sadler, 2009).

E. Alkylphenols [EDC]

Alkylphenols are industrial chemicals used in the production of detergents and other cleaning products, and as antioxidants 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 household contaminants, 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 (Rudel, 2003). Substantial concentrations of these chemicals have also been found in wastewater associated with domestic sewers and municipal landfills (Slack, 2005; Swartz, 2006).

The alkylphenols, including 4-NP, have been shown to mimic the actions of estradiol, mediating their effects through the cellular estrogen receptor. They also bind to the newly described cell membrane ER and mimic cellular signaling responses usually controlled by estradiol (Thomas, 2006). 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 (Moon, 2007). 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 (Acevedo, 2005).

In a study examining the effects of nonylphenol in human breast tumor cells (MCF-7) in vitro, changes in gene expression were observed in several genes involved in cell proliferation, DNA transcription and cell signaling — all systems that are disrupted in tumor formation (Oh, 2009).

F. Polycyclic aromatic hydrocarbons (PAHs) [I-Pr, N-R; EDC]

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 (Bonner, 2005). In the Silent Spring Institute study of environmental contaminants in house dust, three PAHs (pyrene, benz[*a*]anthracene and benz[*a*]pyrene) were found in more than three-quarters of the homes tested (Rudel, 2003). Although they are still found extensively in suspended particulate matter, federally imposed standards on vehicular emissions have led to a significant decrease in PAH release by vehicles from their highest levels in the 1970s (Beyea, 2008).

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. 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 (Pliskova, 2005). However, the major receptor-directed pathway is different, 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 (Kemp, 2006; Santodonato, 1997). 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 (Ralston, 1997).

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 (Gammon, 2002). 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 (Rundle, 2000). Follow-up work indicates that those women who had higher levels of PAH adducts may not necessarily have had higher exposures to PAHs, but instead had particular genetic profiles that encourage the deficits in DNA repair (Gammon, 2008). Other studies support the presence of different genetic profiles for women who have increased numbers of PAH-DNA adducts, including polymorphisms in genes involved in cell metabolism, tumor-suppressor mechanisms and DNA repair (Gammon, 2008; Mahadevan, 2005). Differences were not found in the profiles of genes whose products are involved in the activation and deactivation of the PAHs themselves (McCarty, 2009).

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 (Petrallia, 1999) and also for men. In the case of male breast cancer, PAHs may increase the risk of breast cancer specifically in men carrying a *BRCA1* or *BRCA2* mutation (Palli, 2004).

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 (Bonner, 2005). An extension of this study, examining PAH exposures at critical times in women's reproductive histories, demonstrated a relationship between particulate exposures at the time of menarche (first period) and incidence of pre-menopausal breast cancer, and a relationship between exposure levels at the time of first birth and risk of post-menopausal breast cancer (Nie, 2007). The results are complex, but all contribute to our understanding that exposures to environmental toxicants at critical periods of breast development can influence later cancer risk.

The studies above all looked at breast cancer incidence. One recent analysis examined the relationship between PAH-adduct levels and mortality among women who had been diagnosed with breast cancer. In an extension of the Long Island study described above, researchers found no overall relationship between survivorship and PAH-DNA-adduct levels. Looking more closely at groups of women who had undergone different types of



treatments, however, revealed a twofold increase in deaths from breast cancer among women with high PAH-DNA adduct levels who had received radiation treatment; this was offset partially by an increased survival for women with adducts who had received hormone therapy (Sagiv, 2009).

G. Pesticides and herbicides

1. Triazine herbicides: *Atrazine [EDC]*

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 (O'Connor, 2000), there is relatively little scientific data exploring the relationship between simazine or cyanazine and human breast cancer. The literature on atrazine is more substantial.

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, however, still approved for use in the United States. More than 75 million pounds of atrazine are

applied annually in the United States, primarily to control broadleaf weeds in corn and sorghum crops in the Midwest (EPA, 2008).

Elevated levels of atrazine are found each spring and summer in both drinking water and groundwater in agricultural areas (Hua, 2006; Miller, 2000; Villanueva, 2005). Atrazine is a known endocrine disruptor, causing dramatic damage to reproductive structures in frogs, fish and other wildlife (Hayes, 2003; Rohr, 2009).

High levels of triazines (primarily atrazine) in contaminated waters have been associated with an increased risk of breast cancer (Kettles, 1997), although not all ecological studies support these findings (Hunter, 2008). Because these studies tend to compare countywide average levels of atrazine contamination and incidence rates, it is difficult to understand clearly the difference in results.

Research in rodents has shown that atrazine exposure disrupts pituitary-ovarian function, resulting in decreases in circulating prolactin and luteinizing hormone levels,

changes that contribute to the effects of this herbicide on increases in mammary tumors (Cooper, 2000; O'Connor, 2000). Atrazine also exerts endocrine-disrupting effects by increasing the activity of the enzyme aromatase (Fan, 2007; Sanderson, 2001), an enzyme that 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 or mixtures of atrazine metabolites during gestation delays development of the rat mammary gland in puberty, widening the window of sensitivity to breast carcinogens (Enoch, 2007; Raynor, 2005). 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 pups exposed during gestation. These abnormalities persist into adulthood (Enoch, 2007). Exposure of rats with existing mammary tumors to atrazine increases the rate of cell proliferation in those tumors (Ueda, 2005).

2. Heptachlor [I-Po; EDC]

Heptachlor is an insecticide that was 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 (Siegel, 1995).

Heptachlor use was particularly high in Hawaii, where it was employed 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 (Maskarinec, 2006).

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 (CDC, 2005). Although HE does not act like estrogen, it affects the way the liver processes the hormones, thereby allowing levels of circulating estrogens to rise and increasing breast cancer risk. HE also has been shown to disrupt cell-to-cell communication in human breast cells in tissue culture (Dich, 1997) and to increase production of nitric oxide, a chemical that is found naturally in cells and is known to cause damage to DNA (Cassidy, 2005).

3. Dieldrin and aldrin [EDC]

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 EPA in 1975 banned all uses of aldrin and dieldrin except in termite control; the EPA banned these pesticides altogether in 1987 (ATSDR, 2010). Thus, most of the human body burden of this chemical comes either from past exposures or lingering environmental contamination.

One body burden study showed a clear relationship between breast cancer incidence and dieldrin exposure. Conducted by the Copenhagen Center for Prospective Studies in collaboration with the CDC, the study examined a rare bank of blood samples taken from women before development of breast cancer (Hoyer, 1998). During the late 1970s and early 1980s, blood samples were taken from approximately 7,500 Danish women ranging in age from 30 to 75. In 2000, researchers looking at blood samples of 240 women from the original study who had later been diagnosed with breast cancer detected organochlorine compounds in most of the samples. They found dieldrin, which has exhibited estrogenic activity during in vitro assays, in 78 percent of the women who were later diagnosed with breast cancer. Women who had the highest levels of dieldrin long before cancer developed had more than double the risk of breast cancer compared to women with the lowest levels. This study also showed that exposure to dieldrin correlated with the aggressiveness of breast cancer: Higher levels of dieldrin were associated with higher breast cancer mortality (Hoyer, 2000).

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 pathways. Addition of dieldrin to human breast cancer (MCF-7) cells in vitro stimulated their growth and proliferation (Andersen, 2002; Soto, 1994). The exposure of normal (non-cancerous) human breast epithelial cells to mixtures of organochlorine pesticides, including dieldrin and aldrin, as well as DDT/DDE at levels found

in the environment, led to greater induction of cellular processes linked to cancer than exposures to any of the chemicals individually (Valeron, 2009).

Treatment of mice prenatally and neonatally to environmentally relevant doses of dieldrin increased the number and size of mammary tumors. These effects may have been mediated through changes in the cellular expression of the growth factor BDNF and cell-signal receptor Trks. Both of these were elevated in tumors from the dieldrin-treated animals (Cameron, 2009).

4. Other pesticides [EDC]

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 (Mills, 2005).

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 incidence of breast cancer in women using 2,4,5-trichlorophenoxypropionic acid (2,4,5-TP) and possibly in women using dieldrin and captan, although the small number of cases among those who had personally used pesticides precluded firm conclusions. Incidence was also



modestly elevated in women whose homes were closest to areas of pesticide application (Engel, 2005).

A recent study of farmers and their families shows that young children 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 (Alexander, 2007). This is of concern given the evidence of increased susceptibility of children and young adolescents to the carcinogenic effects of chemicals.

H. Polybrominated diphenyl ether (PBDE) fire retardants [EDC]

PBDEs are a complex group of chemicals that are structurally similar to the PCBs described above. They are used extensively as fire retardants in both consumer and industrial products (Costa, 2008). Major products containing PBDEs include polyurethane foam in furniture (penta-BDE) and electronic and plastic products (octa- and deca-BDEs) (Zota, 2008). Although both penta- and octa-BDEs have been banned in the European Union and have not been produced in the United States

since 2004, products containing them remain throughout the world. PBDEs are found ubiquitously in the environment, detected in air, dust, soil and food as well as in many wildlife species. These chemicals have been found in human fat tissue, as well as in serum and breast tissue and milk (Costa, 2008; Darnerud, 2001; De Wit, 2002). PBDEs cross the placenta, resulting in exposures to developing fetuses (Frederiksen, 2010). Recent data indicate considerable geographic variability in exposures to the chemicals; people in California, with its particularly stringent furniture flammability standards, have much higher levels of PBDE exposures than do people in Massachusetts. Within the California cohort, having a lower socioeconomic status (SES) is associated with higher PBDE levels (Zota, 2008).

New data from young girls (ages 6 to 9) from California and Ohio support these findings. Although PBDEs were found in almost all samples tested, girls in California had significantly higher serum PBDE levels than did girls from Ohio, and young black girls had

higher levels than either white or Hispanic girls (Windham, 2010). PBDEs are endocrine-disrupting compounds, exerting effects on a number of hormonal systems, including the androgens, progestins and estrogens, though the major system affected by PBDEs is that of the thyroid hormone (Costa, 2008). Most studies of health outcomes after PBDE exposures have focused on neural development, given the prominent role of thyroid hormones (especially T4) in regulating brain development (Costa, 2007; Talsness, 2008).

Very few data directly address the possible effects of PBDEs on breast cancer risk. However, at least some PBDEs have been shown to be as effective as many of the other EDCs described in this section in promoting estrogenic-like proliferation of human breast cancer cells in vitro (Meerts, 2001). More recent data on MCF-7 human tumor cells indicate that penta-BDE enhances tumor-cell proliferation through estrogen-like effects on cell pathways that regulate programmed cell death, or apoptosis (Yu, 2009). Given the extensive overlap and interaction of estrogen- and thyroid-mediated responses in the regulation of breast cancer (Davis, 2009), PBDEs will be a class of chemicals of continued concern for scientists interested in understanding environmental links to breast cancer (Birnbaum, 2009).

I. Dioxins [I-K, N-K; EDC]

Dioxins are a group of chemicals that are similar in their chemical

structure and their toxic effects on biological tissues (EPA, 2010). They 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, with half-lives between 7 and 11 years in people (Schechter, 2006). They accumulate in fat of wildlife and bioaccumulate across the food chain. Dioxins are known human carcinogens and endocrine disruptors. One of the dioxins (2,3,7,8-tetra chlorodibenzo-para-dioxin — TCDD) has been classified by IARC as a known human carcinogen (IARC, 1997). In 2000, the U.S. EPA officially declared TCDD to be a known carcinogen (ATSDR, 1999b).

People are exposed to dioxins primarily through consumption of animal and other food products (Kulkarni, 2008) and breast milk (WHO, 1996). Dioxin enters the food chain when vehicle exhaust or soot from incinerated chlorinated compounds falls on field crops later eaten by farm animals or enters waters from which seafood is caught (Kulkarni, 2008).

As a result of numerous regulatory actions taken by the federal government, dioxin levels in our food supplies (Lorber, 2009) and in the environment have been declining over the past three decades. Yet, because the chemicals are persistent and bioaccumulate, most Americans

still have significant levels of dioxins in their bodies (Schechter, 2006). The most recent data in studies of a cross-section of Americans indicate that over 95 percent have measurable levels of dioxins in their bodies, and that older people have significantly higher body burdens of the chemicals than do younger people (Patterson, 2009). The lower concentrations in children and younger adults probably reflect both lower levels of dioxins in the environment and shorter durations of cumulative lifetime exposures (Collins, 2007).

Concentrations of dioxins in breast tissue may change dramatically over the span of a woman's reproductive life. Data indicate that there is a substantial decrease in the amount of dioxin remaining in a woman's breast fat tissue after she has breast-fed (Massart, 2005; cf Lakind, 2009), unfortunately because 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 (Nickerson, 2006). But in addition to potential transfer of dioxins to breast-feeding infants, the release of the chemicals from storage in breast fat cells, initiated by the process of milk synthesis, may actually trigger genotoxic (cancer-causing) effects in the breast tissue (Dip, 2008). Compelling evidence of links between dioxin exposures and risk for breast cancer has emerged from a recent follow-up study on women exposed to dioxins during a chemical plant explosion in 1976 in Seveso, Italy (Pesatori, 2009). Scientists analyzed blood samples taken and stored at the time of the explosion and correlated the results

People are exposed to dioxins primarily through consumption of animal and other food products and breast milk.

with subsequent cases of cancer incidence, including that of breast cancer. Overall levels of cancer incidence were not higher 20 years after the accident in people in areas contaminated by dioxins during and after the accident. Researchers found that a tenfold increase in TCDD levels in the zone closest to the accident was associated with a significantly increased incidence 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.

A retrospective mortality study in Germany 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 (Manz, 1991).

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 (Brown, 1998; Fenton, 2002; Lewis, 2001; Jenkins, 2007; La Merrill, 2009). TCDD may exert its cancer-causing effects both

by decreasing the efficacy of tumor-suppressor mechanisms and by enhancing the estrogenic signaling within the mammary cells (Seifert, 2009).

J. Persistent organochlorines

Two historically important classes of EDCs are the organochlorine pesticide dichloro-diphenyl-trichloroethane (DDT) and its metabolite, DDE, 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 (Rudel, 2003; Simcox, 1995). Due to their historical overlap in exposures, and because of many similarities in structure and function, the two are often discussed together; their effects on disease have also been explored independently.

1. Dichloro-diphenyl-trichloroethane (DDT/DDE) [I-Po, N-K; EDC]

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 (Beard, 2006). Banned in most countries for agricultural use, DDT is still used for malaria control in many countries especially in sub-Saharan Africa (WHO, 2007). Because of its continued use and its persistence in the environment, DDT is found worldwide. Most animals, including 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 as well as in human breast milk and placenta (Rogan, 2007; Shen, 2007; Zheng, 1999).

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 (Gammon, 2002). 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 nor assess key metabolites.

A recent study explored women's estimated DDT levels based on aggregate data from their year of birth as well as blood DDT levels at the time the women gave birth to their first children. Researchers then followed the women over the next two decades, noting cases when women either were diagnosed with invasive or non-invasive breast cancer before the age 50, or had 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" (Cohn, 2007).

Laboratory studies have found the estrogen-like form of DDT enhances the growth of estrogen-positive (ER+) mammary tumors (Robison, 1985; Scribner, 1981). 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. This is the period when women exposed to DDT as young girls in the 1950s were expected to exhibit increased incidence of breast cancer related to DDT exposure (Pujol, 1994). Another study, looking at chemical levels in breast fat 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 that were more aggressive and that had poorer prognoses (Woolcott, 2001).

2. Polychlorinated biphenyls (PCBs) [I-Pr, N-R; EDC]

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 use today. The remaining one-third was discarded, which means that these toxic compounds eventually made their way into landfills and waste dumps (Robinson, 1990).

Levels of PCBs were high before being banned in the United States, but generally their presence in human tissues has decreased slowly over the past decades (Hagmar, 2006). Exposures were high, though, between childhood and young adulthood for many women who are now facing breast cancer diagnoses. PCB levels in neonatal cord serum were correlated with the distance of mothers' residences from a Superfund site; levels were lower after site remediation (Choi, 2006).

The science on PCBs is complicated. There are more than 200 individual PCBs, classified in three types based on their effects on cells. One type

acts like an estrogen. A second type acts like an anti-estrogen. A third type appears not to be hormonally active, but can stimulate enzyme systems of animals and humans in a manner similar to the way certain drugs (such as phenobarbital) and other toxic chemicals do (Connor, 1997). Additionally, metabolites of PCBs can alter the expression of genes involved in hormone synthesis, indicating that these compounds may act as endocrine disruptors through mechanisms not directly involving estrogen or other hormone receptors (Braathen, 2009). PCBs with relatively low chlorination levels may induce damage to DNA in isolated breast tumor cells in vitro. The presence of estrogen receptors in the cells (ER+ cells) may actually offer protection against damage (Lin, 2009).

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. For example, 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 (Charlier, 2004). Another 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 (Aronson, 2000). Interestingly, none of these four PCBs were shown to have estrogenic activity in a study using MCF-7



cell proliferation to test estrogen responses of compounds (Decastro, 2006).

Another report has implicated PCBs in breast cancer recurrence among women with non-metastatic breast cancer. The study found that women with the highest levels of total PCBs, as well as of PCB 118, in their fat tissues were almost three times as likely to have recurrent breast cancer as women with lower levels (Muscat, 2003).

Some studies have found no link between PCBs and breast cancer (Salehi, 2008). New evidence suggests that some of these compounds may have their greatest impact on women with particular susceptibilities and that looking broadly at large samples will not tell the full story of cancer risk as influenced by PCB exposures. Thus, more study is needed to determine the effect of PCB exposure on breast cancer development in specific populations. 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 link between 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 (Laden, 2001). In 2002, new evidence regarding variations in individual susceptibility due to genetic differences prompted these researchers to call for additional studies (Laden, 2002). In a new study examining occupational exposures to PCBs in electrical capacitor production workers and later breast cancer incidence, no overall relationship between exposure levels or duration and



disease incidence was observed for female workers in general. But for non-white women, a significant relationship was found between incidence of breast cancer and earlier PCB exposure duration as well as cumulative exposure amounts (Silver, 2009).

In vitro studies 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-mediated pathways (Andersson, 1999; Gierthy, 1997) and the activation of key enzymes and cellular changes that are characteristic of transformation of cells to a malignant state (Hatakeyama, 1999).

K. Aromatic amines [I-PR, N-R; EDC]

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. They are also found in environmental pollution such as diesel exhaust, combustion

of wood chips and rubber, tobacco smoke and grilled meats and fish (DeBruin, 1999; 2002). There are three types of aromatic amines: monocyclic, polycyclic and heterocyclic.

Three monocyclic amines, including o-toluidine, have been identified in the breast milk of healthy lactating women (Debruin, 1999). o-toluidine is known to cause mammary tumors in rodents (NTP, 2005d; Layton, 1995). These data indicate that the mother's mammary tissue and the nursing child are exposed to environmental carcinogens during breast-feeding. Occupational exposures of female rubber-factory workers to another set of monocyclic aromatic amines derived from p-phenylenediamine are associated with an increased risk of breast cancer in the following several years. The amount of increased risk was correlated with total cumulative exposure levels to the aromatic amines, with lowest levels leading to a 3.7-fold increase in cancer and the highest levels of exposure increasing risk more than tenfold (de Votch, 2009).

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 (Steck, 2007). Studies of both milk and cells from the ducts of women's breasts revealed the presence of DNA adducts in association with HAAs (Thompson, 2002; Turesky, 2007). 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 might enhance the development of tumors (Gooderham, 2006).

L. Sunscreens (UV filters) [EDC]

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. Studies show these chemicals are accumulating in wildlife and humans (Hayden, 1997).

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-methylbenzylidene)-camphor (4-MBC), octyl-methoxycinnamate

(OMC), octyl-dimethyl-PABA (OD-PABA), bexophenone-3 (Bp-3) and homosalate (HMS) (Schlumpf, 2001). The results for 4-MBC have been replicated in another laboratory (Klann, 2005). 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 (Brand, 2007).

M. Tobacco smoke: Active and passive exposures [I-K, N-K; EDC]

Tobacco smoke 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 (Cal-EPA, 2005), including three known human carcinogens (polonium-210, a radioactive element; benzene; and vinyl chloride), as well as toluene, 1,3-butadiene and the nitrosamine NNK, all of which are known to cause mammary tumors in animals. NNK is a tobacco-specific carcinogen that has been shown to increase tumor cell proliferation and carcinogenic transformation of healthy breast epithelial cells (Chen 2007; Mei 2003; Siriwardhana 2008).

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 (Hanaoka, 2005).

A large study of California teachers revealed an increased risk of breast cancer among smokers, particularly those who began smoking during adolescence, who smoked at least five years before their first full-term pregnancy, or who were long-

time or heavy smokers (Reynolds, 2004). Several earlier studies also suggest that women who begin smoking cigarettes as adolescents face increased risks of breast cancer (Band, 2002; Calle, 1994; Gram, 2005; Johnson, 2000; Marcus, 2000). Similarly, results from the Canadian National Breast Screening Study indicated that increased incidence of breast cancer was associated with longer duration of smoking, number of cigarettes per day smoked, cumulative exposure to cigarette smoke, and beginning smoking prior to a woman's first full-term pregnancy (Cui, 2006).

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 women who are exposed to secondhand smoke receive a much lower dose of carcinogens than do active smokers (Ambrosone, 1996; Morabia, 1996). One possible explanation for this is that smoking 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. Women exposed to secondhand smoke, on the other hand, may not get a large enough dose of smoke to depress estrogen levels.

A 2007 report from the Air Resources Board of California's Environmental Protection Agency concluded that regular exposure to secondhand smoke is "causally related to breast cancer diagnosed in younger, primarily pre-menopausal women, and the result is not likely explained by bias or confounding"

(Miller, 2007). 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 (Lee, 2006).

In addition to the chemicals addressed in more detail above, there are scores of industrial chemicals, products of combustion, dyes and pharmaceutical chemicals that have been linked to the induction of mammary tumors in animal models (Rudel, 2007). Many of these are listed in the relevant tables in the section of this document titled “From Science to Action.”

N. Metals [I-K; N-K; EDC]

Higher accumulations of iron, nickel, chromium, zinc, cadmium, mercury and lead have been found in cancerous breast biopsies as opposed 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 (Ionescu, 2006; Wu, 2006).

Laboratory studies have shown that a number of metals including copper, cobalt, nickel, lead, mercury, methylmercury, tin, cadmium and chromium have estrogenic effects on breast cancer cells (MCF-7) cultured in vitro (Brama, 2007; Martin, 2003; Sukocheva, 2005).

In a study exploring dietary intake of cadmium in women who have been diagnosed with breast cancer and appropriate age-matched controls, higher exposure to cadmium was associated with a significant increase in risk for

breast cancer, independent of age at diagnosis (McElroy, 2006).

In young rats, treatment with low doses of cadmium led to an increase in branching and bud formation in mammary tissue, and the induction of several estrogen-associated proteins. Prenatal exposure of rats to cadmium led to early onset of puberty and greater numbers of mammary terminal end buds, both known risk factors for breast cancer (Johnson, 2003).

Estrogenic effects of cadmium have been studied in some detail. It has been shown to interfere with a number of normal estrogen-sensitive pathways and to affect the rates of both endometrial and breast cancers. (Byrne, 2009). In addition to its endocrine effects on mammary tumor cells, cadmium transforms healthy breast epithelial cells into cells with a cancer-like profile through non-hormone-related pathways. Thus, in the presence of cadmium, the cells have altered gene expression and changes in DNA methylation (an epigenetic change) that are typical of cells undergoing transformation from healthy to cancerous cells (Benbrahim-Tallaa, 2009).

IV. Hormones in Foods: Natural and Additive

A. Phytoestrogens (plant estrogens)

Studies leading to concerns about harmful effects of synthetic estrogens must 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 (Cederroth, 2009), the data are conflicting as to whether the soy-based diets have beneficial, harmful or neutral effects on breast cancer risk (Rice, 2006; Ziegler, 2000).

Some of the disparity in the literature may be related to type of soy product or other phytoestrogen-containing vegetables consumed by individuals. The isoflavones genistein and its metabolite genistin are both natural phytoestrogens found in soy. Both have been shown to increase tumor growth in a variety of different models, but highly processed soy flour that does not contain these isoflavones has no effect. Purified soy-protein isolates are often processed to contain different concentrations of isoflavones, and their influence on mammary tumors is related to the amount of isoflavone, not the total amount of soy protein consumed (Helferich, 2008).

Several epidemiological studies have shown that regular consumption of soy-based products or other vegetables high in phytoestrogens, as part of a normal balanced diet, can exert a protective influence with regard to later development of breast cancer. This effect has been studied extensively in China, where soy intake is a regular part of the cultural diet. There, substantial evidence indicates that higher soy intake in adulthood or in adolescence is associated with a decreased risk of pre-menopausal breast cancer (Lee, 2009). Other studies have found protective effects of soy intake for both pre- and post-menopausal cancer, independent of receptor profile (ER and PR positive or negative) of the tumors (Zhang,

2009). For Chinese women who were previously diagnosed with breast cancer, consumption of soy in its many forms found regularly in a woman's diet was correlated with decreased recurrence of cancer and longer survival (Shu, 2009).

Looking at Asian-American women living in California and Hawaii, a recent study reported that soy intake during childhood, adolescence and adulthood all were associated with decreased later risk of breast cancer (Korde, 2009). The protective effect of regular dietary soy intake during childhood was the strongest, and it was not mitigated when other variables, like site of birth (Asian countries or United States), degree of continuing Asian lifestyle and cultural practices, reproductive factors or family history of breast cancer, were factored into the analysis. In general, protective effects of dietary soy intake have been found to be strongest in association with childhood and early adolescent intake (Adlercreutz,

2003). One possible explanation for this association is that peri-pubertal exposures to genistein and other phytoestrogens may mimic the protective changes in breast development that are usually observed during the first pregnancy (Messina, 2009; Warri, 2008).

Studies examining phytoestrogen intake and breast cancer risk in non-Asian populations have found more mixed results (Wu, 2008). This may be related to the difference in both amounts and types of phytoestrogens typically eaten as part of the traditional diets found in both the United States and Europe (Mense, 2008). As examples, a recent French study found that consuming non-soy phytoestrogens as part of a woman's daily diet had a protective effect against post-menopausal breast cancer (Touillaud, 2007), while a British study found no such relationship (Travis, 2008). And a recent multiethnic study conducted in Hawaii demonstrated that the amount of soy in the diet might

interact with other phytoestrogens in protecting against breast cancer. For Japanese Americans who had high soy content in their regular diets, there was a strong and significant relationship with non-soy-based phytoestrogens and decreased risk of breast cancer. A similar strong relationship was not found for white women in the study, who tended to eat diets lower in soy content (Goodman, 2009).

Data from studies on laboratory animals and cell culture models have also indicated a complicated story. In several studies, exposures to phytoestrogens have led to increases in mammary tumor proliferation and growth. The soy phytoestrogens genistein and daidzein, as well as their metabolites, cause oxidative DNA damage, a process that is thought to play a role in tumor initiation (Murata, 2004). Other data suggest that these two soy-based phytoestrogens may have opposing effects on the efficacy of the breast cancer drug tamoxifen (Constantinou, 2005; Liu, 2005).

The effects of the phytoestrogens may be related to the particular mixtures of components in the diet (Dip, 2009), and cellular effects may vary depending on concentration and timing. In a recent study examining the effects of different types and concentrations of phytoestrogens on the expression of estrogen-dependent gene activity in human breast cancer cells grown in vitro (MCF-7 cells), low doses of genistein resulted in a pattern of expression that indicated increased cell proliferation, while higher concentrations led to increased apoptosis, or cell death. On the other hand, the phytoestrogen daidzein (found in soy) slightly



enhanced cell proliferation in the absence of natural estrogen (a possible model for post-menopausal breast cancer), while resveratrol (found in grapes and red wine) significantly decreased tumor cell proliferation (Sakamoto, 2009). These latter data are consistent with other studies finding anti-carcinogenic effects of resveratrol in several models (Athar, 2009; Garvin, 2006).

Recently, concern has been raised about exposure of newborn babies to soy-based products, primarily through infant formulas. Although one study has shown that feeding only soy formula for the first four months of life was associated with a decrease in later development of breast cancer (Boucher, 2008), animal studies have indicated deleterious effects of neonatal soy exposure on development of the female reproductive system and subsequent fertility (Jefferson, 2009).

B. Synthetic and genetically engineered hormones used in food production

1. 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 become part of our bodies. Research suggests that some of these exposures may increase breast cancer risk.

Consumption of animal products may also 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. Concerns about economic and health risks have led the European Union to ban use of these hormones in their own meat production systems and to bar imports of hormone-treated beef, including meat from the United States, since 1989 (Hanrahan, 2000).

2. Zearanol (Ralgro) [EDC]

Zearalenone and its synthetic derivative zearanol (Ralgro) are estrogenic compounds to which cattle and swine in the U.S. meat industry are extensively exposed.

Natural sources of zearalenone come from contamination of feed sources, including corn silage and hay, by the fungus *Fusarium*, which is an active producer of the chemical (Benzoni, 2008; Mirocha, 1979). Contamination of food by zearalenone and its natural metabolites (breakdown products) has been associated with the development of precocious puberty — a known risk factor for breast cancer — in young girls (Massart, 2008). These compounds have also been shown to enhance proliferation of ER+ human breast tumor cells in vitro through estrogen-mediated pathways and activation of gene profiles similar to those activated by the natural hormone estradiol (Khosrokhavar, 2009; Parveen, 2009).

The synthetic compound zearanol is a potent nonsteroidal growth

promoter that mimics many of the effects of estradiol. Zearanol is used extensively in the United States and Canada to promote rapid and more efficient growth rates in animals used as sources of meat (Al-Dobaib, 2009).

Like the natural compound zearalenone, zearanol is a powerful estrogenic chemical, as demonstrated by its ability to stimulate growth and proliferation of human breast tumor cells in vitro at potencies similar to those of the natural hormone estradiol and the known carcinogen diethylstilbestrol (DES) (Leffers, 2001). Adding zearanol to cultured (in vitro) breast epithelial cells led to enhanced cell proliferation, accompanied by stimulation of the activity of protein disulfide isomerase, an enzyme whose activity is often increased in cancerous tissues (Updike, 2005).

Treatment of young adult female mice with zearanol led to increased growth and branching of mammary glands, similar to what is found in mice treated with estradiol (Sheffield, 1985). Increased ductile proliferation, in the absence of full maturation of the ducts through pregnancy and lactation, is associated with an increased risk for mammary (breast) tumors.

Brief (four-day) pre-pubertal exposure of mice or rats to either zearalenone or zearanol accelerated the onset of puberty but did not affect development of the mammary gland structures through early adulthood (Nikaido, 2005; Yuri, 2004).

A series of studies examined estrogenic activity in normal breast epithelial cells and breast cancer cells treated with zearanol. Abnormal

cell growth was significant even at zeranol levels almost 30 times lower than the FDA-established limit in beef (Liu, 2002). 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 (Liu, 2004). Preliminary data indicate that serum from zeranol-treated beef cattle can stimulate the proliferation of normal breast epithelial cells and the transformation of breast tumor cells in vitro (Xu, 2009; Ye, 2009b).

3. Bovine growth hormone (rBGH)/recombinant bovine somatotropin (rBST) [EDC]

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 (Eaton, 2004). 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 potentially carcinogenic effects.

Drinking any type of cow's milk noticeably raises body levels of insulin-like growth factor 1 (IGF-1), a naturally occurring hormone in both cows and humans. Injecting cows with rBST leads to an increase in IGF-1 levels in milk (Daxenberger, 1998), although a recent study has suggested that the increased milk output by treated animals

Pesticides sprayed on crops, antibiotics used on poultry, and hormones injected into cattle, sheep and hogs expose consumers involuntarily to contaminants that become part of our bodies. Research suggests that some of these exposures may increase breast cancer risk.

may dilute the excess production of hormone (Collier, 2008). The content of IGF-1 in dairy milk is not altered by pasteurization (Collier, 1991).

Although the data are complex, with studies reaching different conclusions, several epidemiological studies have indicated a relationship between dairy consumption and breast cancer risk in premenopausal women (Outwater, 1997). Elevated levels of IGF-1, in particular, have been associated with increased risk of breast cancer (Hankinson, 1998).

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 (Xian, 1995).

V. Non-Endocrine-Disrupting Industrial Carcinogens

A. Benzene [I-K; N-K]

Benzene is one of the largest-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 over 42 million metric





tons (over 105 billion pounds) of benzene will be produced globally in the year 2010 (Davis, 2006). Exposures to benzene come from inhaling gasoline fumes, automobile exhaust, cigarette smoke (primary and secondary) and industrial burning. Benzene presents a serious occupational hazard for people exposed through their work in chemical, rubber, shoe-manufacturing, oil and gasoline-refining industries. Both the NTP and IARC have designated benzene as a known human carcinogen (IARC, 1987b; NTP, 2005c).

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, as well as teachers, librarians and accountants. In the same study, looking across professions, benzene exposure was associated with an elevated risk of breast cancer (Petrallia, 1998). Results from recent studies examining occupational exposures among enlisted women in the U.S. Army (Rennix, 2005) and women in various professions in Israel (Shaham, 2006) support these conclusions. A study of a fairly small sample of women for whom researchers have benzene exposure data from their work at a shoe factory in Florence, Italy, also supports a relationship between exposure to benzene and later development of breast cancer (Costantini, 2009).

The largest study implicating benzene and associated chemicals comes from an occupational study of 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 age 40 (Hansen, 2000).

Benzene administration to laboratory mice induces mammary tumors (Huff, 1989). Mice exposed to benzene have frequent mutations of genes that are responsible for suppressing the development of tumors (Houle, 2006).

B. Organic solvents other than benzene [I-Pr; N-R]

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 (Labreche, 1997). Such solvents are also used in other industries, such as manufacturing of cleaning products and cosmetics (EPA, 1996). 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 (Wolff, 1983).

Several epidemiological studies have linked occupational exposures to organic solvents with increases in breast cancer incidence. Two studies showed an increased risk of breast cancer among workers exposed to chlorinated organic solvents in semiconductor plants (Chang, 2003; McElvenney, 2001). A Danish study showed that women ages 20 to 55 employed in solvent-using industries (fabricated metal, lumber, furniture, printing, chemical, textile and clothing) had double the risk of breast cancer of women employed outside these industries

(Hansen, 1999). A 1995 U.S. study suggested an increased breast cancer risk associated with occupational exposure to styrene, as well as to several other organic solvents, including carbon tetrachloride and formaldehyde (Cantor, 1995). These results were validated by studies in Finland, Sweden and Italy (Belli, 1992; Walrath, 1985; Weiderpass, 1999; Wennborg, 1999).

Exposure of young (pre-pubertal) laboratory mice to mixtures of organic solvents similar to those found in an industrial setting induced dose-dependent increases in mammary tumors (Wang, 2002). 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 (Labreche, 1997).

C. Vinyl chloride [I-K; N-K]

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 a known human carcinogen by the National Toxicology Program (NTP, 2005a) and IARC (1998). Vinyl chloride has been linked to increased mortality from breast and liver cancer among workers involved in its manufacture (Chiazze, 1981; Infante, 1994). Animals exposed long-term to low levels of airborne vinyl chloride show an increased risk of mammary tumors (ASTDR, 1996).

D. 1,3-butadiene [I-PR; N-K]

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 (NTP, 1993). Data from research on animals indicate that females may be more vulnerable to the carcinogenic effects of 1,3-butadiene (EPA, 2003), 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 (Melnick, 1999; NTP, 1993).

E. Ethylene oxide [I-K; N-K]

Ethylene oxide is a fumigant used to sterilize surgical instruments and is also used in some cosmetic products (ASTDR, 1999). Ethylene oxide is classified as a known human carcinogen (NTP, 2005b) and one of 221 chemicals identified by researchers at the Silent Spring Institute as being associated with mammary tumors in animals (Rudel, 2007).

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 (Steenland, 2003). 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 (Adam, 2005).

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 (Adam, 2005).

VI. Light-at-Night and Melatonin

Several epidemiological studies have demonstrated that women who consistently work night shifts have increased breast cancer risk. Two major reviews of the literature, one examining only studies of night shift nurses (Kolstad, 2008) and a second looking at studies of airline crews and other night shift workers (Megdal, 2005), reached the conclusion that long-term experience in night shift work increases risk for breast cancer about 1.5- to 2.5-fold (Stevens, 2009). These results are of concern, as about 15 percent of the U.S. work force currently works at least some of the time on non-day shifts, and the proportion of workers engaged in night shift work disproportionately falls to African Americans (Costa, 2010).

The most studied mechanism to explain these effects of night shift work is called the Light-at-Night (LAN) hypothesis (Stevens, 2009). Increasing exposure to light, especially bright indoor lights, at times outside of normal daylight hours, decreases secretion

of melatonin (Stevens, 2009). Melatonin is a hormone secreted by the pineal gland in response to decreases in ambient light. Normal high levels of melatonin at nighttime are important for regulation of both pituitary and ovarian hormones (including estradiol), and also for increasing the efficiency of cell proliferation and DNA-repair mechanisms, enhancing the activity of pathways that can prevent the development of cancer (Blask, 2009; Cos, 2000).

Clinical studies have demonstrated that there is a decrease in the peak amount of melatonin secreted in women with metastatic cancer, as compared with healthy women, and larger tumors are associated with lower levels of melatonin (Cos, 2000).

A recent study examined satellite images of 147 communities and compared the co-distribution of LAN and cancer incidence across these communities. A significant positive relationship was found between intensity of night light and breast cancer, but no such relationship was found between night light intensity and lung cancer (Kloog, 2008).

In further support of the LAN hypothesis, blind women who are completely unable to perceive the presence of environmental light, and therefore have no daily decreases in melatonin levels, have significantly lower risk of diagnosis of breast cancer than do blind



women who do perceive light and have regular decreases in melatonin secretion over the normal 24-hour cycle. This effect, along with its opposite in the night shift work model, both support the conclusion that the greater the secretion of melatonin, the lower the risk of breast cancer (Flynn-Evans, 2009).

In rodent models, higher levels of melatonin are associated with decreased incidence and size of mammary tumors, and when they do occur, the latency period of tumor development is lengthened (Cos, 2000).

One study examined the effects of blood (containing naturally secreted melatonin) taken from women during the day; women during the night (also with natural melatonin); women during the night who had been given a drug that blocked the secretion of melatonin; and women

during the night who were exposed to bright white lights. The blood was injected into human mammary tumors that had been xenografted into laboratory mice. Blood from natural nighttime samples significantly decreased proliferation and growth of mammary tumors, as compared to samples collected during the day. If the blood samples came from women who had either been treated with a melatonin blocker or exposed to bright white lights, this protective effect of nighttime sampling was eliminated (Blask, 2005). In these studies, greater intensity of white light led to lower melatonin secretion rates and greater tumor growth rates (Blask, 2009).

Several recent studies have indicated that genes that are associated with the regulation of the daily melatonin cycle also regulate other pathways that may be involved in the development of breast cancer. For example, structural variation in the gene *Per3* is associated with higher breast cancer rates in young women (Zhu, 2008). *Per2*, another gene associated with the control of daily rhythms, is also poorly

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 Several epidemiological studies have demonstrated that women who consistently work night shifts have increased breast cancer risk.

regulated in many women with breast cancer, with normal structure and expression of this gene being associated with lower effectiveness of estradiol in altering cellular activity. In healthy cells, *Per2* also may act directly as a tumor-suppressor gene, decreasing the activity of pathways associated with tumor formation (Gery, 2007).

VII. Radiation

A. Non-ionizing radiation (electromagnetic fields)

1. 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). Fluorescent lighting, computers and many other types of wired and wireless electronic equipment (e.g., cell phones) all create electromagnetic fields of varying strengths.

Both the IARC and the National Institute of Environmental Health Sciences (NIEHS) EMF Working Group have classified EMF exposures as possible human carcinogens based on the scientific literature related to EMF and childhood leukemias (NIEHS, 1998). More recently, data have suggested a link between EMF exposure, especially from cell phone use, and development of brain cancer and acoustic neuromas (Carpenter, 2010). However, consensus has been more difficult to reach about the relationship between EMF and breast cancer.

2. Research exploring links between non-ionizing radiation and breast cancer risk

Although many epidemiological or occupational studies have found no significant relationships between exposures to EMF and risk for breast cancer, others have reported data supporting these effects (e.g., McElroy, 2007; Peplonska, 2007). Methodological issues may account for some of the discrepancies, given the relatively small effects that are found and the ubiquitous nature of “background” EMF in our daily lives (Ahlbom, 2001).

One example of an occupational study that implicates EMF in increased risk for breast cancer is a study that 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 (Kliukiene, 2003). Research has shown increased mortality from breast cancer in women employed in the telephone industry (Dosemeci, 1994), with pre-menopausal women being at higher risk than post-menopausal women (Coogan, 1996).

Studies of residential and occupational EMF exposure found a 60 percent increase in breast cancer risk among 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 (Feychting, 1998; Kliukiene, 2004).

Nevertheless, two large meta-analyses (sophisticated statistical analyses of a large number of studies, taken together) have concluded that there is no clear relationship between EMF exposure and breast cancer in women (Chen, 2010; Erren, 2001).

Although breast cancer is rare in men, numerous studies point to a connection between EMF exposure and male breast cancer (Loomis, 1992; Matanoski, 1991; Milham, 2004; Tynes, 1992).

In the laboratory, EMF can cause increases in mammary tumors in animals and in vitro systems in which human breast cell tumors are grown in culture. Importantly, effects in rodents 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 (Fedrowitz, 2004). In an in vitro cell system, EMF exposure of human breast tumor (MCF-7) cells led to an activation of genes that have been associated with the induction of metastasis in breast cancer cells (Girgert, 2009).

B. Ionizing radiation [I-K; N-K]

1. Overview and mechanisms

Ionizing radiation is any form of radiation with enough energy to break off electrons from atoms (i.e., 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 (EPA, 2005).

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 (Brenner, 2003; NRPB, 1995). A 2005 National Research Council report confirms this finding, stating that “the risk of cancer proceeds in a linear fashion at lower doses [of ionizing radiation] without a threshold and that the smallest dose has the potential to cause a small increase in risk to humans” (NRC, 2005). Radiation damage to genes is cumulative over a lifetime (Boice, 2001). 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) (Goldberg, 2003; Morgan, 2003; Wright, 2004), and changes in breast cell microenvironments that can lead to damaged regulation

of cell-to-cell interactions within the breast (Barcellos-Hoff, 2005; Tsai, 2005). Ionizing radiation not only affects cells that are directly exposed, but can also alter the DNA, cell growth and cell-cell interactions of neighboring cells, referred to as the “bystander effect” (Little, 2003; Murray, 2007b).

2. Interactions between ionizing 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:

- a. 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 (Boice, 2001).
- b. 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 (Andrieu, 2006; Berrington de Gonzales, 2009a; Turnbull, 2006).
- c. 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 (Calaf, 2000; Imaoka, 2009; Segaloff, 1971). This is of particular concern given the widespread exposure to estrogen-mimicking chemicals in our environment and the multiple sources of ionizing radiation.

3. Evidence linking ionizing radiation and breast cancer risk

The link between radiation exposure and breast cancer has been demonstrated in atomic bomb survivors (Land, 1995; Pierce, 1996; Tokunaga, 1994). 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 (Land, 1998). In addition, scientists reported a significant association between ionizing radiation exposure and the incidence of male breast cancer in Japanese atomic bomb survivors (Ron, 2005).

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 (Gofman, 1996). Decades of research have confirmed the link between radiation and breast cancer in women who were irradiated for many different medical conditions, including tuberculosis (MacKenzie, 1965), benign breast disease (Golubicic, 2008; Mattson, 1995), acute postpartum mastitis (Shore, 1986), enlarged thymus (Adams, 2010; Hildreth, 1989), skin hemangiomas (Lundell, 1999), scoliosis (Morin-Doody, 2000), Hodgkin’s disease (Bhatia, 2003; Guibout, 2005; Horwich, 2004; Wahner-Roeller, 2004), non-Hodgkin’s lymphoma (Tward, 2006) and acne (El-Gamal, 2006). 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.

Female radiology technologists who had sustained daily exposure 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 (Morin-Doody, 2006; Simon, 2006). The susceptibility of radiologists for later diagnosis of breast cancer may be affected by common variants in particular genes that are involved in the metabolism of circulating estrogens (Sigurdson, 2009). A 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 (Ballard, 2000).

4. Medical radiation: Risks and benefits

a. CT SCANS

There is considerable evidence that medical X-rays (including mammography, fluoroscopy and CT scans) are an important and controllable cause of breast cancer (Gofman, 1999; Ma, 2008). Although there has been a

significant decrease in exposures to ionizing radiation from individual X-rays over the past several decades, a recent report indicates a sevenfold increase in exposure to medical sources of radiation from the mid-1980s through 2006, primarily arising from the increased use of CT scans and nuclear medicine (NCRP, 2009). In 2007, approximately 72 million CT scans were conducted in the United States (Berrington de Gonzales, 2009b). When a CT scan is directed to the chest, the individual receives the equivalent radiation of 30 to 442 chest X-rays (Redberg, 2009). Recent modeling estimates that use of chest CTs and CT angiography in 2007 alone will lead to an additional 5,300 cases of lung and breast cancer within the next two to three decades (Berrington de Gonzales, 2009b). Other modeling suggests that 1 in 150 women who are 20 years old when they undergo CT angiograms of the chest, and 1 in 270 women (total) having the procedure, will subsequently develop cancers of the chest, including breast cancer (Smith-Bindman, 2009).

b. MAMMOGRAPHY

Many experts believe that the low-dose exposures to radiation received as a result of

mammography procedures are not sufficient to increase risk for breast cancer. However, damage from lower-energy sources of X-rays, including those delivered by mammography, cannot be predicted by estimating risk from models based on higher doses (Heyes, 2009; Millikan, 2005). Recent evidence indicates that the lower-energy X-rays provided by mammography result in substantially greater damage to DNA than would be predicted by these models. Evidence also suggests that risk of breast cancer caused by exposure to mammography radiation may be greatly underestimated (Heyes, 2009).

As with other risk factors for breast cancer, evidence indicates that both age at exposures and genetic profiles influence the degree of increased risk for disease in women exposed to multiple mammograms. For example, women who had multiple mammograms more than five years prior to diagnosis had an increased risk for breast cancer, but the effect was only statistically significant for women whose first mammograms were before the age of 35 (Ma, 2008).

This age effect is of particular concern, since it is often recommended that women with either of the BRCA mutations begin annual mammography screening at ages 25 to 30. Further complicating this age-related finding are the data now demonstrating that young women with the very mutations that lead them to begin mammography screenings at earlier ages are actually more vulnerable to the cancer-inducing effects of early and repeated exposures to mammograms. This increased vulnerability has been found in women with BRCA mutations



(Berrington de Gonzales, 2009a; Jansen-Van der Weide, 2009) as well as in women with other relatively uncommon polymorphisms in genes known to be involved in various steps of DNA repair (Millikan, 2005).

The detrimental risks from mammography might also be heightened in older women, whose breast epithelial cells have gone through several decades of cell division. Cells derived from older women's breast tissue were more sensitive to the DNA-damaging effects of low-energy radiation, increasing the likelihood of later conversion to cancerous cells (Soler, 2009).

The U.S. Preventive Services Task Force recently recommended against the use of routine mammography screening before the age of 50 (Nelson, 2009; USPSTF, 2009) but supported the use of biennial screening between the ages of 50 and 75. These recommendations were based on models using a number of factors, including positive and negative test results and the psychological consequences on women of those results; number of follow-up imaging procedures and biopsies; actual diagnoses; and, ultimately, mortality rates from breast cancer. Not considered in the analysis was the contribution of radiation from either single or repeated mammograms or other follow-up tests (Nelson, 2009). As women are now facing the need to make their own decisions about whether to undergo routine screening mammography, it is critical that both physicians and women are better educated about mammography's potential harms, along with its potential benefits (Gotzsche, 2009).

c. RADIATION THERAPY

Some studies suggest that doctors and patients should carefully evaluate the risks and benefits of radiation therapy for survivors of early-stage breast cancer, particularly older women. Women older than 55 derive less benefit from radiation therapy in terms of reduced rate of local recurrence (Veronesi, 1999) and may face increased risks of radiation-induced cardiovascular complications (EBGTCG, 2000), as well as secondary cancers such as leukemias and cancers of the lung, esophagus, stomach and breast (Mellemkjaer, 2006; Roychoudhuri, 2004). Using NCI's Surveillance, Epidemiology and End Results (SEER) data, researchers showed a 16-fold increased relative risk of angiosarcoma of the breast and chest wall following irradiation of a primary breast cancer (Huang, 2001).

More recent data indicate that women younger than 45 who received the higher radiation exposure associated with post-lumpectomy radiotherapy (as compared to post-mastectomy radiation) had a 1.5-fold increase in later contralateral breast cancer diagnoses. This effect was especially prominent in younger women with a significant family history of breast cancer (Hooning, 2007).

Mammography Screening: Are We Asking the Wrong Question?

In November 2009, the U.S. Preventive Service Task Force released revised mammography screening guidelines, recommending against the routine use of mammography before age 50, with biennial screening from age 50 to age 75 (USPSTF, 2009). The response from the public, from health care providers and from cancer support organizations was immediate and emotionally charged.

In making its recommendation, the Task Force took into account a number of factors related to the effectiveness of the screening test and the consequences of different test outcomes. The model it developed was based on our understanding of these factors at a population level, not whether any particular woman would benefit from more or less use of mammographic screening. In addition, the guidelines did not consider the possible contribution to breast cancer risk of single or repeated exposures to radiation during mammography or other follow-up tests (Nelson, 2009). (As discussed above, scientific evidence links radiation exposure to increased risk for breast cancer.)

When the Task Force released its findings, the Breast Cancer Fund responded with a statement that tried to change the conversation about mammography to one that was directed toward true prevention. For too long, emphasis on what is called secondary prevention, or detecting cancer early enough to treat, has obscured the fact that detection of an existing tumor is not prevention. True prevention means identifying and eliminating the preventable causes of the disease before it can occur.

Below is an excerpt from the November 19, 2009, statement, signed by Breast Cancer Fund President and CEO Jeanne Rizzo.

At the Breast Cancer Fund, we want to acknowledge the frustration and anxiety that this recommendation has caused among breast cancer survivors and their families, many of whom attribute their diagnosis and survival to either mammography screening or self-exam. The overwhelming sentiment seems to be that these tools are all we have and might be taken away.

Annual screenings have produced an opportunity for women to relieve their fears of a breast cancer diagnosis. When a tumor is found by mammography and then treated, a woman understandably attributes her post-treatment survival to the successful detection. For survivors, mammography often becomes a personal victory story. Sadly, roughly 100 women lose their lives to breast cancer each day.

Our response is to shift the question: Why are we still relying on this method of screening when we have long understood that radiation is a known breast carcinogen? Why has there not been more investment in finding a safer and more effective tool for early detection?

The mission of the Breast Cancer Fund is to identify and advocate for elimination of the environmental and other preventable causes of the disease. We have long held concerns about the risk of exposing women's breasts repeatedly to small amounts of ionizing radiation and the adoption of uniform recommendations about its use, whether lowering the age to 40, changing the intervals or reinstituting the recommendation for age 50.

The reliance on mammography as a tool for detection undermines the need for directing our national health resources toward the development of noninvasive alternatives that truly address prevention.

This is a moment of opportunity, a chance to recognize the weaknesses of our current tools for detecting and predicting the progression of existing breast cancers. And more important, it is time to turn the conversation from the need for finding cancers that may or may not warrant treatment to understanding better the causes of the disease and engaging in our collective efforts to minimize those risks that are controllable.

It is time to fully invest in breast cancer prevention.

For information on personal tips and policy initiatives related to mammography and breast cancer screening, see pages 94-98 in the section "From Science to Action."

Bisphenol A: Bridging Science and Action



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According to the U.S. Centers for Disease Control and Prevention, 93 percent of Americans have detectable levels of BPA in their urine.
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Introduction

Bisphenol A (BPA) is the chemical building block of the hard, shatterproof polycarbonate plastic used to make some baby bottles, water bottles and food storage containers. BPA is also used in the epoxy resins that line metal food and infant formula cans. BPA forms an unstable polymer, which means that heat, acidic conditions, and repeated use can cause BPA to enter the contents of food containers and ultimately make its way into people.

In addition to its uses in food and beverage containers, BPA is also used in thermal receipt paper and has a range of other industrial and consumer uses.

Synthesis of BPA was first reported in 1891. Because of its estrogen-like properties, it was considered for use as a pharmaceutical hormone in the 1930s, but then abandoned in favor of other synthetic estrogens. In the 1940s, scientists in the chemical industry discovered its usefulness in making plastics and resins.

Bisphenol A and endocrine disruption

BPA is an endocrine-disrupting compound (EDC) that, even in very small amounts, can affect health,

particularly when exposures occur during gestation and in early life. Doses in the parts per billion and even parts per trillion have been shown to have effects on laboratory animals and human breast cells. Such amounts are often termed “low doses” because they are magnitudes lower than doses used in traditional toxicological research. But low doses are often environmentally relevant — that is, they approximate typical human exposure in normal daily life (vom Saal, 2007). According to the U.S. Centers for Disease Control and Prevention, 93 percent of Americans have detectable levels of BPA in their urine (Calafat, 2008). Several other studies have detected BPA in cord blood (Ikezuki, 2002), amniotic fluid (Engel, 2006), breast milk (Ye, 2006b), and blood serum, demonstrating significant fetal and newborn exposures, as well as exposures of older children and adults (Calafat 2008, 2009; Schoenfelder, 2002; Wolff, 2007).

BPA provides an ideal model for understanding and discussing EDCs as a group because (1) a growing body of scientific evidence exists related to the health effects of BPA exposures; (2) it is found in everyday objects; (3) it is measurable in humans; and (4) it leaves the body fairly quickly,

making the effects of personal or policy changes easy to measure. Evidence about BPA exposures also illustrates several of the key concepts related to EDCs: Tiny amounts can exert significant effects; health impacts are most notable when exposures occur prenatally, early in life or around puberty; and BPA enhances the effects of the body's own estrogens (von Meeuwen, 2007). Statistically, BPA exposure also shows variations based upon age, race/ethnicity and income, illustrating that chemical exposures are not equitably distributed (Calafat, 2008).

Emerging concerns

Discussion of BPA appeared in the very first edition of *State of the Evidence* in 2002, based upon 2001 research linking in utero exposures to BPA to altered mammary gland development — effects that are consistent with changes associated with later-life development of breast cancer (Markey, 2001). Over the years, the evidence linking BPA to mammary gland changes and development of mammary cancer has grown significantly, and presentation of these findings in *State of the Evidence* has expanded concurrently.

In 2007, the scientific evidence linking BPA to adverse health effects grew rapidly, prompting broad public concern, market-based changes and reviews of BPA by regulatory agencies including the FDA and the National Toxicology Program (NTP). Reports from these reviews were published in 2008. The FDA found that current levels of BPA exposure were within acceptable limits, while the final NTP report concluded

that at current levels of human exposure there was some concern for the effects of BPA on the brain, behavior and prostate gland at current levels, and minimal concern for effects on the mammary gland and early puberty (NTP-CERHR, 2008). These conclusions were at odds with both the growing body of scientific data and the growing public concern about the chemical.

As the evidence of health risks associated with low-dose and early-life BPA exposure has grown, so has the sophistication of the critiques of the evidence. Early critiques of calls for action to limit food-based BPA exposures focused on the long-held assumption that the “dose makes the poison.” Both industry representatives and regulatory agencies in the United States, Canada and the EU asserted that the levels of BPA that leached from water and baby bottles into liquids, or the BPA that migrated from food can linings into the vegetables, soups or beans stored in those cans, were too small to affect health. The EPA sets the reference dose for BPA at 50 ppb (EPA, 2008). This is an infinitesimal level, proportionally equivalent to about 2.5 minutes in a century. However, this small amount is hundreds of times larger than the levels at which exposures to BPA have been found to adversely affect health in laboratory animals (vom Saal, 2007).

Traditional risk assessment relies on the assumption that higher doses of a given chemical exposure will cause more significant and more severe effects. This is called a linear (monotonic) dose-response curve. In the case of exposures to EDCs, very low doses may actually

exert different, and sometimes greater, effects than high doses, leading to a U-shaped or J-shaped (nonmonotonic) dose-response curve. This is especially apparent when low-dose exposures occur during crucial periods of development. The changes are often subtle early in life, but predispose animals, including humans, to significant later-life health effects such as cancers and metabolic disorders.

Another critical factor is the type of health outcome that is measured in research on chemical safety. In the case of breast cancer, effects of chemical exposures on mammary tissue development and increased risk for breast cancer are essential endpoints that need to be studied. Yet in traditional toxicological testing, mammary outcomes are often not included as a standard outcome for assessing health effects (Rudel, 2009). The combination of under-tested low-dose exposures and untested health outcomes can lead to gaps in the data used for setting regulatory standards.

As the body of evidence illustrating low-dose exposure effects has grown, a new critique has emerged. In some of the studies that have found striking adverse health effects from early low-dose exposures, BPA was administered orally — an approach that closely mimics the consumption of BPA by humans. In other cases, however, low doses were given via small pumps or injections. Because BPA is very rapidly metabolized in the gastrointestinal tract before entering the bloodstream, injection of BPA may result in considerably higher active BPA exposure than

oral consumption. Industry leaders invested in defending BPA's safety used this critique to undermine efforts to call for FDA reconsideration of BPA's health effects at low doses, even though several low-dose studies of oral exposure have illustrated detrimental health effects. (See Richter, 2007 for review.) Applying the criterion that only studies using orally administered BPA were methodologically sound had a huge impact on a 2008 review of BPA's safety, which omitted many studies that relied on injected BPA (Borrell, 2010).



Recently, the National Institute of Environmental Health Sciences provided \$30 million in funding for researchers to address many of these methodological concerns in the BPA literature (NIEHS, 2009). Among other things, the NIEHS called for researchers to study both oral and injected doses of BPA; to share tissues from their studies with one another; to use a positive control chemical (a substance known to cause health effects similar to those BPA is suspected of causing); and to collaborate to answer questions about BPA's potential impacts on behavior, obesity, diabetes, reproductive disorders, asthma, cardiovascular disease, and transgenerational or epigenetic effects, as well as development of prostate, breast and uterine cancers.

Evaluating science

Good science requires acknowledging the interests of those who conduct the scientific research and exploring the methodological choices in research studies. More than 200 studies

have found negative health effects in animals exposed to low doses of BPA. Only a small number of studies have not found such effects. Although some of the negative results came from independent (not industry-funded) labs, a substantial portion of the studies that reported no detrimental effects of BPA were funded by chemical companies; all of the studies funded by industry found no evidence of harm as a result of BPA exposure (vom Saal, 2005).

Another subset of the studies that found no evidence of harm used estrogen-insensitive rats to test the hormone-disrupting effects of BPA (Ryan, 2010). Since BPA is a weak estrogen, it is understandable that these studies revealed no health effects as a result of BPA exposure. These methodological choices affect the utility of those studies for understanding mechanisms by which BPA may affect health outcomes. Nevertheless, examining

the variability in sensitivity to exposures across species, strains and individuals will ultimately be helpful in understanding the nuances of how environmental exposures affect risk for people with differing vulnerabilities to later development of breast cancer.

Negotiating conflicting priorities

Translating BPA science into action requires an understanding of both the scientific evidence and the policy avenues available to regulate chemicals, food and food packaging. In the case of BPA, advocates have sought to restrict its use in food packaging through municipal, state and federal legislative action and stricter FDA regulation of BPA as a food contact substance. Over the past year, these multiple strategies have been used to secure stricter municipal and state regulation of food-based exposures to BPA in the face of concerns about the chemical's safety.

The scientific evidence and the debates about that evidence have shaped the legislative discourse over BPA. Several groups are stakeholders invested in the fate of the chemical's use in food and beverage packaging. Among the voices calling for policies that take a precautionary approach to environmental and public health are public interest organizations focused on environmental health and justice issues representing breast cancer prevention, parents, children's health, nursing, the faith community and service providers like WIC (the federally funded health and nutrition program for women, infants and children). Industries that manufacture and use BPA have different priorities, with goals related to maintaining the status quo. Policymakers and regulatory agencies are charged with negotiating these differing priorities. In the case of BPA, findings from industry scientists have frequently contradicted the findings of academic scientists, in part because of the different methodological approaches discussed above. These differences are not always articulated during policy discussions. As a result, interpreting the science can prove challenging for policymakers and regulators who hear two different stories, making efforts to pass legislation or alter regulatory policies difficult.

In reality, regulatory decision-making often relies on evaluating incomplete or even contradictory evidence. In the case of chemicals linked to cancer and reproductive health concerns, the science may be new or just emerging; thus gaps may exist and some questions may

Translating BPA science into action requires an understanding of both the scientific evidence and the policy avenues available to regulate chemicals, food and food packaging.

be unanswered. However, public policy decisions that impact public health should err on the side of precaution and take into account the importance of addressing the effects of cumulative exposures, and protections for vulnerable populations like infants, children and pregnant women (NAS, 2008).

From science to action

Frequently the front-line in policy change is at the state level, and this has held true for regulation of BPA. State and municipal legislative action to restrict food-based exposure to BPA is creating the necessary momentum for federal reform. Over the past year alone, Connecticut and Vermont banned BPA from infant formula cans, baby bottles and sippy cups, while five other states (Minnesota, Washington, Wisconsin, Maryland and New York) enacted laws to ban BPA use in baby bottles and sippy cups. In all, 31 states and localities have introduced legislation to more strictly regulate BPA in food packaging.

In addition, major retailers are phasing out BPA-containing baby bottles, including CVS, Kmart, Kroger, Safeway, Sears, Toys R Us, Walmart, Wegmans Foods and Whole Foods. Comparable efforts are taking place on the part of manufacturers to generate BPA-free options for water bottles (by Aladdin, CamelBak, Nalgene and Polar Bottle) and baby bottles (by

Avent, Born Free, Disney First Years, Evenflo, Dr. Brown, Gerber, Munchkin, Playtex and Think Baby).

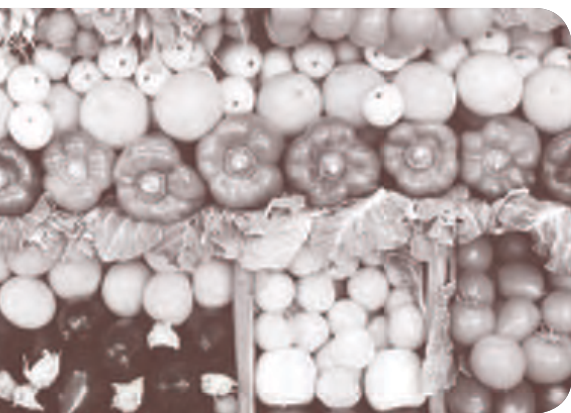
Eden Foods already uses BPA-free cans, and Muir Glen, a subsidiary of General Mills, announced it will begin packaging its tomato products in BPA-free cans in late 2010. Perhaps most notably, the chemical company Sunoco is requiring its customers to guarantee that BPA will not be used to manufacture food and water containers intended for use by children under 3.

While retailer, manufacturer, state and municipal action is commendable, it is resulting in a patchwork of regulation that still leaves the majority of Americans exposed to this well-studied, unsafe chemical. Congress must set a high bar for safety by enacting federal legislation to ban BPA from food and beverage containers and giving the FDA the authority it needs to more strictly regulate other harmful packaging additives.

With legislation already introduced in both the Senate and the House to ban BPA from food and beverage containers regulated by the FDA, Congress has the opportunity — and the obligation — to protect all Americans, especially our children from this toxic, hormonally active chemical.

FROM SCIENCE TO ACTION

From Science to Action



Our goals are to build bridges among...important advocacy communities, to help deepen breast cancer advocates' understanding of environmental health issues and to bring the powerful voice of breast cancer prevention advocates to the environmental health movement.

I. How to Use This Section

“From Science to Action” is intended for advocates of breast cancer prevention, women’s health, public health and environmental health, as well as 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 goals are to build bridges among these important advocacy communities, to help deepen breast cancer advocates’ understanding of environmental health issues and to bring the powerful voice of breast cancer prevention advocates to the environmental health movement.

This guide is not an exhaustive list of public policy and research initiatives needed to fully eliminate the environmental links to breast cancer. Instead, it presents a variety of ways that advocates and policymakers can engage in breast cancer prevention.

“From Science to Action” is divided into the following categories: food, plastics, cosmetics, household products, health care, and air and water. Each section begins with a brief description of key breast carcinogens and endocrine-

disrupting chemicals of concern in this category, as well as the routes of exposure. We then discuss vulnerable populations affected by these exposures, and list the federal agency or agencies responsible for regulating the chemicals. This is followed by detailed information on the current federal regulations for each of the categories. In many sections, multiple federal agencies have jurisdiction over a given exposure, illustrating the vital need for interagency collaboration and for infrastructure that provides a means for data and information sharing. This integrated approach is distinct from the current siloed regulatory structures that lead to redundancies, inefficiencies and ineffective regulatory strategies.

II. Food

A. Exposures of Concern

Chemicals linked to breast cancer are used in many aspects of food production, processing and packaging. Through the food we eat, we are exposed directly to packaging additives, pesticides and hormones. These same chemicals pollute our air, water and soil.

Food packaging

A primary concern is the use of hormone-disrupting and

carcinogenic compounds in materials intended to come into contact with foods. These materials include some plastic food and beverage containers such as take-out containers and the linings of most food cans.

Bisphenol A (BPA) is the chemical building block for clear, shatterproof polycarbonate plastic, which is used in baby bottles, water bottles and food storage containers. It is also in the epoxy-resin linings of metal food cans, including infant formula cans. BPA leaches from containers and can linings, enters food and beverages, and ultimately gets into people.

Other chemicals of concern that have been approved for use in food packaging are formaldehyde; phthalates, which are added to some plastic food containers and have been linked to hormone disruption; and polystyrene, used in some take-out containers, which breaks down into styrene, a breast carcinogen. Like BPA, some of these chemicals migrate into food and then into people. For instance, formaldehyde is used in the creation of melamine (hard plastic) dishes. Danish and British studies of formaldehyde migration from melamine found that formaldehyde leaches into simulated food (a mixture of water and ethanol that matches food acidity) at levels above EU safe exposure limits (Bradley, 2005; Lund, 2006).

Pesticides and food

The widespread use of pesticides on food crops is a significant source of exposure to endocrine-disrupting compounds and carcinogens linked to breast cancer. Pesticides of greatest concern include atrazine, an endocrine-disrupting compound;

heptachlor, an insecticide that was banned from production in 1988 and from use in 1993, but persists in soil and in humans (CDC, 2005; EWG, 2005); dieldrin and aldrin, related pesticides that are endocrine disruptors; and several other pesticides that have been linked to breast cancer in agricultural workers (Mills, 2005; Engel, 2005).

Residual pesticides on produce purchased by consumers are also of concern. Studies have found that shifting children's diets from conventional foods to organic foods, by direct substitution of conventional foods, leads to a reduction of organophosphate pesticides in urine. This suggests that foods are a key source of exposure to some pesticides (Curl, 2003; Lu, 2006).

Hormones in meat and milk

Hormonally active substances are used in food production, primarily in cattle and other herd animals raised for meat or milk. The pharmaceutical zeranol promotes weight gain in cattle and is used in approximately two-thirds of the cattle raised in the United States.

The health effects of recombinant bovine somatotrophin (rBST), a genetically engineered hormone that increases milk production in cattle, are widely debated. The hormone rBST may increase the levels of insulin growth factor 1 (IGF-1; Daxenberger, 1998), a naturally occurring hormone in both cows and humans. Higher levels of IGF-1, in turn, have been linked to increased risk of breast cancer (Allen, 2005; Schernhammer, 2005).

B. Vulnerable Populations

Pesticides, chemicals that migrate from food packaging, and hormones used to increase the production of milk and meat all have potentially global impacts given the magnitude of industrial agriculture. Because these substances are used on such a large scale, they make their way into household air and dust (Rudel, 2003) and into water (Westerhoff, 2005), which facilitates global migration. As a result, individuals may not be able to control all exposures to these chemicals through lifestyle choices or changes in purchasing practices.

Agricultural workers and people working or living on or near farms have higher exposures to pesticides. A study of Latina agricultural workers compared women newly diagnosed with breast cancer to women of similar ages without breast cancer, and found that use of three pesticides — chlordane, malathion, and 2,4-D — was associated with increased risk of disease. This effect was most striking for young women. Another larger study of 30,000 women in Iowa and North Carolina found that women using 2,4,5-trichlorophenoxypropionic acid (2,4,5-TP) had elevated risk of breast cancer, as did women who lived closest to areas of pesticide application. Children living on farms also have increased exposures, and one study of children ages 4 to 11 found higher levels of the pesticide 2,4,5-TP in their urine shortly after the pesticide was applied. This finding is particularly notable given concerns about early-life chemical exposures linked to later-life disease.

Many farmworkers are undocumented immigrants who enjoy fewer legal protections and less access to health care than the general population, limiting their ability to protect themselves from pesticide exposure or to seek medical care in response to chemically induced health problems.

Exposure to endocrine-disrupting pesticides like atrazine and food-packaging additives such as BPA and phthalates during gestation and early childhood can have particularly profound effects on long-term health, including the development of breast cancer in adulthood. Exposure to endocrine disruptors is of special concern at these stages of rapid development and significant hormonal activity.

Research on girls exposed to zearalenone, a chemical similar to the growth-promoting zeranol, suggests that these kinds of chemicals may be linked to precocious puberty, a risk factor for later-life breast cancer (Massart, 2008).

C. Current Regulation

Food packaging

The U.S. Food and Drug Administration maintains a list of more than 3,000 chemicals and other substances that are approved for use in food packaging and reusable food containers. These are considered “indirect food additives,” because they migrate from the packaging or container into food. More than two-thirds of them were approved under a petition-and-review process that was established in 1958, including known or suspected reproductive toxicants like BPA and carcinogens like formaldehyde. The other chemicals



on the list of approved food-contact substances have been added since 2000, when the FDA began the Food Contact Substance Notification program (FCN), which requires industry to notify the agency of a proposed use of a new chemical (or a new use of a previously approved chemical) and wait 120 days before marketing it.

In the early 1960s, nine categories of BPA use in epoxy food packaging and containers were approved under the FDA’s petition-and-review process (FDA, 2010c). Since 2000, eight more uses have been approved under the FCN (FDA, 2010c), and because these uses are classified as confidential business information, these applications are not fully disclosed to consumers. Although FDA officials announced in January 2010 that BPA warrants “some concern,” especially for infants and small children, the agency’s authority and ability to regulate the chemical is limited by

its own petition-and-review process and the FCN.

Substances that were approved under the petition-and-review process (including BPA) are not subject to regular reevaluation, despite advances in food and chemical safety. As a result, the FDA argues, action to ban BPA from food packaging would be costly and time-consuming. Under the petition-and-review process, any manufacturer of food or food packaging was permitted to use it for the approved purpose with no requirement to notify the FDA of that use. As a result, there are hundreds of different formulations for epoxy linings containing BPA. Manufacturers are not required to disclose to the FDA the existence or nature of these formulations. As a result, the FDA cannot compel manufacturers to provide the data needed to review the formulations and uses of BPA in food-contact items. The FDA says that to have BPA (or any substance previously

approved under petition-and-review or FCN) reassessed for possible restriction or prohibition based on new evidence, the best hope is for the manufacturer to voluntarily resubmit it. There is no incentive for manufacturers to take such action.

In addition, the FCN has limited utility for protecting public health from indirect food additives in food packaging. For instance, it requires companies to notify the FDA that they intend to use a new chemical or a previously approved chemical in a new packaging application; they must supply information supporting the claim that it is safe for that use, and then wait 120 days. If the FDA doesn't object in writing, the new packaging formulation can go on the supermarket shelf. The law authorizing the FCN defines "safe" only as "reasonable certainty in the mind of competent scientists that a substance is not harmful under the intended conditions of use."

The list of substances that have been approved under the FCN includes compounds that contain or are manufactured with known hazardous chemicals such as benzene, styrene and butadiene — all classified by the U.S. Environmental Protection Agency as known human carcinogens. Food-contact substances approved as GRAS ("generally regarded as safe") chemicals include propylene glycol and propyl paraben.

The FCN is based on the FDA's review of data and studies generated by the manufacturer, not by government or independent scientists. Depending on the amount of the substance expected to migrate from the packaging

or container to the food, based on manufacturers' estimates, the FCN requires studies evaluating a substance for possible carcinogenicity and reproductive harm, but not for endocrine disruption — a primary concern in the case of BPA. It is unclear how rigorous the FDA's review of data and studies submitted by manufacturers is under the FCN. However, of more than 900 FCN decisions listed on the FDA's Web site, more than 90 percent were approved without the FDA requiring supplemental studies.

Pesticides

The EPA approves pesticides for sale under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), last amended in 1988. Pesticide risk is assessed and managed by conducting research and requiring labels describing proper use and indicating a toxicity class. Restricted-use pesticides, or those considered by the EPA to be too hazardous to sell to the general public, are only allowed for purchase by a certified applicator (Willson, 2009).

FIFRA assessments are based on risk-benefit standards, and do not emerge from safety or health standards established to protect human health and the environment. New pesticides can enter the market before meeting health and safety testing with a "conditional registration," and toxicity testing is obligated only for active ingredients, even though inert ingredients may have toxic qualities. The data that are submitted come internally from pesticide manufacturers, despite research indicating substantive differences with external research from government or academic sources.

The EPA revised the Worker Protection Standards in 1992 to protect farmworkers from agricultural pesticide exposures by requiring pesticide safety training, safety and protective equipment use, and notification of pesticide applications. But research indicates that the implementation of safety training, especially among migrant workers, is inadequate (Jacobs, 2009). In 1996, the Food Quality Protection Act was enacted, requiring the EPA to adopt new standards to assess levels of pesticides and their breakdown compounds in food. Levels are set at 100 to 1,000 times lower than the "no observable effect level" (NOEL) for a person's exposure to one pesticide from all sources. Additionally, if a pesticide has been found to cause cancer in laboratory experiments, then exposure must be proven likely to cause no more than one case of cancer per million people (Jacobs, 2009b).

Internationally, regulations for pesticides differ by country, but the United Nations Food and Agriculture Organization (FAO) conference in 1985 created the International Code of Conduct on the Distribution and Use of Pesticides, a set of voluntary guidelines for pesticide regulation (Willson, 2009). This Code has been updated in 1998 and 2002, with the aim of lowering the number of countries that have no pesticide use restrictions. Additional global efforts include the United Nations London Guidelines for the Exchange of Information on Chemicals in International Trade and the United Nations Codex Alimentarius Commission (Reynolds, 1997). In 2009, the European Union banned the use of pesticide products containing active

ingredients that are carcinogenic, mutagenic or endocrine-disrupting substances (EPA, 2009).

Hormones in meat and milk

The use of zeranol, a nonsteroidal growth promoter that mimics many of the effects of the natural hormone estradiol, in food animals was banned in the European Union in 1985 (EC, 1985). While the United States has taken no regulatory action on zeranol, the EU has taken a strong stance on keeping all meat raised using synthetic hormones out of its member countries. In 2002, the European Commission reassessed and consequently reaffirmed its ruling that all EU countries continue to ban the importation of any beef from the United States or Canada due to the practice of synthetic hormone use. In early 1996, the United States challenged the EU ban on imports of meat from animals that had been administered any of six growth-promoting hormones, using the dispute-settlement procedures of the World Trade Organization, then a year old. The EU Scientific

Committee on Veterinary Measures relating to Public Health (SCVPH) confirmed that the use of hormones as growth promoters for cattle poses a potential health risk to consumers, following a review of 17 studies and other recent scientific data. After several challenges to the EU's ban on imports of meat from animals raised with hormones, the EU maintained its earlier decision to ban the meat despite heavy fines (EC, 2002).

The U.S. Food and Drug Administration has set an allowable level of zeranol for meat sold in the United States. Recent research showed that abnormal cell growth was significant even at zeranol levels almost 30 times lower than the established FDA limit. The use of hormones in calves has also been banned in the United States, although the veal industry was recently found guilty of using banned hormones in up to 90 percent of its veal calves (Weise, 2004).

The synthetic hormone rBST was approved for use in the United

States in 1993. A number of other governments, including the EU, Japan, Australia, New Zealand and Canada, have banned rBST. In the United States, the FDA approves drugs and supplements given to animals, including animals raised for food or milk, through the FDA's Center of Veterinary Medicine. The substance rBST is approved as an animal drug product under the trade name Posilac 1 Step®, registered to Eli Lilly & Co (FDA, 2010b).

The FDA also regulates the labeling of foods. In response to consumer pressure, a number of companies began to label dairy products such as milk, cheese, and butter as containing "Milk from cows not treated with rBST/rBGH." This approach, initiated by companies, is considered voluntary labeling. In a 1994 docket, the FDA said such claims must be put in proper context, and noted that the inclusion of a statement of rBST-free milk should be accompanied by a statement that says: "The federal government has determined that rBST/rBGH milk is safe for humans and cows, and that no significant difference has been shown between milk from rBST/rBGH treated or non-rBST/rBGH treated cows" (FDA, 1994).

D. Policy Recommendations

The woefully outdated Toxic Substances Control Act (TSCA) of 1976 established a process for registering chemicals, but it grants the EPA only limited authority to ban chemicals or require testing. Reform of the TSCA should address cumulative exposures to carcinogenic and endocrine-disrupting compounds from food sources, including the health impacts of mixtures of pesticides,



food-packaging chemicals, and hormones in meat and milk. Since these different exposures are regulated by several agencies, federal interagency coordination will be required to address the cumulative effects of mixtures of endocrine-disrupting compounds from food.

Congress should enact TSCA reform by supporting the Safe Chemicals Act of 2010, introduced by Sen. Frank Lautenberg (D-N.J.), and the Toxic Chemicals Safety Act of 2010, introduced by Reps. Bobby Rush (D-Ill.) and Henry Waxman (D-Calif.).

Food packaging

Chemicals linked to cancer and reproductive harm should be banned from food packaging. FDA regulation of food packaging — including both the FCN and the older petition-and-review process — should be revised to include more rigorous safety standards.

- Policymakers should support the Ban Poisonous Additives Act of 2009, which will ban the use of BPA in food and beverage containers. Sen. Dianne Feinstein (D-Calif.) and Rep. Edward Markey (D-Mass.) are lead sponsors of the legislation (S. 593/H.R. 1523). The legislation would also substantially increase the FDA's authority over other food-contact substances, whether they were approved under the petition-and-review process or under the FCN. It requires the FDA to review the list of substances deemed safe for use in food and beverage containers to determine whether new scientific evidence exists showing that any of the substances poses adverse health risks, and to make necessary changes to the list within one year of enactment and every five

years thereafter. It also adds a requirement that under the FCN, manufacturers must conduct and submit studies on a substance's potential reproductive and developmental toxicity, including endocrine disruption, regardless of the amount of the substance expected to migrate into food.

- The FDA should use its existing authority under the petition-and-review process to promulgate a rule that would ban the use of BPA as a food-contact substance. In addition, a process should be put in place to implement an FDA reassessment of the potential hazards of the more than 2,000 chemicals that were previously approved under the petition-and-review process, sometimes over 40 years ago, or by the earlier letters of approval, including the GRAS ("generally regarded as safe") additives.

Pesticides

Several existing policies should be updated and expanded to allow for more rigorous safety assessments of pesticide uses on food crops, to consider cumulative pesticide exposures from food, to address the exposures and health impacts of pesticides on agricultural workers and their families, and to promote safer alternatives.

- The EPA should follow the EU's lead and ban the use of atrazine in the United States.
- The Federal Insecticide, Fungicide, and Rodenticide Act should be revised so that pesticides cannot enter the market with a conditional registration. Inert ingredients along with active ingredients should be included in toxicity testing. Pesticide registration procedures need to be more stringent, and the EPA

should establish and enforce rigorous testing requirements.

- Strengthened premarket health and safety testing and regulation of pesticides should be included in comprehensive chemical policy reform.
- The Food Quality Protection Act needs to be more vigilantly implemented and to move beyond policy that addresses one pesticide or agent at a time, to consider multiple concurrent pesticide exposures.
- More research is needed on the cumulative exposures of agricultural workers and their families to gain a greater understanding of the role of pesticides in the development of breast cancer and other diseases.
- Manufacturers should be provided with incentives to adopt safer pesticide practices and develop product alternatives.

Hormones in meat and milk

Policy changes are needed that would help limit exposures to hormones in meat and milk resulting from the use of synthetic hormones to increase milk production or to promote cattle growth.

- The federal government should ban the use of zeranol, rBGH and other hormones in meat and milk.
- Federal funding is needed to support exposure studies that will measure the presence and levels of synthetic hormones in meat and dairy sold and consumed in the United States, so that the potential for negative health effects can be assessed.
- Federal funding is needed for research that considers the contributions of synthetic

Food: Tips for Reducing Exposure to Chemicals of Concern



Avoid canned foods

The lining in canned food can leach chemicals like BPA. Choose fresh vegetables if possible, and choose frozen over canned. Look for foods

packaged in glass, Tetra Paks (box packaging commonly used for soy milks, juice boxes and some soups) and other alternatives to BPA-lined cans.

Eat local pesticide-free or fully organic foods

Organic produce is grown without harmful man-made pesticides and herbicides. Visit a farmers' market for locally grown organic fruits and vegetables, or ask your grocer to stock organic produce.

Eat hormone-free meat and dairy

Choose hormone-free beef or dairy to eliminate those traces of hormones that can enter our bodies and contribute to an increased risk of breast cancer.

hormones in meat and milk products to breast cancer.

- In the absence of federal-level action on hormones in meat and milk, state governments should consider guidelines that require across-the-board labeling of hormones in meat and milk; more targeted labeling laws that focus on meats in schools, hospitals and other sites frequented by vulnerable populations; and/or a health warning label on meats that contain synthetic hormones. Legislation should also authorize the creation of a publicly available database with this information, so that consumers can make informed purchases.

E. Agencies Responsible for Regulation

- FDA, Center for Food Safety and Applied Nutrition (CFSAN). Manages food-packaging additives

under the Food Contact Substance Notification Program.

- USDA, Food Safety and Inspection Service. Governs Food Safety and Labeling.
- FDA, Animal and Veterinary Office. Approves drugs for use in animals, such as rBST and zeranol.
- EPA. Sets maximum residue limits (MRLs) for pesticides in food. The USDA and the FDA's CFSAN are responsible for enforcing these limits.
- Federal Food, Drug and Cosmetic Act (FFDCA). Directs the EPA to set pesticide tolerances for products used in or on food.

III. Plastics

A. Exposures of Concern

Plastics are widely used in consumer products, including food packaging, toys, household products and

electronics. The EPA estimates that the United States generated 13 million tons of plastic waste in 2008.

Chemicals of concern in plastics include some of the constituent molecules in plastics, such as styrene, a known carcinogen found in polystyrene; and additives used to give plastic certain properties, such as the endocrine-disrupting compounds bisphenol A (BPA), which makes plastic hard, and phthalates, which make plastic soft and flexible.

Polycarbonate plastic is a hard, shatterproof plastic made with BPA. Polycarbonate plastics are used in drinking cups, water bottles, baby bottles and some dishes, although many manufacturers are shifting to alternative materials due to the health concerns of BPA. Polycarbonate is used in other consumer products such as eyeglass

and sunglass lenses, compact discs and DVDs, and electronics cases.

Phthalates are a family of chemicals used in polyvinyl chloride (PVC) to make it malleable, and they too can be found in a number of everyday products, including cosmetics, pharmaceuticals, baby care products, building materials, modeling clay, automobiles, cleaning materials and insecticides. Styrene is an animal mammary carcinogen and has been identified

by the IARC as a possible human carcinogen. It is a large molecule that is strung together in repeating chains to create the plastic polystyrene. It is found in all Styrofoam food trays and egg cartons and in some food carry-out containers and plastic food utensils. A 1995 study suggested an increased breast cancer risk associated with occupational exposure to styrene (Cantor, 1995).

Vinyl chloride, a known human carcinogen, is released in the manufacture of PVC, which is used in cling wrap, some plastic squeeze bottles, some cooking oil bottles, some cleaning solution bottles, household water pipes and vinyl shower curtains, wall coverings and floor coverings. The incineration of PVC can form dioxins, which are known carcinogens and endocrine-disrupting compounds.

Table 2: What Is the Connection Between Food and Breast Cancer?

Food-Based Exposure	Mammary Carcinogen (Rudel, 2007)	Carcinogenic (IARC, 2009; NTP, 2005)	Endocrine-Disrupting Compound (Brody, 2003)	Use	Regulated by
2,4-Dichlorophenoxyacetic acid			●	Pesticide: herbicide	EPA, USDA, FDA
2, 4, 5-Trichlorophenoxypropionic acid		IARC Possible		Pesticide: herbicide	EPA, USDA, FDA
Atrazine (page 46)	●	IARC not classifiable	●	Pesticide: herbicide, air pollutant; found widely in bodies of water; banned in the EU; 75 million pounds used per year in United States, mainly on corn and sorghum	EPA, USDA, FDA
Bisphenol A (page 42)			●	Food packaging: polycarbonate plastics (baby bottles, water bottles); linings of canned foods; leaches from these materials into foods	FDA

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Table 2: What Is the Connection Between Food and Breast Cancer?

Food-Based Exposure	Mammary Carcinogen (Rudel, 2007)	Carcinogenic (IARC, 2009; NTP, 2005)	Endocrine-Disrupting Compound (Brody, 2003)	Use	Regulated by
Chlordane	●	IARC Probable	●	Pesticide (ticks and mites): veterinary pharmaceutical, air pollutant; has been banned, but persists in meat and fish; found in household dust	EPA, USDA, FDA
Dieldrin/Aldrin/Endrin (-drin pesticides) (page 47)			●	Pesticide: insecticide used on corn and cotton from 1950s to 1970s; banned in 1987; persists in environment	EPA, USDA, FDA
Heptachlor (page 47)		IARC Possible	●	Pesticide: used for termite control through 1980s; agricultural use continued until 1993 (especially on pineapple)	EPA, USDA, FDA
Malathion			●	Pesticide: insecticide	EPA, USDA, FDA
Methyl bromide			●	Pesticide: insecticide and soil sterilant	EPA, USDA, FDA
Phthalates (page 43)			●	Food packaging: some plastic containers	FDA
rBST (page 57)			●	Veterinary pharmaceutical: injected into cows to increase milk production	FDA
Zeranol (page 56)			●	Veterinary pharmaceutical: implants into cattle to increase body weight	FDA, USDA

FROM SCIENCE TO ACTION

B. Vulnerable Populations

Workers in and communities located near plastics manufacturing facilities are at higher risk for exposures to high levels of styrene and vinyl chloride. In addition, communities near waste facilities may be disproportionately exposed to dioxins and materials released from the disintegration of plastics.

The use of plastic products that can leach endocrine-disrupting chemicals is particularly concerning at stages of rapid development, including during pregnancy, in infancy and before and during puberty. Plastics in products intended for use by infants (baby bottles, teething rings, toys) may convey particular risk, especially considering the additive and mixture effects from carcinogens (vinyl chloride) and multiple endocrine-disrupting compounds (BPA and phthalates).

Now that some retailers and manufacturers have removed BPA from plastics as a result of consumer and public health concerns, products made with safer plastics or with stable materials like stainless steel and glass have emerged as alternatives to BPA-based products. However, these products may not be as widely available in low-income or rural communities. In addition, individuals who rely on secondhand items may experience disproportionate exposure to BPA and phthalates.

C. Current Regulation

The EPA regulates the constituent chemicals used in plastics, along with waste and pollution management from plastics production. The EPA measures and manages the release into the environment of chemicals (including components of plastic)

required for manufacturing plastics. In addition to the components of the plastics — such as monomers like styrene and vinyl chloride, additives such as BPA and plasticizers such as phthalates — other chemicals are used in the manufacturing process (EPA, 2005a). These include potentially toxic solvents, catalysts, heat stabilizers and other compounds. The EPA regulates the release of plastic components and chemicals used in manufacturing based on the Clean Air and Clean Water Acts, and industrial pollutants are monitored via the Toxic Release Inventory. However, consumer-based exposures to plastic are regulated by other agencies, depending upon the end use of the product made from plastic.

Food packaging and plastic bottles (baby bottles, bottled water bottles and sports bottles)

The FDA maintains a list of more than 3,000 chemicals and other substances that are approved for use in food packaging and reusable food containers. These are considered “indirect food additives” because they migrate from the packaging or container into food. More than two-thirds of them were approved under a petition-and-review process established in 1958, including known or suspected reproductive toxins and carcinogens like BPA and formaldehyde. The rest have been approved since 2000, when the FDA began the FCN, which requires industry to notify the agency of a proposed use of a new chemical (or a new use of a previously approved chemical) and wait 120 days before marketing it. BPA, some phthalates, styrene (and a number of styrene-based polymers) and various derivatives of polyvinyl chloride are approved for food contact (FDA, 2007).

Recent and growing awareness of the health concerns of BPA has led to legislation to prohibit the chemical’s use, especially in children’s products. In February 2010, Denmark became the first country to adopt legislation banning BPA from infant-food packaging materials. Canada declared BPA a toxic substance and announced in April 2008 that it would ban BPA in baby bottles and restrict its use in infant-formula cans. As of July 2010, seven U.S. states and four localities have banned BPA from baby bottles and sippy cups. Connecticut’s and Vermont’s laws also include in the ban infant-formula, baby-food and reusable storage containers, and Washington’s law includes sports bottles.

Toys

In 2005, the European Union banned six phthalates — DEHP, DBP and BBP — in all toys and child care articles, and banned DINP, DIDP and DNOP in toys and child care articles that can be mouthed. The United States followed the EU’s lead in August 2008, banning DEHP, DBP and BBP in toys intended for children under age 3 and adopting a precautionary ban on DINP, DIDP and DNOP in toys and child care articles that could be mouthed, pending further study by a government-commissioned Chronic Hazard Advisory Panel (CHAP). The CHAP committee is required to look at all potential health effects of phthalates, including endocrine disruption, and to consider cumulative exposures from all sources (such as plastics, personal care products and food-contact items) for children and pregnant women (CPSC, 2009).

Plastics: Tips for Reducing Exposure to Chemicals of Concern



Know your plastics

What's behind the recycling codes on plastic? Learn which numbers are associated with breast cancer risk (see Table).

Choose BPA-free containers for food and beverages

Carry a reusable water bottle made from BPA-free materials (stainless steel and glass are the

safest options). Choose BPA-free baby bottles and plastic cups.

Avoid microwaving in plastic

Instead, transfer foods to glass or ceramic containers.

Choose PVC-free household items

Replace shower curtains made of PVC plastic (which can contain hormone-disrupting phthalates) with fabric shower curtains when it's time for a new one. Look for washable curtains and liners that will last for many years.

Toss old, soft plastic toys

Some soft plastic toys made before a ban that took effect in February 2009 contain harmful phthalates.

Prior to the EU's permanent ban, the following countries had also banned phthalates in toys: Argentina, Austria, Cyprus, Czech Republic, Denmark, Fiji, Finland, Germany, Greece, Italy, Japan, Mexico, Norway and Sweden.

In 2007, California became the first state in the nation to ban phthalates from children's products. Washington followed suit in 2008. In June 2009, Canada replaced a decade-old voluntary ban on phthalates in toys with new regulations requiring companies to get phthalates out of soft vinyl toys.

D. Policy Recommendations

Policies are needed that would limit the use of chemicals linked to endocrine disruption and cancer in plastics used for toys, food

packaging and other consumer products. In addition, research programs both to screen chemicals for endocrine-disrupting effects and to better understand the health effects of endocrine disruptors should be fully funded and implemented in a timely manner.

- Federal legislation is needed that would ban the use of BPA and phthalates in food packaging, food and beverage containers, and toys.
- The Toxic Substances Control Act (TSCA) should be reformed to address cumulative exposures to chemicals from different sources, including chemicals controlled by agencies other than the EPA, such as food-contact substances regulated by the FDA and consumer products regulated by the CPSC.

- The EPA should fully implement the Endocrine Disruptor Screening Program, as mandated by Congress, designed to effectively and efficiently screen chemicals for hormonal activity and to make the results readily available to the public without delay.
- More federal funding is needed for human studies on the relationship between exposure to endocrine-disrupting chemicals — like BPA and phthalates — and breast cancer.
- Federal funding is needed to support research into green chemistry alternatives to petroleum-based plastics.
- Federal tax incentives are needed to stimulate investments in the production of bio-based plastics.

Table 3: What Is the Connection Between Plastic and Breast Cancer?

Plastic Recycling Code and Name	Breast Cancer Fund Rating	Carcinogen from Manufacturing (IARC, 2009; NTP, 2005)	Endocrine-Disrupting Compound Leaches from Plastic (Brody, 2003)	How It is Used
#1 PET or PETE Polyethylene terephthalate ethylene	OK			Single-use soft drink, juice, water containers; detergent and cleaning products
#2 HDPE High-density polyethylene	OK			Opaque plastic milk and water jugs; bleach, detergent and shampoo bottles; some plastic bags
#3 PVC Polyvinyl chloride (page 59)	Avoid	●	●	Cling wrap, some plastic squeeze bottles; cooking-oil, detergent, 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			Food storage containers; syrup and yogurt containers; straws; increasingly used in baby bottles, sippy cups and reusable water bottles
#6 PS Polystyrene	Avoid	●		Styrofoam food trays, egg cartons, disposable cups and bowls, carry-out containers, opaque plastic cutlery
#7 Other, Polycarbonate (page 42)	Avoid		●	Large water jugs for dispensers; some baby bottles, reusable water bottles and sippy cups
#7 Other, Non-polycarbonate	OK			Includes bio-plastics such as those used in to-go cups for cold beverages; also Tritan copolyester, used in reusable water bottles

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.

E. Agencies Responsible for Regulation

- CPSC, Chemical Hazards Program. Regulates plastic toys and children's dishes.
- FDA, Office of Food Additive Safety. Regulates baby bottles through a memorandum of understanding signed with the CPSC in 1976 (FDA, 1976).
- EPA, Office of Chemical Safety and Pollution Prevention. Registers individual monomers that make up polystyrene, polycarbonate and polyvinylchloride plastics.

IV. Cosmetics

A. Exposures of Concern

A number of ingredients used in cosmetics and personal care products have been shown in animal studies to disrupt hormonal systems, contribute to early puberty and lead to altered breast development. Chemicals identified as carcinogens, mutagens or reproductive toxicants are prohibited as ingredients of cosmetics sold in the European Union (EC, 2008), but many of these same ingredients are still used in products sold in the United States. While exposures to an individual chemical in a single personal care product may not cause harm, the average American woman uses 12 personal care products a day, resulting in exposure to 126 unique chemicals (EWG, 2004), a cause for concern about low-dose exposures and exposures to mixtures of chemicals. In addition, childhood exposures and repeat exposures experienced by workers in manufacturing plants and nail and beauty salons must be taken into account.

Cosmetics and personal care products are, by design, meant to come in direct contact with

the body, and a large proportion of what is applied to the skin is absorbed by the body (Bronaugh, 1994; Schettler, 2006; Janjua, 2008). Moreover, cosmetics are only one of many sources of daily toxic exposures. The combined exposure from personal care products adds to an individual's chemical contamination from other consumer products as well as food, water, air and soil. In biomonitoring studies, more than 200 chemicals have been detected in people's body fluids, including breast milk and the cord blood of newborns (CDC, 2009; EWG, 2005; EWG, 2009).

Specific chemicals of concern in cosmetics include phthalates, parabens, alkylphenols, synthetic musks and common sunscreen chemicals. "Emerging chemicals of concern" are also noted in Table 4.

"Fragrance" is of particular concern, as it can contain dozens of constituent chemicals. Because fragrance formulations are considered confidential business information, under current law they are exempted from labeling requirements, so consumers do not know and cannot find out the individual ingredients.

We know from product testing that some of the chemicals in fragrance, such as synthetic musks, phthalates and ethylene oxide, are known endocrine-disrupting compounds or carcinogens. Endocrine-disrupting phthalates are readily absorbed through the skin (Janjua, 2008) and can also enter the body through ingestion and inhalation (Schettler, 2006).

Ethoxylated compounds such as dimethicone, PEG-40, cetareth-12 and other compounds with the syllables "eth" or "PEG" in them constitute another chemical

family of concern, because these compounds can be contaminated with 1,4-dioxane, a mammary carcinogen (Rudel, 2007). In addition, placental extracts, which contain hormones, have long been used in hair care products with marketing aimed toward women of color.

Several chemicals widely used in sunscreens have been shown to enhance the growth of breast tumor cells. Five common sunscreen chemicals — 3-(4-methylbenzylidene)-camphor (4-MBC), octyl-methoxycinnamate (OMC), octyl-dimethyl-PABA (OD-PABA), bexophenone-3 (Bp-3) and homosalate (HMS) — mimic estrogen (Schlumpf, 2001). Like other chemicals applied directly to the skin, they are readily absorbed into the body.

B. Vulnerable Populations

Exposure to cosmetics ingredients linked to adverse health effects is of particular concern during phases of rapid development, including pregnancy, infancy and before and during puberty.

Products marketed to women of color often contain some of the most problematic chemicals. Skin lighteners, hair relaxers, hair dyes and skin moisturizers developed for women of color often contain carcinogens and endocrine-disrupting compounds such as placental extract (hair and skin products), hydroquinone (skin lighteners), and petroleum byproducts.

Professionals in the beauty industry who work with products on a daily basis have particularly high exposures. These professionals come into daily contact with unsafe chemicals used in nail

care products and hair colorings, relaxers and permanents. Workers in manufacturing plants that make chemicals used in cosmetics may also experience higher levels of exposure to carcinogenic and endocrine-disrupting chemicals.

C. Current Regulation

The Food, Drug and Cosmetic Act (FDCA) of 1938 gave the Food and Drug Administration limited authority to ensure the safety of cosmetic products. The FDA has no power to require premarket testing of cosmetics ingredients. In fact, more than 89 percent of ingredients used in cosmetics have never been tested for safety (FDA, 2010a). The FDA has banned or restricted only 10 chemicals from cosmetics (FDA, 2000), whereas 1,100 chemicals are banned from cosmetics by the European Union. The FDA can take regulatory action only if a cosmetic is considered to be adulterated or misbranded.

The FDCA defines cosmetics as products that are “intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body ... for cleansing, beautifying, promoting attractiveness, or altering the appearance.” This includes deodorants, toothpastes, hair colors, permanent waves, shampoos, eye and facial makeup items, fingernail polishes, lipsticks, perfumes and moisturizers.

Some personal care products are defined by the FDA as over-the-counter drugs, including sunscreens and other products that are “intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease ... and intended to affect the structure or any function of the body of man or other animals.” A relatively new subset of personal care products, termed “cosmeceuticals” by the industry, have some characteristics of drug products; in most cases, the FDA treats these as cosmetics.

Cosmetics labeling is overseen by the FDCA Code of Federal Regulations and the Fair Packaging and Labeling Act. Packaging must include the manufacturer, packer, and distributor; material facts such as information regarding safe use and product function; warning and caution statements; and ingredients, excluding those contained in fragrance (FDA, 2010a).

In the absence of effective government oversight, the industry-run Cosmetic Ingredient Review (CIR) Expert Panel, composed largely of dermatologists and other medical experts, conducts safety assessments of ingredients, publishing the results both on its Web site and in the *International Journal of Toxicology*. In more than 30 years, only 11 percent of ingredients in personal care products have been reviewed by the CIR, with only nine determined to be unsafe. Levels of risk are deemed

to be acceptable entirely at the panel’s discretion, with no public accountability or governmental input. Furthermore, the panel has never determined the effects of cumulative lifetime exposure or multiple chemical exposures to cosmetics ingredients.

In 1973 and 1988, unsuccessful attempts were made to amend the law; both were strongly opposed by the cosmetics industry and ultimately defeated. In July 2010, the Safe Cosmetics Act, a far more ambitious effort to reform current law and ensure the safety of personal care products, was introduced in Congress.

At the state level, the 2005 California Safe Cosmetics Act requires all cosmetics manufacturers, packers, and distributors to provide the California Department of Public Health a list of ingredients that are either suspected or known to cause reproductive harm, birth defects or cancer. This information is being compiled in a database and will be made publicly available online (CDPH, 2010).

D. Policy Recommendations

Congress should enact the Safe Cosmetics Act of 2010, introduced by Reps. Jan Schakowsky, Ed Markey and Tammy Baldwin, which will:

- Phase out ingredients linked to cancer, birth defects and developmental harm.
- Create a health-based safety standard that includes protections for children, the elderly, workers and other vulnerable populations.
- Close labeling loopholes by requiring full ingredient disclosure on product labels and company Web sites, including the

While exposures to an individual chemical in a single personal care product may not cause harm, the average American woman uses 12 personal care products a day, resulting in exposure to 126 unique chemicals.

Cosmetics: Tips for Reducing Exposure to Chemicals of Concern



Use fewer products with simpler ingredients

The best way to avoid chemicals in personal care products is to use fewer and simpler products.

Avoid “fragrance”

Fragrance can contain dozens of undisclosed chemicals — including endocrine-disrupting compounds.

Beware of organic and natural claims

Read labels for specific information on a product’s ingredients rather than relying on claims like “organic” or “natural.” A USDA-certified organic seal means that the product contains 95 percent or more organic ingredients.

Read the label to avoid synthetic ingredients

Avoid products with DMDM hydantoin and midazolidinyl urea; parabens; “PEG” and words containing “-eth,” such as cetareth-20; triclosan and triclocarban; triethanolamine (TEA); hydroquinone and oxybenzone.

Products to avoid:

- Anti-aging creams with lactic, glycolic, AHA and BHA acids
- Hair dyes, especially dark permanent dyes
- Liquid hand soaps with triclosan/triclocarban
- Nail polish and removers with formaldehyde, DBP or toluene
- Skin lighteners with hydroquinone

constituent ingredients of fragrance and salon products.

- Give workers access to information about unsafe chemicals in personal care products and cosmetics.
- Require data sharing to avoid duplicative testing and encourage the development of alternatives to animal testing.
- Provide adequate funding to the FDA Office of Cosmetics and Colors so it can provide effective oversight of the cosmetics industry.
- Level the playing field so that small businesses can compete fairly.

E. Agencies Responsible for Regulation

- FDA, Office of Cosmetics and Colors. Addresses cosmetics in general as well as over-the-counter cosmetics that make medical claims, including sunscreens (FDA, 2000).
- Several classes of personal care products fall under the jurisdiction of multiple FDA offices, or both the FDA and other agencies. These include (1) sunscreens, which are regulated by the FDA as both

cosmetics and drugs; (2) any personal care products containing bug repellents, which are also regulated by the EPA Office of Pesticide Programs; and (3) certified-organic products, which are also regulated by the USDA. These products have multiple and uncoordinated formulary and labeling requirements, and there is no clear guidance on which to follow in these cases of joint regulation.

Table 4: What Is the Connection Between Cosmetics and Breast Cancer?

Chemical	Mammary Carcinogen (Rudel, 2007)	Carcinogenic (IARC, 2009; NTP, 2005)	Endocrine-Disrupting Compound (Brody, 2003)	Use
1,3-butadiene (page 59)	●	IARC Probable; NTP Known		May be a contaminant in isobutane, found in shaving creams, hair mousse, hair styling gels and some high-SPF sunscreens
1,4-dioxane	●	IARC Possible; NTP Reasonably Anticipated		May be a contaminant in products containing ethoxylated compounds
Benzene (page 57)	●	IARC Known; NTP Known		Seen in 92 products, as an impurity of toluene, which is found in some nail polish
Bisphenol A (page 42)		IARC Possible; NTP Reasonably Anticipated	●	Cosmetics containers/ packaging
Ethoxylated compounds (commonly contaminated with 1,4-dioxane)	● if 1,4-dioxane-contaminated			Common in shampoos, body wash, children's bath products and other sudsing products
Ethylene oxide (page 59)	●	IARC Known; NTP Known		Found in fragrance
Fragrance	●	varies	●	Often listed as a single ingredient, but may contain carcinogens and endocrine-disrupting compounds, such as ethylene oxide, musks and phthalates
Metals (page 54)		IARC Known; NTP Known	●	Metals such as cadmium and lead may be present in lipsticks and face paints, and mercury is in some mascaras
Musks, synthetic (xylene, ketone, ambrette, moskene, tibetine)			●	Fragrance

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Table 4: What Is the Connection Between Cosmetics and Breast Cancer?

Chemical	Mammary Carcinogen (Rudel, 2007)	Carcinogenic (IARC, 2009; NTP, 2005)	Endocrine-Disrupting Compound (Brody, 2003)	Use
N-nitrosamines		IARC Possible; NTP Reasonably Anticipated		A contaminant that may be present in products containing proteins such as diethanolamine (DEA) or triethanolamine (TEA) in combination with preservatives that can break down into nitrates
Nonylphenol (page 45)			●	Lotions and a wide range of other products
Parabens (page 44)			●	Common antifungal agent, preservative and antimicrobial used in creams, lotions, ointments and other products
Petrolatum (commonly contaminated with PAHs, polycyclic aromatic hydrocarbons) (page 45)	●	IARC Possible; NTP Reasonably Anticipated	●	Common ingredient in petroleum jelly, lipsticks, baby lotions and oils
Phthalates (page 43)			●	Nail polish, fragrance, cosmetics containers/ packaging
Placental extracts	●	NPT Reasonably Anticipated	●	Hair conditioners, shampoos and other grooming aids, particularly those marketed to women of color
Titanium dioxide		IARC Known; NTP Known	●	Sunscreens and mineral makeup. Nanoparticles of titanium dioxide are of particular concern
Triclosan			●	Antibacterial used in soaps, toothpaste, mouthwash and other personal care products
Urethane	●	IARC Possible; NTP Reasonably Anticipated		Hair care products (mousses, gels, sprays), sunscreens, nail polish, mascara, foundation

V. Household Products

A. Exposures of Concern

The word “home” connotes a sense of warmth and safety, but unfortunately our homes are also sources of exposure to endocrine-disrupting and carcinogenic chemicals. We must revise policies that regulate an array of chemicals found in the household, from ingredients of cleaners to the chemicals used to make furniture less flammable.

Chemicals in household products and from outside sources end up in indoor air and dust. One in-depth study tested for 89 hormonally active agents and mammary carcinogens in samples of indoor air and household dust from 120 homes. It found 52 different compounds in air and 66 in dust, including phthalates, parabens, alkylphenols, flame retardants, PAHs, PCBs and BPA, in addition to banned and currently used pesticides (Rudel, 2003).

Biomonitoring studies show that chemicals from household products are also invading our bodies: They have been found in blood, urine (CDC, 2009), breast milk (Allmyr, 2006) and newborns’ umbilical cord blood (Peters, 2005).

Household cleaning products

Those products meant to make our houses clean can also include chemicals linked to health concerns. For instance, the word “fragrance” on a product label can conceal dozens of chemicals, some of which have been linked to cancer, birth defects and other adverse health effects. The International Fragrance Association (IFRA) lists more than 3,000 fragrance ingredients, some of them carcinogens such as benzene (and dozens of benzene derivatives),

formaldehyde and styrene, in addition to chemicals that can cause reproductive harm such as phthalates and synthetic musks (IFRA, 2009). In addition, many of the chemicals used in fragrances are linked to asthma in house-cleaning workers (Medina-Ramon, 2005).

Another common group of endocrine-disrupting chemicals in cleaning products is alkylphenols, which are used in detergents. In the study of household dust described above, alkylphenols were found in 80 percent of homes (Rudel, 2003). Solvents such as trichloroethylene found in household cleaning products have been shown to cause mammary tumors in animals (Labreche, 1997).

Household pesticides

A number of household pesticides are potentially carcinogenic, hormone-disrupting or both (PAN, 2000-2010). Some of the most common household pesticide chemicals, including 2,4-Dichlorophenoxyacetic acid (2,4-D), malathion and permethrin, are endocrine disruptors and possible carcinogens (PAN, 2000-2010). While the active ingredients in pesticides must adhere to strict labeling and use guidelines (EPA, 2010a), inert ingredients do not have to be listed on the labels. This includes any ingredients that are not considered pesticides, regardless of the safety of those ingredients. A number of inert ingredients are of considerable concern because of carcinogenic or endocrine-disrupting properties. These include dioctyl phthalate, formaldehyde, hydroquinone and several phenols (NPIC, 2010).

Furniture and electronics

Certain flame retardants found in furniture and electronics also have endocrine-disrupting characteristics. Like many other endocrine-disrupting chemicals, those in the family of polybrominated diphenyl ether (PBDE) flame retardants have been shown to cause a host of reproductive and neurological disorders, cancer and birth defects. PBDEs are commonly used in furniture foam. Because these compounds are not chemically bound to the foam, they escape into the indoor environment and are found in household dust.

B. Vulnerable Populations

All members of the household are exposed to the adverse health effects associated with chemicals found in household products and household dust. Pregnant women, their developing fetuses and young children are most vulnerable to the effects of chemicals that disrupt the endocrine system at these critical stages of development. In addition, young children may have higher exposures to household dust and chemicals on furniture and in carpeting, since they spend more time on floors and carpets and tend to place items in their mouths. Children are also at much greater risk from accidental poisoning associated with household chemicals. Even the Soap and Detergent Association (SDA) recommends that cleaning take place when children are at school or playing outside (SDA, 2007).

Industrial cleaners can be just as toxic as household cleaners or even more so. These types of cleaners are used in places where vulnerable populations are highly exposed, including hospitals, schools and



elder-care facilities. Americans spend about a third of their lives in workplace settings, and just as they are exposed to dangerous chemicals from their household products, they are exposed to many of the same chemicals in their workplaces. Children are exposed to toxic ingredients in cleaning products used in schools and day-care facilities.

People in certain occupations are especially vulnerable to the effects of toxic cleaning products. Women make up nearly two-thirds of the janitorial and building-cleaner workforce and account for 9 out of 10 maids and housekeepers. More than half of them are either Latina or African American (BOLS, 2005).

Housekeepers and custodians are heavily exposed to cleaning chemicals and are often not given any information about health effects or safety precautions. Little exposure assessment has been done in these occupations, but one study found that each year 6 out of 100 janitors experience acute injuries from chemicals used on

the job (JPPPP, 2002). Many of the same chemicals linked to these injuries, which include incidents of chemical burns and inhalation injuries, are also linked to longer-term health concerns. Nevertheless, even fewer labeling requirements exist for institutional products like industrial cleaners and professional hair products than for consumer products, putting workers at greater risk.

C. Current regulation

Household cleaning products

Current law does not require manufacturers to disclose the ingredients in cleaning products to consumers, unless those products contain substances specifically determined to be hazardous, and likely to cause substantial injury or illness. While some companies are beginning to disclose cleaning product ingredients, many chemicals remain hidden, particularly those found in fragrances.

Similarly, workers in institutions like hospitals and schools that serve vulnerable populations are often denied access to ingredient

information from manufacturers. Sometimes even physicians treating patients who have suffered adverse reactions from exposure to cleaning products cannot get access to ingredient lists.

This lack of disclosure isn't unique to consumers and workers. Product manufacturers who buy chemicals for use in their products are also denied information by suppliers, who claim that the ingredients are a trade secret. In addition, manufacturers who buy fragrances from third-party vendors typically are denied ingredient information and often spend years and thousands of hours negotiating with fragrance houses to obtain ingredient lists and safety information about those ingredients.

Industrial cleaning products

Industrial cleaners have stricter labeling requirements than household cleaners, but they also tend to contain harsher chemicals. These products must include the name and percentage of each active ingredient in the product. Inactive ingredients, which can still include chemicals of concern, do not need to be labeled. Agents used as disinfectants are regulated as pesticides by the EPA and must adhere to EPA pesticide labeling requirements.

Household pesticides

Household pesticides are regulated by the EPA as part of the EPA Office of Pesticide Programs under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). New pesticides must be registered with the EPA prior to sale or distribution. Companies registering a chemical as a pesticide must provide data that illustrates the efficacy of the product as well as data to assess hazards

to humans and domestic animals (EPA 2008c). Pesticide chemicals must be submitted for Registration Eligibility Decisions (RED). RED assessments include acute toxicity studies, and — as available — tests on carcinogenicity and reproductive toxicology. As part of the Endocrine Disruptor Screening Program (EDSP), the EPA is required to assess pesticides' active ingredients for endocrine-disrupting effects (EPA, 2010b).

Current law allows inactive ingredients linked to cancer — including formaldehyde, BPA, toluene and benzene — to be unlabeled in household pesticides. At present, only the active ingredients in household pesticides have to be disclosed on product labels. Other ingredients, referred to as “inert” ingredients, do not have to be disclosed. The EPA is considering requiring disclosure of inert ingredients on pesticide labels (EPA, 2009).

Furniture and flame retardants

There are no federal regulations related to the use of polybrominated diphenyl ethers (PBDEs), compounds used as flame retardants. However, there are federal and state flammability standards. Because flame retardants are not regulated at the federal level, some states have enacted legislation to more strictly regulate these toxic and persistent chemicals.

In 1972, California adopted Technical Bulletin 117 (TB 117), which states that the foam or filling in residential furniture sold in the state must be flame retardant. The test that TB 117 establishes for all residential furniture in the state is called an open-flame test, and it requires foam or filling to be

Current law allows inactive ingredients linked to cancer — including formaldehyde, BPA, toluene and benzene — to be unlabeled in household pesticides. At present, only the active ingredients in household pesticides have to be disclosed on product labels.

resistant to an open flame for 12 seconds. TB 117 does not require the fabric of furniture to be resistant to fire.

In contrast, most states have adopted federal fire retardancy standards that require “smolder” tests for the fabric. A smolder test is more realistic, because it applies to the fabric of the furniture itself and simulates real-world conditions of a lit cigarette being left on fabric. The European Union banned the use of two PBDEs in 2004 and in 2006; research has found that the bans resulted in reduction in human exposure levels. Many companies in Europe and the United States have voluntarily switched to alternatives to PBDEs (HCHW, 2010).

D. Policy Recommendations

Household cleaning products

Policy-makers should support the Household Product Labeling Act (S. 1697), introduced by Sen. Al Franken (D-Minn.) and Rep. Steve Israel (D-N.Y.), which would force full disclosure of ingredients in household cleaning products. This legislation mandates the reporting of all ingredients on product labels, and covers air fresheners and deodorizers; floor and furniture polish; dishwashing soap; drain cleaners; laundry detergent and dryer sheets; epoxies; and paints and stains. It also requires the CPSC to prescribe a standardized list of ingredients that are known to be

included in these products to assure uniform naming and labeling. The bill would take effect 18 months after enactment. The House companion bill, H.R. 3057, would mandate labeling of all ingredients in household cleaning products or similar products.

The Senate legislation covers only cleaning products intended for household use and should be amended to include industrial cleaners, which are often just as toxic as household cleaners or more so. Further, it should be amended to clarify that the law also requires full disclosure of the ingredients in household cleaning products and industrial cleaning products, including fragrance, dyes and preservatives.

A “savings clause” should be provided that will allow states to pass and enforce disclosure laws that are stricter than federal standards.

Additional policies are needed that would support research into the occupational health effects of cleaning products and green-chemistry research for safer alternatives.

- Research is needed to develop and evaluate safe alternatives to toxic chemicals in cleaning products.
- Occupational research should look at workers regularly exposed to cleaning product chemicals and the possible links to breast cancer.

Household Products: Tips for Reducing Exposure to Chemicals of Concern



Use pesticide-free approaches to pest control

Instead of using chemical pesticides, place pantry foods in glass containers, sweep crumbs often, and try nontoxic alternatives.

Avoid chemical herbicides

Weed by hand or mow frequently to minimize weeds or make them hard to spot among your lawn grass. Vinegar, salt, soapy water or rubbing alcohol may help control weeds in limited spots.

Toss (or cover) crumbling furniture

Older furniture with foam stuffing, cushions or mattresses could contain harmful flame-retardants called PBDEs, and if the foam is falling apart, the PBDEs are more likely to be released into the environment.

Use simple, nontoxic cleaning products

Seek out nontoxic cleaning products or make your own. A little baking soda and vinegar go a long way toward everyday household cleaning and even larger jobs.

Avoid chlorine bleach and bleached products

Use nonchlorine alternatives to bleach for household cleaning and laundry. And since paper products are often bleached to make them whiter, choose toilet paper, tissue and office paper labeled “Processed Chlorine Free” (PCF). Look for unbleached coffee filters and organic, unbleached tampons as well.

- Use of biomarkers of exposure and early disease should be explored as soon as possible to shorten the length of studies and allow for occupational health interventions.

Household pesticides

Policies should be established to limit the use of nonessential pesticides and to use nontoxic pest management alternatives.

- Legislation should ban nonessential uses of pesticides by consumers, businesses, hospitals and schools. Federal legislation should restrict the use of pesticides on or near school grounds, including day-care centers and

nurseries. In particular, policy-makers should support the School Environment Protection Act of 2009 (H.R. 4159), introduced by Rep. Rush Holt (D-N.J.).

- Federal legislation should restrict 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 and herbicides, where the weed or pest poses no danger to human health, the environment or property. Cities including San Francisco and Oakland have instituted bans on the use of pesticides in parks.

Flame retardants

Legislation and agency policies should address harmful chemicals used as flame retardants. Research and testing of safer alternatives are needed.

- The Decabromine Elimination and Control Act of 2009 (H.R. 4394), introduced by Rep. Chellie Pingree (D-Maine), would phase out the chemical Decabromodiphenyl ether, commonly used as a flame retardant, by 2013 and require companies to use safer alternatives. Shortly after Rep. Pingree introduced HR 4394, the chemical industry announced it would enter into a voluntary agreement with the EPA to stop producing DecaBDE within three years. Legislation is needed to

ensure companies follow through with the voluntary phase-out.

- Congress should adopt a national ban on all PBDEs and include clauses that require PBDEs to be replaced by alternatives that have been adequately tested for safety.
- State and local governments and other large purchasers of products should adopt procurement policies that require purchase of PBDE-free products and disclosure of chemical flame retardants in products.

Toxic Substance Control Act reform

TSCA reform should address cumulative exposures to carcinogenic and endocrine-disrupting compounds in the home,

including the health impacts of mixtures of pesticides, chemicals in household cleaning products, and chemicals in other household products, such as flame retardants in furniture and nonstick coatings in cookware. Since these different exposures are regulated by several agencies, federal interagency coordination will be required to address the cumulative effects of mixtures of endocrine-disrupting compounds in the home.

E. Agencies Responsible for Regulation

- CPSC, Federal Hazardous Substances Act. Sets requirements for household cleaners.

- EPA, Office of Pesticide Programs. Registers disinfectant chemicals.
- EPA, Office of Chemical Safety and Pollution Prevention (OCSPP). Registers flame retardants.
- EPA, Office of Pesticide Programs. Registers home use pesticides as part of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA).
- Occupational Safety and Health Administration (OSHA). Sets limits for chemical exposures to industrial cleaners.

Table 5: What Is the Connection Between Household Products and Breast Cancer?

Chemicals Found in Household Products	Human Health Concern			Use
	Carcinogen (IARC, 2009; NTP, 2005; EPA, 2005)	Reproductive Toxin (PAN, 2000-2010)	Endocrine-Disrupting Compound (Rudel, 2003; PAN, 2000-2010)	
2,4-D	IARC Possible		⊙	Household pesticide, weed control
Alkylphenol ethoxylates (page 44)			⊙	Detergents, stain removers, cleaning products
Carbaryl	EPA Likely		⊙	Household pesticide: insecticide
Diazinon			⊙	Former residential use pesticide; phased out of home use from 2000 to 2004
Dibutyl phthalate (page 18)			⊙	Floor finish, floor shine and hardener
Dichlorvos	IARC Possible; EPA Suggestive Evidence		⊙	Household pesticides: insecticides. Previously used widely, now home use is limited to pet collars and pest strips

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Chemicals Found in Household Products	Human Health Concern			Use
	Carcinogen (IARC, 2009; NTP, 2005; EPA, 2005)	Reproductive Toxin (PAN, 2000-2010)	Endocrine-Disrupting Compound (Rudel, 2003; PAN, 2000-2010)	
Ethylene glycol monobutyl ether (EGBE) or 2-butoxyethanol		○		Household cleaners, including glass cleaners, carpet/rug cleaners, floor cleaners, oven cleaners
Formaldehyde	IARC Known; NTP Reasonably Anticipated			Glues, sealants, insulation, pet shampoos; inert ingredient in pesticides
Hydramethylnon	EPA Possible	○		Residential and municipal use pesticide: insecticide
Malathion	EPA Suggestive Evidence		○	Residential pesticide: insecticide
Methylene chloride (dichloromethane)	Mammary; IARC Possible; NTP Reasonably Anticipated			Auto products, adhesive and paint removers, herbicides
Nitrilotriacetic acid	IARC Possible; NTP Reasonably Anticipated:			Carpet-care products
Nonylphenol ethoxylate			○	Cleaners, degreasers, foaming cleaners, air freshener, spot and stain treatment, metal polish
Octylphenol ethoxylate			○	Cleaners, degreasers, surface deodorizers
Perfluorocarbons (PFCs) and perfluorooctanoic acid	Mammary; EPA Suggestive Evidence		○	Nonstick coatings on cookware, stain guard on furniture, carpets, clothing
Permethrin	EPA Suggestive Evidence		○	Residential pesticide: insecticide
Phthalates (page 43)			○	Pastes/adhesives, clear enamels, fragrance in cleaning products, air fresheners; inert ingredients in household pesticides

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Table 5: What Is the Connection Between Household Products and Breast Cancer?

Chemicals Found in Household Products	Human Health Concern			Use
	Carcinogen (IARC, 2009; NTP, 2005; EPA, 2005)	Reproductive Toxin (PAN, 2000-2010)	Endocrine-Disrupting Compound (Rudel, 2003; PAN, 2000-2010)	
Polyvinyl chloride (page 59)	IARC Known; NTP Known			Household maintenance cements
Pyrethrins & pyrethroids	EPA Suggestive Evidence			Pesticide: insecticide; pyrethrins are derivatives of chrysanthemum; pyrethroids are synthesized pyrethrins
Resmethrin	EPA Likely	●	●	Residential pesticide: insecticide
Styrene	IARC Possible; NTP Reasonably Anticipated		●	Household paints, adhesives, inkjet printer ink
Tetrachloroethylene	IARC Probable; NTP Reasonably Anticipated			Spray polish, spot remover
Toluene (page 58)	Mammary; NTP Reasonably Anticipated	●		Inert ingredient in pesticides
Trichlorethylene	NTP Reasonably Anticipated			Auto care, sealants

Adapted from: (WSPPN, 1999); (PAN, 2000-2010); (WVE, 2007); (NPIC, 2010)

VI. Health Care

A. Exposures of Concern

Health care screenings, treatments, and medical and dental devices aim to keep people healthy and to catch and treat disease early. However, some detection methods and treatments can expose patients to unsafe chemicals and radiation that may actually increase the risk of breast cancer.

Hormone therapies

Long-term use of estrogen-based hormone therapies, including hormone replacement therapy (HRT) and oral contraceptives, can increase lifetime exposure to estrogen, a risk factor for breast cancer. HRTs that include combinations of estrogen and progestin appear to be linked to the greatest increased risk. Risk of breast cancer from oral contraceptive use appears to be highest among current users

and individuals who use oral contraceptives for a decade or longer.

Medical radiation

Increases in breast cancer risk are associated with exposure to ionizing radiation used for radiation therapy, as well as medical and dental screening, including X-rays, mammography, fluoroscopy and CT scans. Combinations of exposures to radiation and to certain synthetic chemicals, including estrogens, can

magnify the effect of radiation. In addition, the deleterious effects of radiation are cumulative over the life span.

Chemicals in medical devices and dental materials

Many medical devices, including IV tubing and bags, catheters and other materials, are made from polyvinyl chloride (PVC) plastics, and many of these are softened with phthalates. Vinyl chloride, the constituent molecule of PVC, is a known human carcinogen and can be released during PVC production. The incineration of PVC can form dioxins, which are known carcinogens and endocrine disruptors. A number of alternatives exist for PVC-based medical devices (HCWH, 2002a).

Similarly, a number of devices and materials also contain BPA, including dialysis and cardiopulmonary bypass machines, some cardiac stents and other implantable devices, and dental composite fillings and dental sealants (AdvaMed, 2009).

Hospital disinfectants

Cleanliness in hospitals is vital to the prevention of health care–associated infections (HAIs) and of infection in traumatic and surgical wounds. The recognition of pathogens, and the resulting hygiene practices both in municipal waste management and in hospitals,

have greatly reduced the burden of pathogen-based diseases, the spread of communicable diseases in hospitals, and death from childbirth, surgery and other procedures. However, a number of antimicrobial cleaners and sterilization chemicals can have longer-term negative health and environmental impacts. Of particular concern is ethylene oxide disinfection of surgical instruments. Ethylene oxide is a known carcinogen (IARC, 2009) and a mammary carcinogen (Rudel, 2007).

Medical waste

Medical waste, particularly infectious waste, hazardous-chemical waste and radioactive waste, poses a particular conundrum with regard to disposal. Biological and pharmaceutical agents call for careful waste management to avoid contamination. Incineration can be an effective way to eliminate risks of biological contamination by bacterial and viral agents, but incineration of PVC and other materials can release health-compromising materials into the environment. PVC incineration, for instance, releases highly toxic dioxins. Most medical incinerators in the United States have closed due to stricter federal legislation, and those that remain open have more rigorous emissions standards (HCWH, 2002b).

Hospital food

Hospitals, like other institutions, rely heavily on canned foods and conventionally grown fruits and vegetables that may contain pesticide residues or leach BPA. In recent years, some hospitals have sought to create healthier food programs that draw from local, organic and fresh or frozen ingredients.

B. Vulnerable Populations

Toxic exposures in health care settings can not only affect patients but also create occupational risks for workers. In particular, female clinical laboratory technicians (Zheng, 2002), physicians (Weiderpass, 1999; Goldberg, 1996), nurses (Goldberg, 1996) (especially chemotherapy nurses), radiologic technicians (Sigurdson, 2003), dentists and dental hygienists (Goldberg, 1996) all have elevated rates of breast cancer relative to women in other occupations.

As with many other exposures, medical exposures to hormones and radiation early in life are more dangerous and can lead to breast cancer decades later. This is particularly true for long-term and repetitive exposures, such as long-term use of oral contraceptives (Kumle, 2002; Pasanisi, 2009; Rosenberg, 2009), repeated use of X-rays (Golubucic, 2008; Adams, 2010), and radiation treatment in childhood and adolescence (Schellong, 1998; Clemons, 2000; Tward, 2006).

C. Current Regulation

Medical devices, including radiological devices

The FDA Center for Devices and Radiological Health regulates the manufacture, repackaging, relabeling and/or importation

Toxic exposures in health care settings can not only affect patients but also create occupational risks for workers. In particular, female clinical laboratory technicians, physicians, nurses, radiologic technicians, dentists and dental hygienists all have elevated rates of breast cancer relative to women in other occupations.



Lower your exposure to radiation

Although X-rays and CT scans can give critical information for diagnosing medical problems, there is no such thing as a safe dose of radiation. Discuss with your medical care team whether the tests are necessary and whether there may be alternative tests that don't use radiation, such as an MRI or ultrasound.

Make sound decisions about mammography

Consider using the United States Preventive Services Task Force recommendations as a

guideline for mammography screening. The Task Force Guidelines recommend women begin mammography screening at age 50. Consult with a trusted health care provider to make a personalized decision about what age to begin mammography, and if mammography does not feel right for you, act as your own advocate and seek out alternative screening methods that do not rely on ionizing radiation.

Avoid synthetic hormone replacement therapy

Hormone replacement therapy is associated with a significantly increased risk of post-menopausal breast cancer. You can mitigate some of the side effects of menopause by regular exercise, cutting out caffeine and alcohol, and eating a balanced diet. If you do decide to use HRT, try an estrogen-only formulation and use it for as brief a time as possible.

Avoid dental sealants made with BPA

Ask your dentist about the materials in his/her dental sealants, so you can avoid unnecessary BPA exposure.

of medical devices sold in the United States. This includes setting standards for radiation emission of medical radiography devices and approval of materials for use in medical devices.

The FDA regulates medical devices under the Medical Device User Fee and Modernization Act (MDUFMA) of 2002. The Medical Devices Technical Corrections Act (MDTCA) of 2004 amends and expands MDUFMA.

Hospital-use disinfectants

Disinfectants used at health care facilities on noncritical medical

devices are termed general purpose disinfectants and must be registered with the EPA pursuant to the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA).

D. Policy Recommendations

Ionizing radiation

The most rigorous possible standards should be established at the federal level to achieve consistency among radiation-emitting medical devices being used in all 50 states and ensure that the lowest possible level of radiation is used to generate the necessary imaging. Policy-makers should support the 2009 Consistency,

Accuracy, Responsibility, and Excellence in Medical Imaging and Radiation Therapy bill (CARE bill, H.R. 3652), sponsored by Rep. John Barrow (D-Ga.), which amends the Public Health Service Act and Title XVIII of the Social Security Act to make the provision of technical services for medical imaging examinations and radiation therapy treatments safer, more accurate and less costly. The bill requires that 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

Table 6: What Is the Connection Between Health Care Exposures and Breast Cancer?

Medical exposure	Mammary Carcinogen (Rudel, 2007)	Carcinogenic (IARC, 2009; NTP, 2005)	Endocrine-Disrupting Compound (Brody, 2003)	Use
Bisphenol A (page 42)				Dental composite fillings, dental sealants, dialysis and cardiopulmonary bypass machines, cardiac stents and other implantable devices
Dioxin (page 49)		IARC Known; NTP Known		Byproduct of the incineration of PVC-containing medical devices
Ethylene oxide (page 59)		IARC Known		Sterilization of surgical tools
Ionizing radiation (page 61)		IARC Known; NTP Known		CT scans, X-rays, mammograms
Ortho phenyl phenol		CA Prop 65		Disinfectants
Phthalates, especially Di(2-ethylhexyl) (page 43)				PVC-based IV bags, IV tubing, feeding tubes, catheters
Polyvinyl chloride (page 59)		IARC Known; NTP Known		IV bags, IV tubing, feeding tubes, catheters
Triclosan				Microbicide

administered by the Department of Health and Human Services; in addition, 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.

To supplement the CARE bill, guidelines regarding medical radiation should be established to set strict quality assurance standards for radiation-emitting equipment, to establish methods of tracking

patients' exposure to diagnostic and therapeutic radiation, to establish alternatives to radiation-based health screening methods, and to research interactions between exposure to toxic chemicals and ionizing radiation.

- Federal quality-assurance standards should be established for all radiation-emitting equipment and should meet or exceed standards currently in place for mammography equipment. Quality-assurance standards should require physicians and technologists to use the smallest

dose of radiation possible to capture the highest-quality image. All states should be required to license 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.
- Educational materials should be used 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.

- Federal funding is needed for research to develop safer, noninvasive technologies for breast cancer screening, diagnosis and treatment.
- Federal funding is needed for research to better understand the possible cumulative, additive and synergistic effects that could result from combined exposure to toxic chemicals and ionizing radiation.
- Research should support the development of effective and safe breast cancer screening strategies based upon a woman's age and risk factors, and as these screening technologies are developed, health care funding should make safe and effective screening methods available to all women.

Medical devices

Federal legislation is needed to phase out the use of BPA and phthalates in medical devices and dental materials. Legislation should include provisions for the testing of alternative materials used in medical devices to ensure medical devices are manufactured from materials that are noncarcinogenic and are not endocrine disruptors.

Medical waste

Green building technologies should be applied to hospitals in order to integrate green cleaning modalities, such as improved air circulation; sink designs and water management that reduce building moisture and splashing; HVAC systems that

reduce airborne contaminants; and room design that minimizes cleaning. In addition, hospitals should integrate thoughtful waste-segregation approaches, since a considerable portion of hospital waste is from nonhazardous products such as waste paper (Shaner, 2002).

E. Agencies Responsible for Regulation

- FDA, Center for Devices and Radiological Health (CDRH). Regulates manufacture, repackaging, relabeling, and/or importation of medical devices sold in the United States, including standards for radiation emission of medical radiography devices and approval of materials for use in medical devices.
- EPA, Office of Pesticide Programs. Registers hospital disinfectants as part of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA).

VII. Air and Water

A. Exposures of Concern

Chemicals in products — from plastic candy wrappers to sport-utility vehicles to chemicals used as fuels in agriculture and other industries — make their way into the environment at multiple points in the product life cycle. Chemicals are released into air and water when these products are made — as “externalities,” or byproducts of the manufacturing process — and then again when we dispose of these products in landfills and hazardous waste facilities. The cost of this pollution — in terms of what it takes to clean it up, what it costs to treat resulting health problems, and what the impact is on the quality of life of humans and wildlife — is not calculated in the cost of production.

When chemicals make their way into the air and water, they become mobile and are not confined to geographic or political boundaries. Mobility means that chemicals leave the factories and landfills and can pollute nearby communities, which often experience the greatest ongoing health impacts, as well as distant communities.

Air pollutants

In a comprehensive review of chemicals associated with increased animal mammary gland tumors, 35 of the 216 chemicals were air pollutants (Rudel, 2007). There is widespread public exposure to many of these chemicals in outdoor air, as well as in offices, homes, restaurants and schools. The presence of multiple chemicals linked to breast cancer in the air means that individuals and communities are exposed regularly to a mixture of different chemicals linked to breast cancer. These mixtures of chemicals can enhance one another's effects, and in some cases the effects of the mixtures are greater than would be expected by simply adding together the impacts of the individual chemicals.

Chemicals of concern in air pollution include polycyclic aromatic hydrocarbons (PAHs), which are created as a result of combustion and are found in vehicle exhaust (especially diesel), tobacco smoke and incineration byproducts. PAHs have been linked to elevated risk of breast cancer, particularly when women are exposed early in life (Bonner, 2005). Other airborne chemicals that are implicated in increased risk for breast cancer include dioxins, which are created during the production and burning of plastics; organic solvents such as toluene, methylene



chloride, trichloroethylene and formaldehyde, all used in the manufacture of computer parts; cleaning products; and some cosmetics and pesticide residues including atrazine, heptachlor, dieldrin, and DDT (Brody, 2007; Rudel, 2007, Warner, 2002). Household dust can contain these compounds as well as larger particulate matters, all of which combine in the air people breathe. Researchers at the Silent Spring Institute found 66 endocrine-disrupting compounds in household dust, and households averaged 19 chemicals in the air and 26 in dust samples (Rudel, 2003).

Water pollutants

Chemicals used in manufacturing and disposed in waste sites also make their way into water. Pesticides used in agriculture make their way into streams and groundwater sources, which merge into larger water sources and can travel long distances. Some of the sources of water pollution are closer to home. For instance, chemicals used in household and personal care

products, including BPA, phthalates, triclosan and pharmaceutical hormones, such as post-menopausal hormone replacement therapies and oral contraceptives, can make their way into household drains (Antoniou, 2009; Benotti, 2009; Duran-Alvarez, 2009; Xu, 2009a; Yu, 2009a). This disposal goes to wastewater treatment plants, where these compounds are often only partially removed (Benotti, 2009). As this water is recirculated into municipal water supplies, some of the estrogens and endocrine-disrupting compounds often remain in the final treated water and are directly consumed, adding to the total burden of these chemicals in people's bodies.

Triazine herbicides, which are also endocrine-disrupting compounds, are also found in water. Each spring and summer, these herbicides can be detected in the groundwater in agricultural areas (Villanueva, 2005; Hua, 2006; Miller, 2000).

B. Vulnerable Populations

Like breast cancer rates, pollution is also distributed unequally in the United States. For instance, a recent study found that three groups — African Americans, people with less formal education and people with lower socioeconomic status — were more likely to live within a mile of a polluting facility as identified by the EPA (Mohai, 2009). This recent study reiterates findings from a number of other studies conducted in the past 20 years (Brulle, 2006). In addition, pregnant African American, Latina, and Asian/Pacific Islander women were more likely to live in counties with higher air pollution (Woodruff, 2003). Many communities are home to multiple sources of environmental exposure, including factories, waste disposal sites and other sources that regularly spew toxic chemicals or radiation into the environment. Some of these sources are recorded by the EPA's Toxic Release Inventory (TRI) database. In many cases, these sources of pollution are clustered in a small area, meaning that communities near one TRI site are often near several different pollution sources (Perlin, 2001). TRI facilities are more likely to be located near communities with higher proportions of people of color or people with lower socioeconomic status (Perlin, 2001; Mohai, 2009).

Agricultural communities and agricultural workers experience elevated levels of pesticide exposure. In addition, farmers and agricultural workers are likely to live in the closest proximity to the locale where these chemicals enter the air and water and, thus, where the concentrations are likely to be highest.

Since many pollutants from these sources make their way into water or air, allowing the pollutants to travel long distances, these concerns are not limited to the immediate area, although exposures are higher closer to factories and waste disposal sites. Pollutants may accumulate at significant levels in areas far from where they are used. For instance, high levels of some chemicals tend to move more easily into colder waters. As a result, animals and humans in colder parts of the world — often in areas of the world that are less industrialized — experience very high levels of exposure to chemicals from thousands of miles away (Courtney, 2000).

C. Current Regulation

Toxic Substances Control Act (TSCA)

TSCA is the broadest chemical regulatory policy in the United States. It was passed in 1976 and was intended to ensure the safety of chemical manufacturing and use. TSCA requires reporting and record-keeping regarding chemicals and chemical mixtures. It also has authority to require testing of chemicals for safety and to restrict chemical use, although these two

provisions are limited. Food, drugs, cosmetics and pesticides are not regulated under TSCA.

A major limitation of TSCA is the requirement that evidence of harm exist before chemicals are tested for harmful effects on health and the environment. Currently, TSCA regulates approximately 84,000 chemicals (EPA, 2010c), and 62,000 of these chemicals were grandfathered in, or automatically approved without any testing, when TSCA was passed. Approximately 3,000 of these chemicals are produced in annual volumes of over one million pounds. These high-production-volume (HPV) chemicals are the main focus of the EPA's Office of Chemical Safety and Pollution Prevention (OCSPP), formerly the Office of Pollution Prevention and Toxics (OPPT).

When companies submit chemicals for review under TSCA, they are only required to submit existing data on the substance. If no information on the chemical's safety for health or the environment has been developed, companies are not expected to conduct or commission such research. Once review materials are submitted, the

EPA has a limited time frame within which to respond to manufacturers, and if the EPA does not establish a restriction within that time frame, the chemical proceeds to market. This means numerous chemicals enter the market with no health or safety testing and no limitations on use. The EPA estimates that 43 percent of the 3,000 HPV chemicals imported or produced in the United States each year had no testing for basic toxicity. Only 7 percent of the HPV chemicals had full toxicity data (EPA, 1998). Only 22 percent of the HPV chemicals have been tested for reproductive toxicity, and only 33 percent have been tested for mutagenicity (EPA, 1998).

New leadership at the EPA is seeking to use TSCA's regulatory authority to enhance data collection and management of chemicals of greatest concern. Today, in addition to using the current provisions in TSCA to the greatest extent possible, the EPA recognizes the need for TSCA reform (EPA, 2010d).

Air

The EPA regulates indoor air under the Clean Air Act and the Toxic Substances Control Act (Hecht, 2003). In addition, the Occupational Safety and Health Administration protects indoor air quality by limiting specific airborne exposures in workplaces (Jacobs, 2009). At the state level, measures to reduce environmental tobacco smoke have been successful in 26 states and the District of Columbia, with 100 percent bans on smoking in public places, including restaurants and bars. While the EPA has established a recommended level at which action should be taken to remediate radon and has the authority to regulate indoor levels under Title III of the Toxic Substance Control Act



or the Indoor Radon Abatement Act of 1988, regulation is on a voluntary basis (PCP, 2008).

The EPA administers the Clean Air Act of 1970 to regulate the impact of stationary and mobile sources of pollution on outdoor air (EPA, 1970). The Act established National Ambient Air Quality Standards (NAAQS) for six common air pollutants: ozone, particulate matter, carbon monoxide, nitrogen oxides, sulfur dioxide and lead. States were required to adopt federal standards and develop a general plan to meet the NAAQS by 1975. NAAQS was amended in 1977 and in 1990. The 1990 Clean Air Act amendments expanded regulations to major stationary sources that emit more than 10 tons of hazardous air pollutants per year. The EPA sets standards for reductions in pollution, and these standards are re-evaluated every eight years. The amendments also included a list of 188 hazardous air pollutants in need of research and review, but since then no more have been added, even with the rapid introduction of new compounds (PCP, 2008).

Water

The Clean Water Act (CWA), enacted in 1948 and officially called the Federal Water Pollution Control Act, is administered by the EPA and was expanded in 1972 and amended in 1977 (EPA, 1972). This Act works to set quality standards for surface water and develop pollution control programs. Under the CWA, it is against the law to discharge point-source pollutants into surface waters. In addition, the EPA regulates the nation's drinking water supply with the Safe Drinking Water Act of 1974, amended in 1986 and 1996, which works to establish

health-based standards for tap water (Jacobs, 2009a; EPA, 2010). Eighty-six drinking water contaminants are regulated, but only arsenic has data from human studies, with the remainder of contaminant data coming from animal studies (PCP, 2008).

Pesticides

The EPA approves pesticides for sale under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), last amended in 1988. Pesticide risk is assessed and managed by conducting research and creating a label describing the substance's proper use and stating its toxicity class. Restricted use pesticides, or those that are considered by the EPA to be too hazardous to sell to the general public, are only allowed for purchase by a certified applicator (Willson, 2009).

The FIFRA assessments are based only on risk-benefit standards and do not follow safety or health standards. New pesticides can enter the market before meeting health and safety testing with a "conditional registration," and toxicity testing is obligatory only for active ingredients, even though inert ingredients may have toxic qualities. The data submitted are generated by the pesticide manufacturers themselves, even though research has found substantive differences between these data and external research from government or academic sources.

The EPA revised the Worker Protection Standards in 1992 to cover farmworker safety and agricultural pesticides. The regulations included requirements for pesticide safety training, safety and protective equipment use, and

worker notification of pesticide applications. Research has found that worker safety training is inadequate, especially among migrant workers (Jacobs, 2009a). In 1996 the Food Quality Protection Act (FQPA) was passed, requiring the EPA to adopt new standards to assess levels of pesticides and their breakdown compounds in food. Levels are set at 100 to 1,000 times lower than the "no observable effect level" (NOEL) for a person's exposure to one pesticide from all sources. Additionally, if a pesticide has been found to cause cancer in laboratory experiments, the EPA stipulates its use should be less than the amount calculated to cause one case of cancer per million people (Jacobs, 2009a).

Internationally, regulations for pesticides differ by country, but the United Nations Food and Agriculture Organization (FAO) conference in 1985 created the International Code of Conduct on the Distribution and Use of Pesticides, a set of voluntary guidelines for pesticide regulation (Willson, 2009). This Code has been updated in 1998 and 2002, with the aim of lowering the number of countries that have no pesticide use restrictions. Additional global efforts include the United Nations London Guidelines for the Exchange of Information on Chemicals in International Trade and the United Nations Codex Alimentarius Commission (Reynolds, 1997). In 2009, the European Union banned the use of pesticide products containing active ingredients that are carcinogenic, mutagenic or endocrine-disrupting substances (EP, 2009).

D. Policy Recommendations

Toxic Substance Control Act

TSCA should be overhauled to require rigorous testing of chemicals already on the market for effects on human health and for persistence in the environment. In addition, new chemicals should be tested for health effects before entry into the market. TSCA reform should mandate:

- Quick action to reduce exposures to chemicals linked to cancer, negative reproductive and developmental health effects, and negative neurological health outcomes.
- Basic safety information on all chemicals in commerce, with industry bearing the burden of proof to show that chemicals are safe.
- A health standard that will truly protect the public, especially our most vulnerable citizens, including infants and children.

Policy-makers should support the Safe Chemicals Act of 2010 (S. 3209), introduced by Sen. Frank Lautenberg (D-N.J.) and the Toxic Chemicals Safety Act of 2010, introduced by Rep. Bobby Rush (D-Ill.) and Rep. Henry Waxman (D-Calif.), which would reform TSCA by establishing these requirements:

- The EPA must have adequate information on chemical hazards, uses and exposures to effectively judge a chemical's safety.
- The EPA must use hazard, use and exposure information to categorize chemicals, and to establish priorities on the basis of hazard and exposure.
- The EPA must expedite action to reduce the use of or exposures to chemicals of highest concern.

- Manufacturers must demonstrate the safety of all chemicals in order for them to remain in or enter into commerce.
- The public, the market, and workers must have access to reliable chemical information.
- The EPA must develop a program to create incentives for innovation and the development and use of green chemistry and safer alternatives to chemicals of concern.

Air pollution

Policies are needed to minimize exposure to carcinogenic and endocrine-disrupting compounds in outdoor and indoor air.

- Vehicle and industrial emissions standards should be raised to reduce the level of PAH emissions.
- Current regulatory standards should be enforced more strictly for outdoor air pollution under the Clean Air Act.
- The development of nonpolluting technologies should be encouraged.
- The list of hazardous air pollutants should be researched and updated to include newly developed compounds.
- Indoor air regulations should be implemented by a single governmental entity rather than by multiple agencies and laws.
- All states should adopt environmental secondhand tobacco smoke bans in public locations, including restaurants and bars.
- Legislation is needed both at the state and federal levels to create radon action level standards based on the scientific health effects.

Water pollution

Policies are needed to reduce the contamination of surface water and to establish more rigorous standards for safe drinking water. The standards should be expanded to address endocrine disruptors in drinking water.

- Federal policy-makers should support the Endocrine Disruptor Screening Enhancement Act (H.R. 5210), which would require the EPA to test substances that may be found in drinking water to determine whether they are endocrine disruptors and to what extent they interfere with the body's hormonal system. The law would create a publicly searchable database with information about the program, including testing status, schedules and results.
- Federal policy-makers should support the Safe Drinking Water for Healthy Communities Act of 2009 (H.R. 3206), introduced by Rep. Jackie Speier (D-Calif.), which amends the Safe Drinking Water Act to require the Administrator of the EPA to promulgate a national primary drinking water regulation for perchlorate.
- Federal policy-makers should support the Drug Free Water Act of 2009 (H.R. 276), introduced by Rep. Candice Miller (R-Mich.), which requires the Administrator of the EPA to convene a task force to develop (1) recommendations on the proper disposal of unused pharmaceuticals to prevent or reduce the detrimental effects on water systems and (2) a strategy for educating the public on such recommendations.
- Federal legislation is needed that would direct the EPA to revise the water pollution standards so they better protect public health by including more of the common

Air and Water: Tips for Reducing Exposure to Chemicals of Concern



Stay far, far away from cigarettes

Avoid smoking and breathing in secondhand smoke, both of which have high levels of cadmium and polycyclic aromatic hydrocarbons (PAHs).

Find safe ways to fight germs

Avoid “antibacterial” agents in soaps, toothpaste, clothing, bedding, socks, band-aids, toys and cutting boards. Many of these products contain triclosan, an antimicrobial agent that is suspected of interfering with the hormone systems of humans and wildlife. If you need a hand sanitizer, choose those with an alcohol or herbal base.

Avoid chemical-based dry cleaning

Tetrachloroethylene, also known as perchloroethylene or PERC for short, is a harmful chemical commonly used in dry cleaning. To avoid exposure, don’t buy clothes that say “dry clean only.” For the dry-clean-only clothes you already own, remember that they can oftentimes be hand-washed and air dried with little consequence. If you do use a dry cleaner, take off the plastic bag as soon as possible and air the clothes out, preferably outdoors.

Get a water filter for drinking water

Choose a water filter that can remove hormones, endocrine-disrupting compounds, and pesticides, and replace the filter as directed.

Buy low-emission vehicles and avoid car exhaust

Car exhaust releases a carcinogen known as polycyclic aromatic hydrocarbons (PAHs). When purchasing a car (especially used), make sure the emissions system meets government standards and that the catalytic converter and the computer system controlling emissions work properly.

water pollutants such as radon and arsenic.

- Federal legislation is needed that would authorize the creation of a watershed protection program to reduce contamination of surface waters.
- The Federal Insecticide, Fungicide, and Rodenticide Act should be revised so that pesticides cannot enter the market with a conditional registration, since pesticides can enter surface water and groundwater systems that feed municipal water systems and residential water wells. Pesticide

registration procedures need to be more rigorous, and testing data should be required to come from government-funded or academic research entities rather than directly from pesticide manufacturers. Manufacturers should be provided with incentives to adopt safer pesticide practices and develop product alternatives, in light of persistent water pollution from health-harming pesticides banned decades ago.

E. Agencies Responsible for Regulation

- EPA, Office of Air and Radiation. Regulates chemical releases into air.
- EPA, Office of Water. Regulates chemical releases into water.
- EPA, Office of Chemical Safety and Pollution Prevention (OCSPP). Manages the overall regulation of chemical production, use, and reporting.
- EPA, Office of Pesticide Programs. Regulates the registration, restriction and use of pesticides.

Table 7: What Is the Connection Between Air and Water Contaminants and Breast Cancer?

Environmental Exposures	Mammary Carcinogen (Rudel, 2007)	Carcinogenic (IARC, 2009; NTP, 2005)	Endocrine-Disrupting Compound (Brody, 2003)	Source of Exposure
1,3-butadiene (page 59)		●	IARC Probable; NTP Known	Outdoor and indoor air; tobacco smoke; manufacture of rubber and some pesticides; occupational
Alkylphenols (4-nonylphenol) (page 44)			●	Indoor air and dust; waste and tap water; personal care products (hair products, spermicides); cleaning product and detergent manufacture; occupational
Aromatic amines (monocyclic; polycyclic; heterocyclic) (page 52)	●	IARC Probable; NTP Reasonably Anticipated	●	Outdoor and indoor air; tobacco smoke; combustion of wood chips and rubber; formed in production of polyurethane foams, dyes, pesticides and pharmaceuticals; diesel auto exhaust; dietary intake of grilled meats and fish
Benzene (page 57)	●	IARC Known; NTP Known		Outdoor and indoor air; tobacco smoke; gasoline fumes; diesel auto exhaust; industrial burning/combustion; intensive occupational use
Bisphenol A (page 42)			●	Wastewater; household dust
Dioxins (e.g., tetra chlorodibenzo-p-dioxin) (page 49)		IARC Known; NTP Known	●	Created from combustion of PCBs, PVC and other chlorinated compounds. Outdoor air pollution; waste incineration; pulp and paper manufacture; diet, especially from fatty foods, occupational
Estrogens (estrone, estradiol) (page 54)	●	IARC Known; NTP Known		Wastewater
Ethylene oxide (page 59)	●	IARC Known		Indoor air pollution; possibly from cosmetics; occupational exposures in sterilization facilities and cosmetics manufacture

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Table 7: What Is the Connection Between Air and Water Contaminants and Breast Cancer?				
Environmental Exposures	Mammary Carcinogen (Rudel, 2007)	Carcinogenic (IARC, 2009; NTP, 2005)	Endocrine-Disrupting Compound (Brody, 2003)	Source of Exposure
Organic solvents (toluene, methylene chloride, trichloroethylene, formaldehyde) (page 58)	○	NTP Reasonably Anticipated		Outdoor and indoor air pollution; wastewater-irrigated soils; waste incineration; used in manufacture of computer parts, cleaning products and some cosmetics; occupational
Pesticides				
1,2-Dibromo-3-chloropropane	○	IARC Possible; NTP Reasonably Anticipated		Banned as a soil fumigant in 1985; Air pollutant, Ingestion of previously contaminated food and water
Atrazine (page 46)	○	IARC Not Classifiable	○	Through ingestion of food or water; found widely in bodies of water; in waste and tap water
Chlordane	○		○	Banned as an insecticide; outdoor and indoor air pollutant; household dust
Clonitralid	○			Dermal contact or ingestion of water treated with clonitralid (for water snail and sea lamprey control)
DDT/DDE (page 50)		NTP Reasonably Anticipated	○	Banned in U.S. in 1973; still found in environment, in fat of animals and humans
Dichlorvos	○	IARC Possible		Air pollutant; contact with no-pest strips, sprays or flea powders; food prepared where dichlorvos was used
Dieldrin, aldrin, endrin (page 47)			○	Banned in 1987; persists in environment; indoor dust
Simazine	○	IARC Not Classifiable		Air pollution, rainwater, surface water
Phthalates (page 43)			○	Wastewater; indoor dust
Polybrominated diphenyl ethers (PBDE's) (page 48)		NTP Reasonably Anticipated	○	Indoor dust

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Table 7: What Is the Connection Between Air and Water Contaminants and Breast Cancer?

Environmental Exposures	Mammary Carcinogen (Rudel, 2007)	Carcinogenic (IARC, 2009; NTP, 2005)	Endocrine-Disrupting Compound (Brody, 2003)	Source of Exposure
Polycyclic aromatic hydrocarbons (e.g., benzo(a)pyrene (page 45))	●	IARC Probable	●	Outdoor and indoor air; tobacco smoke, coal and coke burners; diesel auto exhaust; dietary intake of smoked and grilled foods; food contaminated by outdoor air pollution; occupational
Triclosan			●	Wastewater
Vinyl chloride (page 59)		IARC Known; NTP Known		Outdoor and indoor air; tobacco smoke; air near hazardous waste sites and landfills; occupational exposures in PVC manufacture

Adapted from: (Antoniou, 2009); (Benotti, 2009); (Brody, 2007); (Duran-Alvarez, 2009); (Rudel, 2003, 2007); (Swartz, 2006); (Xu, 2009); (Yu, 2009); (Zota, 2008)

VIII. Conclusion

Moving Forward

While the growing environmental health movement is poised to make significant progress in reforming chemical policy, there are still a number of institutional challenges to be addressed. First, we must simplify the coordination of chemicals management between government agencies. Take phthalates for example, a family of endocrine-disrupting compounds linked to early puberty and increased breast cancer risk. Phthalates used in toys are regulated by the Consumer Product Safety Commission; those used in fragrance are regulated by the FDA Office of Cosmetics and Colors; those used in food packaging are regulated by the FDA Office of Food Additive Safety; and those used in medical devices are regulated by

yet another FDA office. Phthalates in industrial cleaning products are regulated by OSHA, while phthalates in household cleaning products are regulated by the CPSC. Phthalates in our rivers are regulated by the EPA. The study of phthalates in people is investigated by the CDC and the impact of phthalates on human health is researched by NIEHS. Responsibility for managing chemicals is distributed by product category, exposure or environmental medium as opposed to more logically by chemical, resulting in a regulatory quagmire in which change can happen only very slowly.

On a more positive note, public awareness of unsafe chemical exposures has never been higher, with more legislative activity and wins at the state level than ever before, and the growth of the

sustainable business community is providing real-time examples of how industry can make safer products and still be profitable. Also heartening are the broad-based coalitions that have come together to advocate for TSCA reform, stronger regulation of the cosmetics industry and getting BPA out of food and beverage containers.

Fixing our broken chemical-regulatory system will take more than just legislative reform of TSCA, cosmetics and food safety. It will take more and better research on environmental links to disease; state and federal infrastructures for conducting biomonitoring and health tracking; better interagency coordination; an engaged federal administration; and, most important, a vision that clearly articulates where we need to go and a coordinated effort to get there.

REFERENCES

References

A

- Acevedo R, Parnell PG, Villanueva H, *et al.* (2005). The contribution of hepatic steroid metabolism to serum estradiol and estrone concentrations in nonylphenol treated MMTVneu mice and its potential effects on breast cancer incidence and latency. *J Appl Toxicol*, 25:339-353.
- ACS: American Cancer Society (2009). *Breast Cancer Facts & Figures 2009-2010*. Atlanta: American Cancer Society, Inc.
- Adam A, Bardo H, Adany R (2005). Increased genotoxic susceptibility of breast epithelial cells to ethylene oxide. *Mutation Res*, 585:120-126.
- Adams MJ, Dozier A, Shore RE, *et al.* (2010). Breast cancer risk 55+ years after irradiation for an enlarged thymus and its implications for early childhood medical irradiation today. *Cancer Epidemiol Biomarkers Prev*, 19:48-58.
- Adlercreutz H (2003). Phytoestrogens and breast cancer. *J Steroid Biochem Mol Biol*, 83:113-118.
- AdvaMed (2009). Medical devices and articles used in product manufacturing containing bisphenol-a related materials. www.thegraysheet.com/nr/FDC/SupportingDocs/gray/2009/011209_AdvaMed_BPA_chart.pdf (7/12/2010).
- Ahlbom A, Cardis E, Green A, *et al.* (2001). Review of the epidemiological literature on MF and health. *Environ Health Perspect*, 109 (Suppl 6):911-933.
- Aksela L, Juul A, Leffers H, Skakkebaek NE, Andersson AM (2006). The sensitivity of the child to sex steroids: possible impact of exogenous estrogens. *Hum Reprod Update*, 12:341-349.
- Al-Dobaib SN, Mousa HM (2009). Benefits and risks of growth promoters in animal production. *J Food Agric Environ*, 7:202-208.
- Alexander BH, Mandel JS, Baker BA, *et al.* (2007). Biomonitoring of 2,4-dichlorophenoxyacetic acid exposure and dose in farm families. *Environ Health Perspect*, 115:370-376.
- Allen NE, Roddam AW, Allen DS, *et al.* (2005). A prospective study of serum insulin-like growth factor-I (IGF-1), IGF-II, IGF-binding protein-3 and breast cancer risk. *Br J Cancer*, 92:1283-1287.
- Allmyr M *et al.* (2006). Triclosan in plasma and milk from Swedish nursing mothers and their exposure via personal care products. *Sci Total Environ*, 372:87-93.
- Althuis MD, Brogan DD, Coates RJ, *et al.* (2003). Breast cancers among very young premenopausal women (United States). *Cancer Causes Control*, 14:151-160.
- Althuis MD, Dozier JM, Anderson WF, *et al.* (2005). Global trends in breast cancer incidence and mortality 1973-1997. *Int J Epidemiol*, 34:405-412.
- Altman RG, Morello-Frosch R, Brody JG, *et al.* (2008). Pollution comes home and gets personal: Women's experience of household chemical exposure. *J Health Soc Behav*, 49:417-434.
- Ambrosone CB, Freudenheim JL, Graham S, *et al.* (1996). Cigarette smoking, N-acetyltransferase 2 polymorphisms, and breast cancer risk. *J Am Med Assoc*, 276:1494-1501.
- Andersen HR, Vinggaard AM, Rasmussen TH, *et al.* (2002). Effects of currently used pesticides in assays for estrogenicity, androgenicity, and aromatase activity *in vitro*. *Toxicol Appl Pharmacol*, 179:1-12.
- Anderson GL, Limacher M (2004). Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: The Women's Health Initiative randomized controlled study. *J Am Med Assoc*, 291:1701-1712.
- Anderson HA, Wolff MS (2000). Environmental contaminants in human milk. *J Expos Anal Environ Epidemiol*, 10 (II Suppl.):755-760.
- Anderson WF, Matsuno RK, Sherman ME, *et al.* (2007). Estimating age-specific breast cancer risks: a descriptive tool to identify age interactions. *Cancer Causes Control*, 18:439-447.
- Andersson PL, Blom A, Johannisson A, *et al.* (1999). Assessment of PCBs and hydroxylated PCBs as potential xenoestrogens: In vitro studies based on MCF-7 cell proliferation and induction of vitellogenin in primary culture of rainbow trout hepatocytes. *Arch Environ Contam Toxicol*, 37:145-150.
- Andersson TML, Johansson ALV, Hsieh CC, *et al.* (2009). Increasing incidence of pregnancy-associated breast cancer in Sweden. *Obstet Gynecol*, 114:568-572.
- Andreeva VA, Unger JB, Pentz MA (2007). Breast cancer among immigrants: a systematic review and new research directions. *J Immigrant Minor*, 9:307-322.
- Andrieu N, Easton DF, Chang-Claud J, *et al.* (2006). Effect of chest X-rays on the risk of breast cancer among BRCA1/2 mutation carriers in the International BRCA1/2 Carrier Cohort Study: A report from EMBRACE, GEGNNEPSO, GEO-HEBON, and IBCCS Collaborators' Group. *J Clin Oncol*, 24:3361-3366.
- Angerer J, Bird MG, Burke TA, *et al.* (2006). Strategic biomonitoring initiatives: Moving the science forward. *Toxicol Sci*, 93:3-10.
- Antoniou CV, Koukouraki EE, Diamadopoulos E (2009). Analysis of selected pharmaceutical compounds and endocrine disruptors in municipal wastewater using solid-phase microextraction and gas chromatography. *Water Environ Res*, 81:664-669.
- Arnold SE, Klotz DM, Collins BM, *et al.* (1996). Synergistic activation of estrogen receptor with combinations of environmental chemicals. *Science*, 272:1489-1492.

- Aronson KJ, Miller AB, Woolcott CG, *et al.* (2000). Breast adipose tissue concentrations of polychlorinated biphenyls and other organochlorines and breast cancer risk. *Cancer Epidemiol Biomarkers Prev*, 9:55-63.
- Arslan AA, Zeleniuch-Jacquotte A, Lukanova A, *et al.* (2006). Effects of parity on pregnancy hormonal profiles across ethnic groups with a diverse incidence of breast cancer. *Cancer Epidemiol Biomarkers Prev*, 15:2123-2130.
- Athar M, Back JH, Kopelovich L, *et al.* (2009). Multiple molecular targets of resveratrol: anti-carcinogenic mechanisms. *Arch Biochem Biophys*, 486:95-102.
- ATSDR: Agency for Toxic Substances and Disease Registry (1996). ToxFAQs for vinyl chloride. www.atsdr.cdc.gov/toxprofiles/tp20.html (7/12/2010).
- ATSDR: Agency for Toxic Substances and Disease Registry (1999). ToxFAQs for ethylene oxide. www.atsdr.cdc.gov/toxfaqs/TF.asp?id=733&tid=133 (7/12/2010).
- ATSDR, Agency for Toxic Substances and Disease Registry (1999). ToxFAQs for chlorinated dibenzo-p-dioxins. www.atsdr.cdc.gov/toxfaqs/TF.asp?id=363&tid=63 (7/12/2010).
- ATSDR: Agency for Toxic Substances and Disease Registry Fact Sheet (2010). ToxFAQs for aldrin/dieldrin. www.atsdr.cdc.gov/tfacts1.html (7/12/2010).
- ## B
- Baccarelli A, Bollati V (2009). Epigenetics and environmental chemicals. *Curr Opin Pediatr*, 21:243-251.
- Ballard T, Lagorio S, De Angelis G, *et al.* (2000). Cancer incidence and mortality among flight personnel: A meta-analysis. *Aviat Space Environ Med*, 71:216-224.
- Balmain A, Harris CC (2000). Carcinogenesis, in mouse and human cells: parallels and paradoxes. *Carcinogenesis*, 21:371-377.
- Band PR, Le ND, Fang R *et al.* (2002). Carcinogenic and endocrine disrupting effects of cigarette smoke and risk of breast cancer. *Lancet*, 360:1033-1034.
- Barcellos-Hoff MH, Park C, Wright EG (2005). Radiation and the microenvironment: Tumorogenesis and therapy. *Nat Rev Cancer*, 5:867-875.
- Barlow BK, Cory-Slechta DA, Richfield EK, *et al.* (2007). The gestational environment and Parkinson's disease: Evidence for neurodevelopmental origins of a neurodegenerative disease. *Reprod Toxicol*, 23: 457-470.
- Bauer KR, Brown M, Cress RD, *et al.* (2007). Descriptive analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype: A population-based study from the California Cancer Registry. *Cancer*, 109:1721-1728.
- BCERC: Breast Cancer and the Environment Research Centers (2010). BCERC research. www.bcerc.org/research.htm (7/12/2010).
- Beard J (2006). DDT and human health. *Sci Total Environ*, 355:78-89.
- Belli S, Comba P, De Santis M, *et al.* (1992). Mortality study of workers employed by the Italian National Institute of Health, 1960-1989. *Scand J Work Environ Health*, 18:64-67.
- Benbrahim-Tallaa L, Tokar EJ, Diwan BA, *et al.* (2009). Cadmium malignantly transforms normal human breast epithelial cells into a basal-like phenotype. *Environ Health Perspect*, 117:1847-1852.
- Bennett M, Davis BJ (2002). The identification of mammary carcinogens in rodent bioassays. *Environ Mol Mutagenesis*, 39:150-157.
- Benotti MJ, Trenholm RA, Vanderford BJ, *et al.* (2009). Pharmaceuticals and endocrine disrupting compounds in U.S. drinking water. *Environ Sci Technol*, 43:597-603.
- Benzoni E, Minervini F, Giannoccaro A, *et al.* (2008). Influence of in vitro exposure to mycotoxin zearalenone and its derivatives on swine sperm quality. *Reprod Toxicol*, 25: 461-467.
- Bernstein L, Allen M, Anton-Culver H, *et al.* (2002). High breast cancer incidence rates among California teachers: Results from the California Teachers Study (United States). *Cancer Causes Control*, 13:625-635.
- Berrington de Gonzalez A, Berg C, Visvanathan K, Robson M (2009a). Estimated risk of radiation-induced breast cancer from mammographic screening for young BRCA mutation carriers. *J Natl Cancer Inst*, 101:205-209.
- Berrington de Gonzalez A, Mahesh M, Kim K-P *et al.* (2009b). Projected cancer risks from computed tomographic scans performed in the United States in 2007. *Arch Intern Med*, 169:2071-2077.
- Beyea J, Stellman SD, Hatch M, Gammon MD (2008). Airborne emissions from 1961 to 2004 of benzo(a)pyrene from U.S. vehicles per km of travel based on tunnel studies. *Environ Sci Technol*, 47:7315-7320.
- Bhatia S, Yasui Y, Robison LL, *et al.*: Late Effects Study Group (2003). High risk of subsequent neoplasms continues with extended follow-up of childhood Hodgkin's disease: report from the Late Effects Study Group. *J Clin Oncol*, 21:4386-94.
- Bhatti P, Doody MM, Alexander BH, *et al.*, (2007). Breast cancer risk polymorphisms and interactions with ionizing radiation among U.S. radiologic technologists. *Cancer Epidemiol Biomarkers Prev*, 17:2007-2011.
- Bibbo M, Gill WB, Azizi F, *et al.* (1977). Follow-up study of male and female offspring of DES-exposed mothers. *Obstet Gynecol J*, 49:1-8.
- Biglia N, Sgro L, Defabiani E, *et al.* (2005). The influence of hormone replacement therapy on the pathology of breast cancer. *EJSO: J Cancer Surg*, 31:467-472.
- Birnbaum LS (2009). Halogenated flame retardants: Does the benefit justify the risk? Keynote address: 6th Annual Early Environmental Exposures Conference of the Breast Cancer and the Environment Research Centers, Sausalito, CA.
- Birnbaum LS, Fenton SE (2003). Cancer and developmental exposure to endocrine disruptors. *Environ Health Perspect*, 111: 389-394.
- Blask DE, Brainard GC, Dauchy RT, *et al.* (2005). Melatonin-depleted blood from premenopausal women exposed to light at night stimulates growth of human breast cancer xenografts in nude rats. *Cancer Res*, 65:11174-11184.
- Blask DE (2009). Melatonin, sleep disturbance and cancer risk. *Sleep Med Rev*, 13:257-264.
- Boice JD (2001). Radiation and breast carcinogenesis. *Med & Pediatr Oncol*, 36:508-513.
- BOLS: Bureau of Labor Statistics (2005). Table 11. Employed Persons by Detailed Occupation, Sex, Race, and Hispanic or Latino ethnicity, age 16 years or older.
- Bonner MR, Han D, Nie J, *et al.* (2005). Breast cancer risk and exposure in early life to polycyclic aromatic hydrocarbons using total suspended particulates as a proxy measure. *Cancer Epidemiol Biomarkers Prev*, 14:53-60.
- Borch J, Axelstad M, Vinggaard AM, *et al.* (2006). Mechanisms underlying the anti-androgenic effects of diethylhexyl phthalate in fetal rat testis. *Toxicol*, 223:144-155.
- Borgquist S, Anagnostaki L, Jirstom K, *et al.* (2007). Breast tumours following combined hormone replacement therapy express favorable prognostic factors. *Int J Cancer*, 120:2202-2207.
- Borrell B. (2010). The big test for bisphenol A. *Nature*, 464:1122-1124.
- Boucher BA, Cotterchio M, Krieger N, Thompson L (2008). Soy formula and breast cancer risk. *Epidemiology*, 19:165-168.
- Bourguignon J-P, Rasier G, Lebrethon M-C, *et al.* (2010). Neuroendocrine disruption of pubertal timing and interactions between homeostasis of reproduction and energy balance. *Mol Cell Endocrinol*, 324:110-120.

- Bowen RL, Stebbing J, Jones LJ (2006). A review of the ethnic differences in breast cancer. *Pharmacogenomics* 7:935-942.
- Braathén M, Mortensen AS, Sandvik M, *et al.* (2009). Estrogenic effects of selected hydroxy polychlorinated biphenyl congeners in primary culture of Atlantic salmon (*Salmo salar*) hepatocytes. *Arch Environ Contam Toxicol* 56:111-122.
- Bradbury AR, Olopade OI (2007). Genetic susceptibility to breast cancer. *Rev Endocr Metab Disord*, 8:255-267.
- Bradley EL, Boughtflower V, Smith TL, *et al.* (2005). Survey of the migration of melamine and formaldehyde from melamine food contact articles available on the UK market. *Food Addit Contam.* 22:597-606.
- Brama M, Gnassi L, Basciani S, *et al.* (2007). Cadmium induces mitogenic signaling in breast cancer cell by an Eralpha-dependent mechanism. *Mol Cell Endocrinol*, 264:102-108.
- Brand RM, McMahon L, Jendrzewski JL, *et al.* (2007). Transdermal absorption of the herbicide 2,4-dichlorophenoxyacetic acid is enhanced by both ethanol consumption and sunscreen application. *Food Chem Toxicol*, 45:93-97.
- Braun JM, Yoltón K, Dietrich KN, *et al.* (2009). Prenatal bisphenol A exposure and early childhood behavior. *Environ Health Perspect*, 117:1945-1952.
- Brenner DJ, Doll R, Goodhead DT, *et al.* (2003). Cancer risks attributable to low doses of ionizing radiation. *Proc Natl Acad Sci*, 100 (24):13761-13766.
- Brinton LA, Scoccia B, Moghissi KS, *et al.* (2004). Breast cancer risk associated with ovulation-stimulating drugs. *Hum Reprod*, 19:2005-2013.
- Brody JG, Rudel RA, Melly SJ, *et al.* (1998). Endocrine disruptors and breast cancer. *Forum Appl Res Public Policy*, 13:24-31.
- Brody JG, Rudel RA (2003). Environmental pollutants and breast cancer. *Environ Health Perspect* 111:1007-1009.
- Brody JG, Aschengrau A, McKelvey W, *et al.* (2004). Breast cancer risk and historical exposure to pesticides from wide-area applications assessed with GIS. *Environ Health Perspect*, 112:889-897.
- Brody JG, Moysich KB, Humblet O, *et al.* (2007). Environmental pollutants and breast cancer. *Epidemiol Stud Cancer*, 109 (S12):2667-2711.
- Brody JG, Morello-Frosch R, Zota A, *et al.* (2009). Linking exposure assessment science with policy objectives for environmental justice and breast cancer advocacy: The Northern California Household Exposure Study. *Am J Public Health*, 99:S600-S609.
- Bronaugh RL, Collier SW, Macpherson SE, *et al.* (1994). Influence of metabolism in skin on dosimetry after topical exposure. *Environ Health Perspect* 102(S11):71-74.
- Brophy JT, Keith MM, Gorey KM, *et al.* (2006). Occupation and breast cancer: A Canadian case-control study. *Ann NY Acad Sci*, 1076:765-777.
- Brotóns JA, Olea-Serrano MF, Villalobos M, *et al.* (1995). Xenoestrogens released from lacquer coatings in food cans. *Environ Health Perspect*, 103:608-612.
- Brown NM, Manziolillo PA, Zhang JX, *et al.* (1998). Prenatal TCDD and predisposition to mammary cancer in rats. *Carcinogenesis*, 19:1623-1629.
- Brulle RJ, Pellow DN (2006). Environmental justice: human health and environmental inequalities. *Ann Rev Public Health*, 27:103-124.
- Bruner Huber LR, Huber KR (2009). Contraceptive choices of women 35-44 years of age: Findings from the behavioral risk factor surveillance system. *Ann Epidemiol*, 19:823-833.
- Byford JR, Shaw LE, Drew MGB, *et al.* (2002). Oestrogenic activity of parabens in MCF7 human breast cancer cells. *J Steroid Biochem Mol Biol*, 80:49-60.
- Byrne C, Divekar SD, Storch GB, *et al.* (2009). Cadmium: a metalloestrogen? *Toxicol Appl Pharmacol*, 238:266-271.
- C**
- Calabrese EJ (2004). Hormesis: from marginalization to mainstream. A case for hormesis as the default dose-response model in risk assessment. *Toxicol Pharmacol*, 197:125-136.
- Calabrese EJ, Staudenmayer JW, Stanek EJ, Hoffmann GR (2006). Hormesis outperforms threshold model in National Cancer Institute antitumor drug screening database. *Toxicol Sci*, 94:368-378.
- Calaf GM, Hei TK (2000). Establishment of a radiation- and estrogen-induced breast cancer model. *Carcinogenesis*, 21:769-776.
- Calafat AM, Kuklenyik Z, Reidy JA, *et al.* (2005). Urinary concentrations of bisphenol A and 4-nonylphenol in a human reference population. *Environ Health Perspect*, 113:391-395.
- Calafat AM, Ye X, Wong L-Y, Reidy JA, Needham LL. (2008). Exposure of the U.S. population to bisphenol A and 4-tertiary-octylphenol: 2003-2004. *Environ Health Perspect*, 116:39-44.
- Calafat AM, Weuve J, Ye X, *et al.* (2009). Exposure to bisphenol A and other phenols in neonatal intensive care unit premature infants. *Environ Health Perspect*, 117:639-644.
- Calderon-Margalit R, Friedlander Y, Yanetz R, *et al.* (2009). Cancer risk after exposure to treatments for ovulation induction. *Am J Epidemiol*, 169:365-375.
- Cal-EPA: California Environmental Protection Agency (2005). Proposed identification of environmental tobacco smoke as a toxic air contaminant. www.oehha.ca.gov/air/environmental_tobacco/pdf/app3partb2005.pdf (7/12/2010).
- Calle EE, Miracle-McMahill HL, Thun MJ, *et al.* (1994). Cigarette smoking and risk of fatal breast cancer. *Am J Epidemiol*, 139:1001-1007.
- Cameron HL, Foster WG (2009). Developmental and lactational exposure to dieldrin alters mammary tumorigenesis in her2/neu transgenic mice. *Plos One*, 4:e4303.
- Cantor KP, Stewart, PA, Brinton LA, *et al.* (1995). Occupational exposures and female breast cancer mortality in the United States. *J Occup Environ Med*, 37:336-348.
- Carey LA, Perou CM, Livasy CA, *et al.* (2006). The poor prognosis basal-like breast cancer subtype is over-represented in young African-American women. *J Am Med Assoc*, 297:2492-2502.
- Carpenter DO (2010). Electromagnetic fields and cancer: The cost of doing nothing. *Rev Environ Health*, 25:75-80.
- Carwile JL, Luu HT, Bassett LS, *et al.* (2009). Polycarbonate use and urinary bisphenol A concentrations. *Environ Health Perspect*, 117:1368-1372.
- Cassidy RA, Natarajan S, Vaughan GM (2005). The link between the insecticide heptachlor epoxide, estradiol, and breast cancer. *Breast Cancer Res Treat*, 90: 55-64.
- CDC: Center for Disease Control and Prevention. (2005). Third National Report on Human Exposure to Environmental Chemicals. Atlanta: Centers for Disease Control and Prevention.
- CDC: Center for Disease Control and Prevention. (2007). Decline in breast cancer incidence: United States, 1999-2003. *Morbid Mortal Weekly Rep*, 56: 549-553.
- CDC: Center for Disease Control and Prevention. (2009). Fourth national report on human exposure to environmental chemicals. Atlanta: Centers for Disease Control and Prevention.
- CDPH: California Department of Public Health (2010). California safe cosmetics program. www.cdph.ca.gov/programs/cosmetics/Pages/default.aspx (7/12/2010).
- CEC: Commission of the European Communities (2004). Commission staff working document

- on implementation of the community strategy for endocrine disruptors: a range of substances suspected of interfering with the hormone systems of humans and wildlife. http://ec.europa.eu/environment/endocrine/documents/sec_2004_1372_en.pdf (7/12/2010).
- Cederroth CR, Nef S (2009). Soy, phytoestrogens and metabolism: a review. *Mol Cell Endocrinol*, 304:30-42.
- CEPA: CEPA Environmental Registry (2009). Consultation document phenol, 4,4'-(1-methylethyldene)bis-(bisphenol A). www.ec.gc.ca/ceparegistry/documents/participation/pba/p3.cfm (7/12/2010).
- CGHFBC: Collaborative Group on Hormonal Factors in Breast Cancer (1996). Breast cancer and hormonal contraceptives: Collaborative reanalysis of individual data on 53,297 women with breast cancer and 100,239 women without breast cancer from 54 epidemiological studies. *Lancet*, 347:1713-1727.
- CGHFBC: Collaborative Group on Hormonal Factors in Breast Cancer (1997). Breast cancer and hormone replacement therapy: Collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. *Lancet*, 350:1047-1059.
- Chan MM, Lu X, Merchant FM, Iglehart JD, Miron PL (2005). Gene expression profiling of NMU-induced rat mammary tumors: cross species comparison with human breast cancer. *Carcinogenesis*, 26:1343-1353.
- Chang YM, Tai CF, Lin RS, *et al.* (2003). A proportionate cancer morbidity ratio study of workers exposed to chlorinated organic solvents in Taiwan. *Ind Health*, 41:77-87.
- Charlier CJ, Albert AI, Zhang L, *et al.* (2004). Polychlorinated biphenyls contamination in women with breast cancer. *Clin Chim Acta*, 347:177-181.
- Chen C, Ma X, Zhong M, Yu Z (2010). Extremely low-frequency electromagnetic fields exposure and females breast cancer risk: a meta-analysis based on 24,338 cases and 60,628 controls. *Breast Cancer Res Treat*, doi:10.1007/s10549-010-0782-6.
- Chen JW, Wang SL, Y HY, *et al.* (2006). Body burden of dioxins and dioxin-like polychlorinated biphenyls in pregnant women residing in a contaminated area. *Chemosphere*, 65: 1667-1677.
- Chen Z-B, An Y, Wang Z, *et al.* (2007). Tobacco-specific carcinogen 4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanone (NNK) activating ERK1/2 MAP kinases and stimulating proliferation of human mammary epithelial cells. *Chem Res Chin Univ*, 23:76-80.
- Chiam K, Tilley W, Butler L, Bianco-Miotto T (2009). The dynamic and static modification of the epigenome by hormones: A role in the developmental origin of hormone related cancers. *Biochim Biophys Acta*, 1795:104-109.
- Chiazze L Jr., Ference LD (1981). Mortality among PVC fabricating employees. *Environ Health Perspect*, 41:137-143.
- CHNSC: California Healthy Nail Salon Collaborative (2010a). Framing a proactive research agenda to advance worker health and safety in the nail salon and cosmetology communities. http://saloncollaborative.files.wordpress.com/2009/03/collab_researchrpt_final.pdf (7/12/2010).
- CHNSC: California Healthy Nail Salon Collaborative (2010b). Do you work in a nail salon? Brochure.
- Choi AL, Levy JL, Dockery DW, *et al.* (2006). Does living near a Superfund site contribute to higher polychlorinated biphenyl (PCB) exposure? *Environ Health Perspect*, 114:1092-1098.
- Chou YY, Huang PC, Lee CC, *et al.* (2009). Phthalate exposure in girls during early puberty. *J Pediatr Endocrinol Metab*, 22:69-77.
- Clavel-Chapelon F and the E3N-EPIC Group (2002). Differential effects of reproductive factors on the risk of pre- and postmenopausal breast cancer. Results from a large cohort of French women. *Br J Cancer*, 86:723-727.
- Clemons MM, Loijens L, Goss P (2000). Breast cancer risk following irradiation for Hodgkin's disease. *Cancer Treat Rev*, 26:291-300.
- Cohn BA, Wolff MA, Cirillo PM, *et al.* (2007). DDT and breast cancer in young women: New data on the significance of age at exposure. *Environ Health Perspect*, 115:1406-1414.
- Colditz GA, Hankinson SE, Hunter DJ, *et al.* (1995). The use of estrogens and progestins and the risk of breast cancer in postmenopausal women. *N Engl J Med*, 332:1589-1593.
- Collier RJ, Miller MA, Hildebrandt JR, *et al.* (1991). Factors affecting insulin-like growth factor-I concentration in bovine milk. *J Dairy Sci*, 74:2095-2911.
- Collier RJ, Miller MA, McLaughlin CL, *et al.* (2008). Effects of recombinant bovine somatotropin (rbST) and season on plasma and milk insulin-like growth factors I (IGF-I) and II (IGF-II) in lactating dairy cows. *Domest Anim Endocrinol*, 35:16-23.
- Collins JJ, Bodner K, Burns CJ, *et al.* (2007). Body mass index and serum chlorinated dibenzo-p-dioxin and dibenzofuran levels. *Chemosphere*, 66:1079-1085.
- Colton T, Greenberg ER, Noller K, *et al.* (1993). Breast cancer in mothers prescribed diethylstilbestrol in pregnancy. Further follow-up. *J Am Med Assoc*, 269:2096-2100.
- Conde J, Silva SN, Azevedo AP, *et al.* (2009). Association of common variants in mismatch repair genes and breast cancer susceptibility: a multigene study. *BioMed Cent*, 9:344.
- Connor K, Ramamoorthy K, Moore M, *et al.* (1997). Hydroxylated polychlorinated biphenyls (PCBs) as estrogens and antiestrogens: Structure-activity relationships. *Toxicol Appl Pharmacol*, 145:111-123.
- Constantinou AI, White BE, Tonetti D, *et al.* (2005). The soy isoflavone daidzein improves the capacity of tamoxifen to prevent mammary tumors. *Eur J Cancer*, 41:647-654.
- Coogan PF, Clapp RW, Newcomb PA, *et al.* (1996). Occupational exposure to 60-hertz magnetic fields and risk of breast cancer in women. *Epidemiology*, 7:459-464.
- Cooper RL, Stoker TE, Tyrey L, *et al.* (2000). Atrazine disrupts the hypothalamic control of pituitary-ovarian function. *Toxicol Sci*, 53:297-307.
- Cos S, Sanchez-Barcelo EJ (2000). Melatonin and mammary pathological growth. *Front Neuroendocrinol*, 21:133-170.
- Costa G, Haus E, Stevens R (2010). Shift work and cancer: considerations on rationale, mechanisms, and epidemiology. *Scand J Environ Health*, 36:163-179.
- Costa LG, Giordano G (2007). Developmental neurotoxicity of polybrominated diphenyl ether (PBDE) flame retardants. *Neurotoxicology*, 28:1047-1067.
- Costa LG, Giordano G, Tagliaferri S, *et al.* (2008). Polybrominated diphenyl ether (PBDE) flame retardants: environmental contamination, human body burden and potential adverse health effects. *ACTA Biomed*, 79:172-183.
- Costantini AS, Gorini G, Consonni D, *et al.* (2009). Exposure to benzene and risk of breast cancer among shoe factory workers in Italy. *Tumori*, 95:8-12.
- Courtney D, Sandau CD, Ayotte P (2000). Analysis of hydroxylated metabolites of PCBs (OH-PCBs) and other chlorinated phenolic compounds in whole blood from Canadian Inuit. *Environ Health Perspect*, 108:611-616.
- CPIC: Cancer Prevention Institute of California (2010). Breast cancer risks in California nail salon workers. www.cpic.org/site/apps/nlnet/content3.aspx?c=skI0L6MKJpE&b=5730937&ct=7811371&no toc=1 (7/12/2010).
- CPSC: Consumer Product Safety Commission (2009). CPSIA: Section 108. Products containing certain phthalates. www.cpsc.gov/about/cpsia/sect108.html (7/12/2010).

Cui Y, Miller AB, Rohan TE (2006). Cigarette smoking and breast cancer risk: update of a prospective cohort study. *Breast Cancer Res Treat*, 100:293.

Curl CL, Fenske RA, Elgethun K (2003). Organophosphorus pesticide exposure of urban and suburban preschool children with organic and conventional diets. *Environ Health Perspect*, 111:377-82.

Curwin BD, Hein MJ, Sanderson WT, et al. (2005). Pesticide contamination inside farm and nonfarm homes. *J Occup Environ Hygiene*, 2:357-367.

D

Daewood S, Cristofanilli M (2007). What progress have we made in managing inflammatory breast cancer? *Oncology*, 21:673-685.

Dai Q, Liu B, Du Y (2009). Meta-analysis of the risk factors of breast cancer concerning reproductive factors and oral contraceptive use. *Front Med China*, doi:10.1007/s11685-009-0080-z.

Dairkee SH, Seok J, Champion S, et al. (2008). Bisphenol A induces a profile of tumor aggressiveness in high-risk cells from breast cancer patients. *Cancer Res*, 68:2076-2080.

Darbre PD, Aljarrah A, Miller WR, et al. (2004). Concentrations of parabens in human breast tumours. *J Appl Toxicol*, 24:5-13.

Darbre PD, Harvey PW (2008). Paraben esters: review of recent studies of endocrine toxicity, absorption, esterase, and discussion of possible health risks. *J Appl Toxicol*, 28:561-578.

Darnerud PO, Eriksen GS, Johannesson T, et al. (2001). Polybrominated diphenyl ethers. *Occurrence Dietary Toxicol Environ Health Perspect*, 109 (Suppl 1):49-68.

Davis DL, Bradlow HL, Wolff M et al. (1993). Medical hypothesis: Xenoestrogens as preventable causes of breast cancer. *Environ Health Perspect*, 101:371-377.

Davis FB, Lin H-Y, Luidens MK, et al. (2009). Similar and shared nongenomic mechanisms of action of estrogen and thyroid hormone. *Immunol Endocr Metab Agents Med Chem*, 9:84-89.

Davis S (2009). Benzene: CEH marketing research report abstract. *Chemical Industries Newsletter*. www.sricsconsulting.com/CEH/Public/Reports/452.0000/ (7/12/2010).

Daxenberger A, Breier BH, Sauerwein H (1998). Increased milk levels of insulin-like growth factor 1 (IGF-1) for the identification of bovine somatotropin (bST) treated cows. *Analyst*, 123: 2429-2435.

DeBruin LS, Josephy PD (2002). Perspectives on the chemical etiology of breast cancer. *Environ Health Perspect*, 110:119-128.

DeBruin LS, Pawliszyn JB, Josephy PD (1999). Detection of monocyclic aromatic amines, possible mammary carcinogens, in human milk. *Chem Res Toxicol*, 12:78-82.

Decastro BR, Korrick SA, Spengler JD, et al. (2006). Estrogenic activity of polychlorinated biphenyls present in human adipose tissue and the environment. *Environ Sci Technol*, 40:2819-2825.

De Hond E, Schoeters G (2006). Endocrine disruptors and human puberty. *Int J Androl*, 29:264-271.

del Valle J, Feliubadalo L, Nadal M et al. (2009). Identification and comprehensive characterization of large genomic rearrangements in the *BRCA1* and *BRCA2* genes. *Breast Cancer Res Treat*, doi:10.1007/s10549-009-0613-9.

Delort L, Kwiatkowski F, Chalabi N, et al. (2007). Risk factors for early age at breast cancer onset: The "COSA Program" population based study. *Anticancer Res*, 27:1087-1094.

de los Santos JF, Buchholz TA (2000). Carcinogenesis of the male breast. *Curr Treat Options Oncol*, 1:221-227.

de Vocht F, Sobala W, Wilczynska U, et al. (2009). Cancer mortality and occupational exposure to aromatic amines and inhalable aerosols in rubber tire manufacturing in Poland. *Cancer Epidemiol*, 33: 94-102. De Wit CA. (2002). An overview of brominated flame retardants in the environment. *Chemosphere*, 46:583-624.

Dewan MZ, Ahmed A, Iwasaki Y, et al. (2006). Stromal cell-derived factor-1 and CXCR4 receptor interaction in tumor growth and metastasis of breast cancer. *Biomed & Pharmacother*, 60:273-276.

Diamanti-Kandarakis E et al. (2009). Endocrine-Disrupting Chemicals: An Endocrine Society Scientific Statement. *Endocr Rev*, 30:293-342.

Dich J, Zahm SH, Hanberg A, et al. (1997). Pesticides (heptachlor) and cancer. *Cancer Causes Control*, 8:420-443.

Dip R, Buterin T, Wenger D, et al. (2008). Genetic reprogramming of human mammary cells by environmental carcinogens released into breast milk. *Chimia*, 62:410-416.

Dip R, Lenz S, Gmuender H, Naegeli H (2009). Pleiotropic combinatorial transcriptomes of human breast cancer cells exposed to mixtures of dietary phytoestrogens. *Food Chem Toxicol*, 47:787-795.

Donovan M, Tiwary CM, Axelrod D, et al. (2007). Personal care products that contain estrogens or

xenoestrogens may increase breast cancer risk. *Med Hypotheses*, 68:756-766.

Dosemeci M, Blair A (1994). Occupational cancer mortality among women employed in the telephone industry. *J Occup Med*, 36:1204-1209.

dos Santos Silva I, Wark PA, McCormack VA et al. (2009). Ovulation-stimulation drugs and cancer risks: a long-term follow-up of a British cohort. *Br J Cancer*, 100:1824-1831.

Draeos ZD (2005). Topical and oral estrogens revisited for antiaging purposes. *Fertil Steril*, 84:291-292.

Drost RM, Jonkers J (2009). Preclinical mouse models for *BRCA1*-associated breast cancer. *Br J Cancer*, 101:1651-1657.

Dumeaux V, Borresen-Dale A-L, Frantzen J-O, et al. (2008). Gene expression analyses in breast cancer epidemiology: The Norwegian women and cancer postgenome cohort study. *Breast Cancer Res*, 10. <http://breast-cancer-research.com/content/10/1/R13> (7/12/2010).

Dumitrescu RG, Cotarla I (2007). Understanding breast cancer risk: where do we stand in 2005? *J Cell Mol Med*, 9:208-221.

Duran-Alvarez JC, Becerril-Bravo E, Castro VS, et al. (2009). The analysis of a group of acidic pharmaceuticals, carbamazepine, and potential endocrine disrupting compounds in wastewater irrigated soils by gas chromatography-mass spectrometry. *Talanta*, 78:1159-1166.

Durando M, Kass L, Piva J, et al. (2007). Prenatal bisphenol A exposure induces preneoplastic lesions in the mammary gland in Wistar rats. *Environ Health Perspect*, 115:592-598.

Durmaz E, Ozmert EN, Erkekoglu P, et al. (2010). Plasma phthalate levels in pubertal gynecomastia. *Pediatrics*, 125:e122-e129.

Dworkin AM, Huang THM, Toland AE (2009). Epigenetic alterations in the breast: implications for breast cancer detection, prognosis and treatment. *Semin Cancer Biol*, 19:165-171.

E

Eaton ML (2004) Ethics analysis applied to Monsanto and the labeling of rBST. In: *Ethics and the Business of Bioscience*, pp. 70-105. Palo Alto, CA: Stanford University Press.

EBCTCG: Early Breast Cancer Trialists' Collaborative Group (2000). Favorable and unfavorable effects on long-term survival of radiotherapy for early breast cancer: An overview of the randomized trials. *Lancet*, 355:1757-1770.

- EC: European Commission (1985). Council Directive 85/469/EEC, Council Directive prohibiting the use in livestock farming of certain substances having hormonal action. Official Journal No L 382, 31 12 1985, pp. 228-231 <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31996L0023:EN:HTML> (7/12/2010).
- EC: European Commission, Health & Consumer Protection Directorate General (2002). Opinion of the scientific committee on veterinary measures relating to public health. Review of previous SCVPH opinions of 30 April 1999 and 3 May 2000 on the potential risks to human health from hormone residues in bovine meat and meat products. http://ec.europa.eu/food/fs/sc/scv/out50_en.pdf (7/12/2010).
- EC: European Commission, Enterprise and Industry Directorate General (2008). Consumer goods: Cosmetics. Consolidated version of cosmetics directive 76/768/EEC. http://ec.europa.eu/enterprise/cosmetics/html/consolidated_dir.htm (7/12/2010).
- El-Gamal H, Bennett RG (2006). Increased breast cancer risk after radiotherapy for acne among women with skin cancer. *J Am Acad Dermatol*, 55:981-989.
- Engel LS, Hill DA, Hoppin JA, *et al.* (2005). Pesticide use and breast cancer risk among farmers' wives in the Agricultural Health Study. *Am J Epidemiol*, 161:121-135.
- Engel SM, Levy MB, Liu Z, Kaplan D, Wolff MS. (2006). Xenobiotic phenols in early pregnancy amniotic fluid. *Reprod Toxicol*, 21:110-2.
- Enoch RR, Stanko JP, Greiner SN, *et al.* (2007). Mammary gland development as a sensitive end point after acute prenatal exposure to an atrazine metabolite mixture in female Long-Evans rats. *Environ Health Perspect*, 115:541-547.
- EP: European Parliament. (2009). MEPs approve pesticide legislation. www.europarl.europa.eu/news/expert/infopress_page/066-45937-012-01-03-911-20090112IPR45936-12-01-2009-2009-false/default_en.htm (7/12/2010).
- EPA: U.S. Environmental Protection Agency (1970). Summary of the Clean Air Act. www.epa.gov/lawsregs/laws/caa.html (7/12/2010).
- EPA: U.S. Environmental Protection Agency (1972). Summary of the Clean Water Act. www.epa.gov/lawsregs/laws/cwa.html (7/12/2010).
- EPA: U.S. Environmental Protection Agency (1974; 1996). Safe Drinking Water Act. www.epa.gov/safewater/sdwa/ (7/12/2010).
- EPA: U.S. Environmental Protection Agency (1998). Chemical hazard data availability study. www.epa.gov/hpv/pubs/general/hazchem.pdf (7/12/2010).
- EPA: U.S. Environmental Protection Agency (2003). Health assessment of 1,3-Butadiene. <http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=54499> (7/12/2010).
- EPA: U.S. Environmental Protection Agency (2005a). Understanding radiation: Gamma rays. www.epa.gov/radiation/understand/gamma.html (7/12/2010).
- EPA: U.S. Environmental Protection Agency (2005b). EPA Office of Compliance sector notebook project. Profile of the rubber and plastics industry, 2nd Edition. www.epa.gov/compliance/resources/publications/assistance/sectors/notebooks/rubplasn.pdf (7/12/2010).
- EPA: U.S. Environmental Protection Agency (2007a). Overview: Office of pollution prevention and toxics programs. www.epa.gov/oppt/pubs/oppt101c2.pdf (7/12/2010).
- EPA: U.S. Environmental Protection Agency (2007b). Protecting the health of nail salon workers. www.epa.gov/dfe/pubs/projects/salon/nailsalonguide.pdf (7/12/2010).
- EPA: U.S. Environmental Protection Agency (2008a). Atrazine: Third report of the hazard identification assessment review committee. Office of Pesticide Programs. www.epa.gov/pesticides/factsheets/atrazine_background.htm (7/12/2010).
- EPA: U.S. Environmental Protection Agency (2008b). Bisphenol a. (CASRN 80-05-7). Integrated risk information system (IRIS). www.epa.gov/iris/subst/0356.htm (7/12/2010).
- EPA: U.S. Environmental Protection Agency (2008c). Data requirements for pesticide registration. <http://ecfr.gpoaccess.gov/cgi/t/text/text-idx?c=ecfr&sid=013b05537f6069487ae3f2252ae1d5a0&rgn=div5&view=text&node=40:23.0.1.1.9&sidno=40#40:23.0.1.1.9.6.1.1> (7/12/2010).
- EPA: U.S. Environmental Protection Agency (2009a). Common wastes and materials: Plastics. www.epa.gov/osw/conservation/materials/plastics.htm (7/12/2010).
- EPA: U.S. Environmental Protection Agency (2009b). Rulemaking underway related to disclosure of all pesticide ingredients. www.epa.gov/oppr001/inerts/ (7/12/2010).
- EPA: U.S. Environmental Protection Agency (2010a). Dioxins and furans. www.epa.gov/pbt/pubs/dioxins.htm (7/12/2010).
- EPA: U.S. Environmental Protection Agency (2010b). Label Review Manual. Chapter 3: General labeling requirements. www.epa.gov/oppead1/labeling/lrm/chap-03.htm (7/12/2010).
- EPA: U.S. Environmental Protection Agency (2010c). Endocrine disruptor screening program (EDSP). www.epa.gov/endo/ (7/12/2010).
- EPA: U.S. Environmental Protection Agency (2010d). What is the TSCA chemical substance inventory? www.epa.gov/opptintr/newchems/pubs/inventory.htm (7/12/2010).
- EPA: U.S. Environmental Protection Agency (2010e). Essential principles for reform of chemicals management Legislation. www.epa.gov/oppt/existingchemicals/pubs/principles.html (7/12/2010).
- Erren TC (2001). A meta-analysis of epidemiologic studies of electric and magnetic fields and breast cancer in women and men. *Bioelectromagnetics Suppl*, 5:S105-119.
- Eskenazi B, Warner M, Marks AR, *et al.* (2005). Serum dioxin concentrations and age at menopause. *Environ Health Perspect*, 113:858-862.
- Euling SY, Herman-Giddens ME, Lee PA, *et al.* (2008). Examination of U.S. puberty-timing data from 1940 to 1994 for secular trends: Panel findings. *Pediatrics*, 122:1:S172-S191.
- EWG: Environmental Working Group (2004). Exposures add up: survey results. www.cosmetic-sdatabase.com/research/exposures.php (7/12/2010).
- EWG: Environmental Working Group (2005). Body burden 2: The pollution in newborns. www.ewg.org/reports/bodyburden2 (7/12/2010).
- EWG: Environmental Working Group (2009). Pollution in minority newborns. www.ewg.org/minoritycordblood/home (7/12/2010).
- EWG: Environmental Working Group (2010). Skin Deep: Cosmetic safety database. www.cosmeticsdatabase.com/ (7/12/2010).
- Fan WQ, Yanase T, Morinaga H, *et al.* (2007). Atrazine-induced aromatase expression in SF-1 dependent: Implications for endocrine disruption in wildlife and reproductive cancers in humans. *Environ Health Rep*, 115:720-727.
- Fang H, Tong W, Branham WS, *et al.* (2003). Study of 202 natural, synthetic, and environmental chemicals for binding to the androgen receptor. *Chem Res Toxicol*, 16:1338-1358.
- FDA: U.S. Food and Drug Administration, Partnerships and Collaborations (1976). MOU 225-76-2003: Memorandum of understanding between the U.S. Consumer Product Safety Commission and the U.S. Food and Drug Administration. www.fda.gov/AboutFDA/PartnershipsCollaborations/MemorandaofUnderstandingMOUs/DomesticMOUs/ucm116207.htm (7/12/2010).
- FDA: U.S. Food and Drug Administration, Center for Food Safety and Applied Nutrition Organization (1994). Voluntary labeling of milk and milk products from cows that have not been treated with recombinant bovine somatotropin. Interim Guid

- ance. www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/FoodLabelingNutrition/ucm059036.htm (7/12/2010).
- FDA: U.S. Food and Drug Administration (2000). Ingredients prohibited & restricted by FDA regulations. www.fda.gov/Cosmetics/ProductandIngredientSafety/SelectedCosmeticIngredients/ucm127406.htm (7/12/2010).
- FDA: U.S. Food and Drug Administration, Office of Food Additive Safety (2007). CEDI/ADI database. www.fda.gov/Food/FoodIngredientsPackaging/FoodContactSubstancesFCS/CEDIADIDatabase/default.htm (7/12/2010).
- FDA: U.S. Food and Drug Administration. (2008). Draft assessment of bisphenol A for use in food contact applications. www.fda.gov/ohrms/dockets/ac/08/briefing/2008-0038b1_01_02_fda%20bpa%20draft%20assessment.pdf (7/12/2010).
- FDA: U.S. Food and Drug Administration (2009). Safety assessment of BPA in medical products. www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/ScienceBoardtotheFoodandDrugAdministration/UCM176835.pdf (7/12/2010).
- FDA: U.S. Food and Drug Administration (2010a). Cosmetics Q&A. www.fda.gov/Cosmetics/ResourcesForYou/Consumers/CosmeticsQA/default.htm (7/12/2010).
- FDA: U.S. Food and Drug Administration, Center for Veterinary Medicine (2010b). FDA approved animal drug products. www.accessdata.fda.gov/scripts/animaldrugsatfda/index.cfm?gb=2 (7/12/2010).
- FDA: U.S. Food and Drug Administration (2010c). Inventory of effective food contact substance (FCS) notifications. www.cfsan.fda.gov/~dms/opa-fcn.html (7/12/2010).
- Fedrowitz M, Kamino K, Loscher W (2004). Significant differences in the effects of magnetic field exposure on 7,12-dimethylbenz(a)anthracene-induced mammary carcinogenesis in two substrains of Sprague-Dawley rats. *Cancer Res*, 64:243-251.
- Fenton SE (2006). Endocrine-disrupting compounds and mammary gland development: Early exposure and later life consequences. *Endocrinology*, 147:S18-S24.
- Fenton SE, Hamm JT, Birnbaum LS, *et al.* (2002). Persistent abnormalities in the rat mammary gland following gestational and lactational exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). *Toxicol Sci*, 67:63-74.
- Fernandez MF, Molina-Molina JM, Lopez-Espinosa M-J, *et al.* (2007). Biomonitoring of environmental estrogens in human tissues. *Int J Hyg Environ Health*, 210:429-432.
- Feychting M, Forssen U, Rutqvist LE, *et al.* (1998). Magnetic fields and breast cancer in Swedish adults residing near high-voltage power lines. *Epidemiology*, 9:392-397.
- Figueiredo JC, Haile RW, Bernstein L, *et al.* (2010). Oral contraceptives and postmenopausal hormones and risk of contralateral breast cancer among *BRCA1* and *BRCA2* mutation carriers and noncarriers: The WECARE study. *Breast Cancer Res Treat*, 120:175-183.
- Flynn-Evans EE, Stevens RG, Tabandeh H, Schernhammer ES, Lockley SW (2009). Total visual blindness is protective against breast cancer. *Cancer Causes Control*, 20:1753-1756.
- Foster PM (2005). Disruption of reproductive development in male rat offspring following in utero exposure to phthalate esters. *Int J Androl*, 29:140-147.
- Foster WG, Younglai EV, Boutross-Tadross O, *et al.* (2004). Mammary gland morphology in Sprague-Dawley rats following treatment with an organochlorine mixture *in utero* and neonatal genistein. *Toxicol Sci*, 77: 91-100.
- Frederiksen M, Thomsen C, Froshaug M, *et al.* (2010). Polybrominated diphenyl ethers in paired samples of maternal and umbilical cord blood plasma and associations with house dust in a Danish cohort. *Int J Hygiene Environ Health*, doi:10.1016/j.ijheh.2010.04.008.
- Fromme H, Diemer J, Dietrich S, *et al.* (2008). Chemical and morphological properties of particulate matter (PM 10, PM 2.5) in school classrooms and outdoor air. *Atmospheric Environ*, 42:6597-6605.
- Gaffield ME, Culwell KR, Ravi A (2009). Oral contraceptives and family history of breast cancer. *Contraception*, 80:372-380.
- Gammon MD, Santella RM (2008). PAH, genetic susceptibility and breast cancer risk: an update from the Long Island breast cancer study project. *Eur J Cancer*, 44:636-640.
- Gammon MD, Santella RM, Neugut AI, *et al.* (2002). Environmental toxins and breast cancer on Long Island. I. Polycyclic aromatic hydrocarbon DNA adducts. *Cancer Epidemiol Biomarkers Prev*, 11:677-685.
- Garvin S, Ollinger K, Dabrosin C (2006). Resveratrol induces apoptosis and inhibits angiogenesis in human breast cancer xenografts *in vivo*. *Sci Direct Cancer Lett*, 231:113-122.
- Gauthier E, Paoletti X, Clavel-Chapelon F (2004). Breast cancer risk associated with being treated for infertility: results from the French e3n cohort study. *Hum Reprod*, 19:2216-2221.
- Gery S, Virk RK, Chumakov K, Yu A, Koeffler HP (2007). The clock gene *Per2* links the circadian system to the estrogen receptor. *Oncogene*, 26:7916-7920.
- Ghoussaini M, Pharoah PDP (2009). Polygenic susceptibility to breast cancer: current state-of-the-art. *Future Oncol*, 5:689-701.
- Gierthy JF, Arcaro KE, Floyd M (1997). Assessment of PCB estrogenicity in a human breast cancer cell line. *Chemosphere*, 34:1495-1505.
- Ginsberg GL, Asgharian B, Kimbell JS, Ultman JS, Jarabek AM (2008). Modeling approaches for estimating the dosimetry of inhaled toxicants in children. *J Toxicol Environ Health*, 71:166-195.
- Girgert R, Emons, G Hanf V, Grundker C (2009). Exposure of MCF-7 breast cancer cells to electromagnetic fields up-regulates the plasminogen activator system. *Int J Gynecol Cancer*, 19: 334-338.
- Gitlitz J, Franklin P (2007). Water, Water Everywhere: The Growth of Non-Carbonated Beverages in the United States. Container Recycling Institute. www.container-recycling.org/assets/pdfs/reports/2007-waterwater.pdf (7/12/2010).
- Giusti RM, Iwamoto K, Hatch EE. (1995). Diethylstilbestrol revisited: A review of the long-term health effects. *Annals Intern Med* 122:778-788.
- Glass AG, Lacey JV, Carreon JD, *et al.* (2007). Breast cancer incidence, 1980-2006: Combined roles of menopausal hormone therapy, screening mammography, and estrogen receptor status. *J Natl Cancer Inst* 99:1152-1161.
- Gofman J W (1996). *Preventing Breast Cancer: The Story of a Major, Proven, Preventable Cause of this Disease*, 2nd ed.. San Francisco: CNR Book Division, Committee for Nuclear Responsibility.
- Gofman JW (1999). *Radiation from Medical Procedures in the Pathogenesis of Cancer and Ischemic Heart Disease: Dose-response studies with Physicians per 100,000 Population*. San Francisco: CNR Book Division, Committee for Nuclear Responsibility.
- Goldberg Z, Lehnert BE (2003). Radiation-induced effects in unirradiated cells: A review and implications in cancer. *Int J Oncol*, 21:337-349.
- Golubicic I, Borojevic N, Pavlovic T (2008). Risk factors for breast cancer: is ionizing radiation among them? *J BUON*, 13: 487-494.
- Gooderham NJ, Creton S, Lauber SN, *et al.* (2006). Mechanisms of action of the carcinogenic heterocyclic amine PhIP. *Toxicol Lett*, 168:269-277.

- Goodman MT, Shvetsov YB, Wilkens LR, *et al.* (2009). Urinary phytoestrogen excretion and postmenopausal breast cancer risk: the multiethnic cohort study. *Cancer Prev Res*, 2:887-894.
- Gotzsche P, Hartling O, Nielsen M, *et al.* (2009). Breast screening: the facts or maybe not. *Br Med J*, 338: b86.
- Goyal R, Khare M (2009). Indoor-outdoor concentrations of RSPM in classroom of a naturally ventilated school building near an urban traffic roadway. *Atmospheric Environ*, 43:6026-6038.
- Gram IT, Braaten T, Terry PD, *et al.* (2005). Breast cancer among women who started smoking as teenagers. *Cancer Epidemiol Biomarkers Prev*, 14:61-66.
- Graves BA (2008). Integrative literature review: a review of literature related to geographical information systems, healthcare access, and health outcomes. *Perspect Health Info Manag*, 5:1-13.
- Gray LE, Ryan B, Hotchkiss AK, Crofton KM. (2010). Rebuttal of "Flawed experimental design reveals the need for guidelines requiring appropriate positive controls in endocrine disruption research" by vom Saal. *Toxicol Sci*, 115:614-620.
- Guibout C, Adjadj E, Rubino C, *et al.* (2005). Malignant breast tumors after radiotherapy for a first cancer during childhood. *J Clin Oncol*, 23:197-204.
- Guillette LJ, Edwards TM (2008). Environmental influences on fertility: can we learn lessons from studies of wildlife? *Am Soc Reprod Med*, 89:21-24.
- Gwinn MR, Whipkey DL, Tennant LB, Weston A (2007). Gene expression profiling of di-n-butyl phthalate in normal human mammary epithelial cells. *J Environ Pathol Toxicol Oncol*, 26:51-61.
- Hagmar L, Wallin E, Vessby B, *et al.* (2006). Intra-individual variations and time trends 1991-2001 in human serum levels of PCB, DDE, and hexachlorobenzene. *Chemosphere*, 64:1507-1513.
- Haile RW, Thomas DC, McGuire V, *et al.* (2006). *BRCA1* and *BRCA2* mutation carriers, oral contraceptive use and breast cancer before age 50. *Cancer Epidemiol Biomarkers Prev*, 15:1863-1870.
- Hanaoka T, Yamamoto S, Sobue T *et al.* (2005). Active and passive smoking and breast cancer risk in middle-aged Japanese women. *Int J Cancer*, 114:317-322.
- Hance KW, Anderson WF, Devesa SS, Young HA, Levine PH (2005). Trends in inflammatory breast carcinoma incidence and survival: The Surveillance, Epidemiology, and End Results Program at the National Cancer Institute. *J Nat Cancer Inst*, 95:966-975.
- Hankinson S, Willett WC, Colditz GA, *et al.* (1998). Circulating concentrations of insulin-like growth factor 1 and risk of breast cancer. *Lancet*, 351:1393-1396.
- Hanrahan C (2000). CRS Report for Congress: RS20142: The European Union's ban on hormone-treated meat. www.ncseonline.org/NLE/CRSReports/Agriculture/ag-63.cfm (7/12/2010).
- Hansen J (1999). Breast cancer risk among relatively young women employed in solvent-using industries. *Am J Ind Med*, 36:43-47.
- Hansen J (2000). Elevated risk for male breast cancer after occupational exposure to gasoline and vehicular combustion products. *Am J Ind Med*, 37:349-352.
- Hatakeyama M, Matsumura F (1999). Correlation between the activation of Neu tyrosine kinase and promotion of foci formation induced by selected organochlorine compounds in the MCF-7 model system. *J Biochem Mol Toxicol*, 13:296-302.
- Hayden CG, Roberts MS, Benson HA (1997). Systemic absorption of sunscreen after topical application. *Lancet*, 350:853-864.
- Hayes T, Haston K, Tsui M, *et al.* (2003). Atrazine-induced hermaphroditism at 0.1 ppb in American leopard frogs (*Rana pipiens*): Laboratory and field evidence. *Environ Health Perspect*, 111:568-575.
- Health Canada (2008). Health Risk Assessment of Bisphenol A from food packaging applications. Bureau of Chemical Safety, Food Directorate, Health Products and Food Branch.
- HCHW: Healthy Child, Healthy World. Chemical encyclopedia: Polybrominated diphenyl ethers (PBDEs). http://healthychild.org/issues/chemical-pop/polybrominated_diphenyl_ETHERS/ (7/12/2010).
- HCWH: Health Care Without Harm. (2002a). Alternatives to polyvinyl chloride (PVC) and di(2-Ethylhexyl) phthalate (DEHP) medical devices. From Going green: A resource kit for pollution prevention in health care. www.noharm.org/lib/downloads/pvc/Alternatives_to_PVC_DEHP.pdf (7/12/2010).
- HCWH: Health Care Without Harm. (2002b). Dioxin, PVC, and health care institutions. From Going green: A resource kit for pollution prevention in health care. www.noharm.org/lib/downloads/pvc/Dioxin_PVC_Health_Care.pdf (7/12/2010).
- Hecht A, Lee E. (2003). How to fight indoor air pollution. Penton Media. http://nreionline.com/commentary/nmhcr/real_estate_fight_indoor_air/ (7/12/2010).
- Heiss G, Wallace R, Anderson G, *et al.* (2008). Health risks and benefits 3 years after stopping randomized treatment with estrogen and progestin. *J Am Med Assoc*, 299:1036-1045.
- Helferich WG, Andrade JE, Hoagland MS (2008). Phytoestrogens and breast cancer: a complex story. *Inflammopharmacol*, 16:219-226.
- Hemminki K, Li X (2002). Cancer risks in second-generation immigrants to Sweden. *Int J Cancer*, 99:229-237.
- Heneweer M, Muusse M, Dingemans M, *et al.* (2005). Co-culture of primary human mammary fibroblasts and MCF-7 cells as an in vitro breast cancer model. *Toxicol Sci*, 83:257-263.
- Herbst AL, Scully RE (1970). Adenocarcinoma of the vagina in adolescence. A report of seven cases including six clear cell carcinomas (so-called mesonephromas). *Cancer*, 25:745-757.
- Herbst AL, Ulfelder H, Poskanzer DC (1971). Adenocarcinoma of the vagina: Association of maternal stilbestrol therapy with tumor appearance in young women. *New England J Med*, 284:878-881.
- Heyes GJ, Mill AJ, Charles MW (2009). Mammography: oncogenecity at low doses. *J Radiol Protect*, 29:A123-A132.
- Hiatt RA, Haslam SZ, Osuch J (2009). The Breast Cancer and the Environment Research Centers: Transdisciplinary research on the role of the environment in breast cancer etiology. *Environ Health Perspect*, 117:1814-1822.
- Hilakivi-Clarke L, de Assis S (2006). Fetal origins of breast cancer. *Trends Endocrinol Metab*, 17:340-348.
- Hildreth NG, Shore RE, Dvoretzky PM (1989). The risk of breast cancer after irradiation of the thymus in infancy. *New England J Med*, 1989:1281-1284.
- Hines EP, Calafat AM, Silva MJ, *et al.* (2009). Concentrations of phthalate metabolites in milk, urine, saliva, and serum of lactating North Carolina women. *Environ Health Perspect*, 117:86-92.
- Hines CJ, Nilsen Hopf NB, Deddens JA, *et al.* (2009). Urinary phthalate metabolite concentrations among workers in selected industries: A pilot biomonitoring study. *Ann Occup Hyg*, 53:1-17.
- Hoffman G (2009). A perspective on the scientific, philosophical, and policy dimensions of hormesis. *Dose-Response*, 7:1-51.
- Holmberg L, Anderson H (2004). HABITS (hormonal replacement therapy after breast cancer—is it safe?) trial stopped. *Lancet*, 363:453-455.
- Homburg R, Insler V (2002). Ovulation induction in perspective. *Hum Reprod Update*, 8:449-462.

- Honma N, Takubo K, Sawabe M, *et al.* (2007). Estrogen-metabolizing enzymes in breast cancers from women over the age of 80 years. *J Clin Endocrinol Metab*, 607-613.
- Hoening M, Aleman B, Hauptmann M, *et al.* (2007). Roles of radiotherapy and chemotherapy in the development of contralateral breast cancer. *J Clin Oncol*, 10.1200/JCO.2007.16.0192.
- Horner MJ, Ries LAG, Krapcho M, *et al.* (2009). *SEER Cancer Statistics Review, 1975-2006*. National Cancer Institute. Bethesda, MD. http://seer.cancer.gov/csr/1975_2006/, based on November 2008 SEER data submission, posted to the SEER web site, 2009.
- Hortobagyi GN, de la Garza Salazar J, Pritchard K, *et al.* (2008). The global breast cancer burden: variations in epidemiology and survival. *Clin Breast Cancer*, 6:391-401.
- Horwich A, Swerdlow AJ (2004). Secondary primary breast cancer after Hodgkin's disease. *Br J Cancer*, 90:294-298.
- Houle CD, Ton TV, Clayton N, *et al.* (2006). Frequent p53 and H-ras mutations in benzene- and ethylene oxide-induced mammary gland carcinomas from B6C3F1 mice. *Toxicol Pathol*, 34:752-762.
- Howe GR, McLaughlin J (1996). Breast cancer mortality between 1950 and 1987 after exposure to fractionated moderate-dose-rate ionizing radiation in the Canadian fluoroscopy cohort study and a comparison with breast cancer mortality in the atomic bomb survivors study. *Radiat Res*, 145:694-707.
- Hoyer AP, Grandjean P, Jorgensen T, *et al.* (1998). Organochlorine exposure and risk of breast cancer. *Lancet*, 352:1816-1820.
- Hoyer AP, Jorgensen T, Brock JW, *et al.* (2000). Organochlorine exposure and breast cancer survival. *J Clin Epidemiol*, 53:323-330.
- Hoyer AP, Gerdes AM, Jorgensen T, *et al.* (2002). Organochlorines, p53 mutations in relation to breast cancer risk and survival. A Danish cohort-nested case-controls study. *Breast Cancer Res Treat*, 71:59-65.
- Hsieh CC, Trichopoulos D, Katsouyanni K, *et al.* (1990). Age at menarche, age at menopause, height and obesity as risk factors for breast cancer: Associations and interactions in an international case-control study. *Int J Cancer*, 46:796-800.
- Hua WY, Bennett ER, Maio X-S, *et al.* (2006). Seasonality effects on pharmaceuticals and S-triazine herbicides in wastewater effluent and surface water from the Canadian side of the upper Detroit River. *Environ Toxicol Chem*, 25:2356-2365.
- Huang J, Mackillop WJ (2001). Increased risk of soft tissue sarcoma after radiotherapy in women with breast carcinoma. *Cancer*, 92:532-536.
- Huff JE, Haseman JK, DeMarini DM, *et al.* (1989). Multiple-site carcinogenicity of benzene in Fisher 344 rats and B6C3F1 mice. *Environ Health Perspect*, 82:125-163.
- Hunter L, Gadbury GL, Huang Y (2008). Atrazine exposure and breast cancer incidence: an ecologic study of Missouri counties. *Toxicol Environ Chem*, 90:367-376.
- Hwang H-M, Park E-K, Young TM, Hammock BD (2008). Occurrence of endocrine-disrupting chemicals in indoor dust. *Sci Total Environ*, 404:26-35.
- IARC: International Agency for Research on Cancer (1987a). *IARC Monogr*, Suppl 7: Oestrogens, steroidal. www.inchem.org/documents/iarc/suppl7/oestrogenssteroidal.html (7/12/2010).
- IARC: International Agency for Research on Cancer (1987b). *IARC Monogr*, Suppl 7: Benzene. www.inchem.org/documents/iarc/suppl7/benzene.html (7/12/2010).
- IARC: International Agency for Research on Cancer (1994). *IARC Monogr*, on the evaluation of carcinogenic risks to humans. Summaries and Evaluations: Ethylene Oxide. Volume 64. www.inchem.org/documents/iarc/vol60/m60-02.html (7/12/2010).
- IARC: International Agency for Research on Cancer (1997). *IARC Monogr*, on the evaluation of carcinogenic risks to humans. Polychlorinated dibenzo-dioxins and polychlorinated dibenzofurans. Volume 69. <http://monographs.iarc.fr/ENG/Monographs/vol69/volume69.pdf> (7/12/2010).
- IARC: International Agency for Research on Cancer (1998). *IARC Monogr*, Summary and evaluation, Suppl 7: Vinyl chloride. www.inchem.org/documents/iarc/suppl7/vinylchloride.html (7/12/2010).
- IARC: International Agency for Research on Cancer (1999a). *IARC Monogr*, on the evaluation of carcinogenic risks to humans. Volume 71. www.inchem.org/documents/iarc/vol71/002-butadiene.html (7/12/2010).
- IARC: International Agency for Research on Cancer (1999b). *IARC Monogr*, on the evaluation of carcinogenic risks to humans. Hormonal contraception and postmenopausal hormonal therapy. Volume 72. <http://monographs.iarc.fr/ENG/Monographs/vol72/mono72.pdf> (7/12/2010).
- IARC: International Agency for Research on Cancer (2009). *IARC Monogr*, on the evaluation of carcinogenic risks to humans. Complete list of agents evaluated and their classification. monographs.iarc.fr/ENG/Classification/index.php (7/12/2010).
- Ibarluzea JM, Fernandez MF, Santa-Marina L, *et al.* (2004). Breast cancer and the combined effects of environmental estrogens. *Cancer Causes Control*, 15:591-601.
- IFRA: International Fragrance Association (IFRA). IFRA survey: Transparency list. www.ifraorg.org/public/index_ps/parentid/1/childid/15/leafid/111 (7/12/2010).
- Ikezuki Y, Tsutsumi O, Takai Y, *et al.* (2002). Determination of bisphenol A concentrations in human biological fluids reveals significant early prenatal exposure. *Hum Reprod*, 17:2839-2841.
- Imaoka T, Nishimura M, Teramoto, *et al.* (2005). Cooperative induction of rat mammary cancer by radiation and 1-methyl-1-nitrosourea via the oncogenic pathways involving c-Myc activation and H-ras mutation. *Int J Cancer*, 115:187-193.
- Imaoka T, Nishimura M, Iizuka D, *et al.* (2009). Radiation-induced mammary carcinogenesis, in rodent models: what's different from chemical carcinogenesis? *J Radiat Res*, 50:281-293.
- Infante PF, Pesak J (1994). A historical perspective of some occupationally related diseases of women. *J Occup Med*, 36:826-831.
- Ionescu JG, Novotny J, Stejskal V, *et al.* (2006). Increased levels of transition metals in breast cancer tissue. *Neuroendocrinology Lett*, 27 (Suppl 1):36-39.
- Iso T, Watanabe T, Iwamoto T, *et al.* (2006). DNA damage caused by bisphenol A and estradiol through estrogenic activity. *Biol Pharm Bull*, 29:206-210.
- Jacobs M, Clapp R (2009a). Cancer Air and Water Pollutants: A Need for Action. The Collaborative on Health and the Environment. http://www.healthandenvironment.org/cancerpanel/che_resources (7/27/10).
- Jacobs M, Clapp R (2009b). Agriculture and Cancer: A Need for Action. The Collaborative on Health and the Environment. http://www.healthandenvironment.org/cancerpanel/che_resources. (7/27/10).
- Janjua NR, Frederiksen H, Skakkebaek NE, *et al.* (2008). Urinary excretion of phthalates and paraben after repeated whole-body topical application in humans. *Int J Androl*, 31:118-130.

- Jansen-Van Der Weide M (2009). Mammography screening and radiation-induced breast cancer among women with a familial or genetic predisposition: a metaanalysis. Published abstract of presentation at the 95th annual meeting of the Radiological Society of North America, Chicago.
- Jatoi I, Anderson WF, Rao SR, *et al.* (2005). Breast cancer trends among black and white women in the United States. *J Clin Oncol*, 23:7836-7841.
- Jayapal M, Bhattacharjee RN, Melendez A, Hande MP (2010). Environmental toxicogenomics: a post-genomic approach to analyzing biological responses to environmental toxins. *Int J Biochem Cell Biol*, 42:230-240.
- Jefferson WN, Doerge D, Padilla-Banks E, *et al.* (2009). Oral exposure to genistin, the glycosylated form of genistein, during neonatal life adversely affects the female reproductive system. *Environ Health Perspect*, 117:1883-1889.
- Jemal A, Siegel R, Ward E, *et al.* (2009). Cancer statistics, 2009. *Cancer*, 59:225-249.
- Jenkins S, Raghuraman N, Eltoum I, *et al.* (2009). Oral exposure to bisphenol-A increases dimethylbenzanthracene-induced mammary cancer in rats. *Environ Health Perspect*, 117:910-915.
- Jenkins S, Rowell C, Wang J, *et al.* (2007). Prenatal TCDD exposure predisposes for mammary cancer in rats. *Reprod Toxicol*, 23:191-196.
- Jernstrom H, Chu W, Vesprini D, *et al.* (2001). Genetic factors related to racial variation in plasma levels of insulin-like growth factor-1: Implications for premenopausal breast cancer risk. *Molec Genetics Metab*, 72:144-154.
- Jiang JT, Ma L, Yuan L, *et al.* (2007). Study on developmental abnormalities in hypospadiac male rats induced by maternal exposure to di-n-butyl phthalate (DBP). *Toxicol*, 232:286-293.
- Jobling S, Reynolds T, White R, *et al.* (1995). A variety of environmentally persistent chemicals, including some phthalate plasticizers, are weakly estrogenic. *Environ Health Perspect*, 103:582-587.
- John EM, Phipps AI, Koo J (2005). Migration history, acculturation, and breast cancer risk in Hispanic women. *Cancer Epidemiol Biomarkers Prev*, 14:2905-2913.
- Johnson KC, Hu J, Mao Y (2000). Passive and active smoking and breast cancer risk in Canada, 1994-1997, The Canadian Cancer Registries Epidemiology Research Group. *Cancer Causes Control*, 11:211-221.
- Johnson MD, Kenney N, Stoica A, *et al.* (2003). Cadmium mimics the in vivo effects of estrogen in the uterus and mammary gland. *Nat Med*, 9:1081-1084.
- Jones BA, Kasl SV, Howe CL, *et al.* (2004). African American/White differences in breast cancer carcinoma. *Cancer*, 101: 1293-1301.
- JPPPP: Janitorial Products Pollution Prevention Project (2002). Southern California janitorial chemicals safety project. www.westp2net.org/Janitorial/jp4.cfm (7/12/2010).
- Kamel F, Hoppin JA (2004). Association of pesticide exposure with neurologic dysfunction and disease. *Environ Health Perspect*, 112:950-958.
- Kang SC, Lee BM (2005). DNA methylation of estrogen receptor α gene by phthalates. *J Toxicol Environ Health*, 68:1995-2003.
- Kato K, Silva MJ, Reidy JA, *et al.* (2003). Mono-(2-ethyl-5-hydroxyhexyl) phthalate and mono-(2-ethyl-5-oxohexyl) phthalate as biomarkers for human exposure assessment to di-(2-ethylhexyl) phthalate. *Environ Health Perspect*, 112:327-330.
- Kaupilla A, Kyronen P, Hinkula M, Pukkala E (2009). Birth intervals and breast cancer risk. *Br J Cancer*, 101:1213-1217.
- Kemp MQ, Liu W, Thorne PA, *et al.* (2006). Induction of the transferring receptor gene by benzo[a]pyrene in breast cancer MCF-7 cells: Potential as a biomarker of PAH exposure. *Environ Mol Mutagenesis*, 47:518-526.
- Kettles MA, Browning SR, Prince TS, *et al.* (1997). Triazine herbicide exposure and breast cancer incidence: An ecological study of Kentucky counties. *Environ Health Perspect*, 105:1222-1227.
- Khosrokhavar R, Rahimifard N, Shoeibi S, *et al.* (2009). Effects of zearalenone and α -zearalenol in comparison with Raloxifene on T47D cells. *Toxicol Mech Methods*, 19:246-250.
- Kim IS, Baek SH (2010). Mouse models for breast cancer metastasis. *Biochem Biophys Res Commun*, 394:443-447.
- Kim IY, Han SY, Moon A (2004a). Phthalates inhibit tamoxifen-induced apoptosis in MCF-7 human breast cancer cells. *J Toxicol Environ Health*, 67:2025-2035.
- Kim JB, O'Hare MJ, Stein R (2004b). Models of breast cancer: is merging human and animal models the future? *Breast Cancer Res*, 6:22-30.
- King MC, Marks JH, Mandell JB (2003). Breast and ovarian cancer risks due to inherited mutations in *BRCA1* and *BRCA2*. *Science*, 302:643-46.
- Klann A, Levy G, Lutz I, *et al.* (2005). Estrogen-like effects of ultraviolet screen 3-(4-methylbenzylidene)-camphor (Eusolex 6300) on cell proliferation and gene induction in mammalian and amphibian cells. *Environ Res*, 97:274-281.
- Kleinerman RA (2006). Cancer risks following diagnostic and therapeutic radiation exposure in children. *Ped Radiol*, 36 (Suppl. 2):121-125.
- Klip H, Burger CW, Kenemans P, van Leeuwen FE (2000). Cancer risk associated with subfertility and ovulation induction: A review. *Cancer Causes Control*, 11:319-344.
- Kliukiene J, Tynes T, Anderson A (2003). Follow-up of radio and telegraph operators with exposure to electromagnetic fields and risk of breast cancer. *Eur J Cancer Prev*, 12:301-307.
- Kliukiene J, Tynes T, Andersen A (2004). Residential and occupational exposures to 50-Hz magnetic fields and breast cancer in women: A population-based study. *Am J Epidemiol*, 159:852-861.
- Kloog I, Haim A, Stevens RG, Barchana M, Portnov BA (2008). *Chronobiol Int*, 25:65-81.
- Kolstad, H.A. (2008). Nightshift work and risk of breast cancer and other cancers: A critical review of the epidemiologic evidence. *Scand J Work Environ Health*, 34:5-22.
- Korde LA, Wu AH, Fears T, *et al.* (2009). Childhood soy intake and breast cancer risk in Asian American women. *Cancer Epidemiol Biomarkers Prev*, 18:1-10.
- Koppe JG, Bartonova A, Bolte G, *et al.* (2006). Exposure to multiple environmental agents and their effect. *Acta Paediatr*, 95 (Suppl 453):106-113.
- Kortenkamp A (2006). Breast cancer, oestrogens and environmental pollutants: a re-evaluation from a mixture perspective. *Int J Androl*, 29:193-198.
- Kotsopoulos J, Librach CL, Lubinski J, *et al.* (2008). Infertility, treatment of infertility, and the risk of breast cancer among women with *BRCA1* and *BRCA2* mutations: a case-control study. *Cancer Causes Control*, 19:1111-1119.
- Kotzias D, Geiss O, Tirendi S, *et al.* (2009). Exposure to multiple air contaminants in public buildings, schools, and kindergartens — the European indoor air monitoring and exposure assessment (airmex) study. *Fresenius Environ Bull*, 18:670-681.
- Krieger N, Löwy I, Aronowitz R, *et al.* (2005). Hormone replacement therapy, cancer, controversies, and women's health: historical, epidemiological, biological, clinical, and advocacy perspectives. *J Epidemiol Community Health*, 59:740-748.
- Kruk J, Aboul-Enein HY (2006). Environmental exposure, and other behavioral risk factors in breast cancer. *Curr Cancer Ther Rev*, 2: 3-21.

- Kulkarni PS, Crespo JG, Afonso CAM (2008). Dioxins sources and current remediation technologies: A review. *Environ Int*, 34:139-153.
- Kumle M, Weiderpass E, Braaten T, *et al.* (2002). Use of oral contraceptives and breast cancer risk: The Norwegian-Swedish Women's Lifestyle and Health Cohort Study. *Cancer Epidemiol Biomarkers Prev*, 11:1375-1381.
- Kuruto-Niwa R, Tateoka Y, Usuki Y, *et al.* (2006). Measurement of bisphenol A concentration in human colostrum. *Chemosphere*, 66: 1160-1164.
- Laban C, Bustin SA, Jenkins PJ (2003). The GH-IGF-1 axis and breast cancer. *Trends Endocrinol Metab*, 14:28-34.
- Labreche, FP, Goldberg, MS (1997). Exposure to organic solvents and breast cancer in women: A hypothesis. *Am J Ind Med*, 32:1-14.
- Lacroix M, Leclercq G (2004). Relevance of breast cancer cell lines as models for breast tumours: an update. *Breast Cancer Res Treat*, 83:249-289.
- Laden F, Collman G, Iwamoto K, *et al.* (2001). 1,1-Dichloro-2,2-bis(p-chloro-phenyl) ethylene and polychlorinated biphenyls and breast cancer: Combined analysis of five U.S. studies. *J Natl Cancer Inst*, 93:768-776.
- Laden F, Ishibe N, Hankinson SE, *et al.* (2002). Polychlorinated biphenyls, cytochrome P450 1A1, and breast cancer risk in the Nurses' Health Study. *Cancer Epidemiol Biomarkers Prev*, 11:1560-1565.
- LaKind JS, Berlin CM, Sjodin A, *et al.* (2009). Do human milk concentrations of persistent organic chemicals really decline during lactation? Chemical concentrations during lactation and milk/serum partitioning. *Environ Health Perspect*, 117:1625-1631.
- LaMerrill M, Kuruvilla BS, Pomp D, *et al.* (2009). Dietary fat alters body composition, mammary development, and cytochrome P450 induction after maternal TCDD exposure in DBA/2J mice with low-responsive aryl hydrocarbon receptors. *Environ Health Perspect*, 117:1414-1419.
- Land CE (1995). Studies of cancer and radiation dose among A-bomb survivors: The example of breast cancer. *J Am Med Assoc*, 274:402-407.
- Land CE (1998). Epidemiology of radiation-related breast cancer. Workshop Summary: National Action Plan on Breast Cancer, Breast Cancer Etiology Working Group, Workshop on Medical Ionizing Radiation and Human Breast Cancer. November 17-18, 1997.
- Land CE, Tokunaga M, Koyama K, *et al.* (2003). Incidence of female breast cancer among atomic bomb survivors, Hiroshima and Nagasaki, 1950-1990. *Radiat Res*, 160:707-717.
- Landrigan PJ, Sonawane B, Butler RN, *et al.* (2005). Early environmental origins of neurodegenerative disease in later life. *Environ Health Perspect*, 113:1230-1233.
- Lang IA, Galloway TS, Scarlett A, *et al.* (2008). Association of urinary bisphenol A concentration with medical disorders and laboratory abnormalities in adults. *J Am Med Assoc*, 300:1303-1310.
- LaPensee EW, Tuttle TR, Fox SR, Ben-Jonathan N (2009). Bisphenol A at low nanomolar doses confers chemoresistance in estrogen receptor alpha positive and negative breast cancer cells. *Environ Health Perspect*, 117: 175-180.
- LaPensee EW, LaPensee CR, Fox S, *et al.* (2010). Bisphenol A and estradiol are equipotent in antagonizing cisplatin-induced cytotoxicity in breast cancer cells. *Cancer Lett*, 290:167-173.
- Larson PS, Ungarelli RA, de las Morenas A, *et al.* (2006). In utero exposure to diethylstilbestrol (DES) does not increase genomic instability in normal or neoplastic breast epithelium. *Cancer*, 107:2122-2126.
- Latini G, Del Vecchio A, Massaro M, *et al.* (2006). Phthalate exposure and male infertility. *Toxicol*, 226:90-98.
- Layton DW, Bogen KT, Knize MG, *et al.* (1995). Cancer risk of heterocyclic amines in cooked foods: An analysis and implications for research. *Carcinogenesis*, 16:39-52.
- Lee PN, Hamling J (2006). Environmental tobacco smoke exposure and risk of breast cancer in nonsmoking women: A review with meta-analyses. *Inhalation Toxicol*, 18:1053-1070.
- Lee S-A, Shu X-O, Li H, *et al.* (2009). Adolescent and adult soy food intake and breast cancer: Results from the Shanghai Women's Health Study. *Am J Clin Nutr*, 89:1920-1926.
- Leffers H, Naesby M, Vendelbo B, *et al.* (2001). Oestrogenic potencies of zearanol, oestradiol, diethylstilbestrol, bisphenol-A and genistein: Implications for exposure assessment of potential endocrine disrupters. *Hum Reprod*, 16:1037-1045.
- Lerner-Geva L, Keinan-Boker L, Blumstein T, *et al.* (2006). Infertility, ovulation induction treatments and the incidence of breast cancer: A historical prospective cohort of Israeli women. *Breast Cancer Res Treat*, 100:201-212.
- Lewis BC, Hudgins S, Lewis A, *et al.* (2001). In utero and lactational treatment with 2,3,7,8-tetrachlorodibenzo-p-dioxin impairs mammary gland differentiation but does not block the response to exogenous estrogen in the postpubertal rat. *Toxicol Sci*, 62:63-74.
- Li D, Zhou Z, Qing Y, *et al.* (2009). Occupational exposure to bisphenol-A (BPA) and the risk of self-reported male sexual dysfunction. *Human Reprod*, doi:10.1093/humrep/dep381.
- Li S, Hursting SD, Davis BJ, *et al.* (2003). Environmental exposure, DNA methylation, and gene regulation: Lessons from diethylstilbestrol-induced cancers. *Annals NY Acad Sci*, 983:161-169.
- Li ST, Lozano P, Grossman DC, *et al.* (2002). Hormone-containing hair product use in prepubertal children. *Arch Pediatr Adolesc Med*, 156:85-86.
- Lin CH, Huang CL, Chuang MC, *et al.* (2009). Protective role of estrogen receptor-alpha on lower chlorinated PCB congener-induced DNA damage and repair in human tumoral breast cells. *Toxicol Lett*, 188:11-19.
- Little JB (2003). Genomic instability and radiation. *J Radiol Protection*, 23:173-181.
- Liu B, Edgerton S, Yang X, *et al.* (2005). Low-dose dietary phytoestrogen abrogates tamoxifen-associated mammary tumor prevention. *Cancer Res*, 65:879-886.
- Liu S, Kulp SK, Sugimoto Y, *et al.* (2002). Involvement of breast epithelial-stromal interactions in the regulation of protein tyrosine phosphatase-gamma (PTPgamma) mRNA expression by estrogenically active agents. *Breast Cancer Res Treat*, 71:21-35.
- Liu S, Lin YC (2004). Transformation of MCF-10A human breast epithelial cells by zearanol and estradiol-17B. *Breast J*, 10:514-521.
- Loomis DP (1992). Cancer of breast among men in electrical occupations (letter). *Lancet*, 339:1482-1483.
- Lorber M, Patterson D, Huwe J, Kahn H (2009). Evaluation of background exposures of Americans to dioxin-like compounds in the 1990s and the 2000s. *Chemosphere*, 77:640-651.
- Love S. (2005). Ch 20. Diagnosis and types of breast cancer. *Dr. Susan Love's Breast Book* (4th ed.). Cambridge, MA: Perseus Publishing.
- Lovekamp-Swan T, Davis BJ (2003). Mechanisms of phthalate ester toxicity in female reproductive system. *Environ Health Perspect*, 111:139-145.
- Lu C, Toepel K, Irish R. (2006). Organic diets significantly lower children's dietary exposure to organophosphorus pesticides. *Environ Health Perspect*, 114: 260-263.

- Lund E, Bakken K, Dumeaux V, *et al.* (2007). Hormone replacement therapy and breast cancer in former users of oral contraceptives: The Norwegian Women and Cancer Study. *Int J Cancer*, 121:645-648.
- Lund E, Dumeaux V (2008). Systems epidemiology in cancer. *Cancer Epidemiol Biomarkers Prev*, 17:2954-2957.
- Lundell M, Mattsson A, Karlsson P, *et al.* (1999). Breast cancer risk after radiotherapy in infancy: A pooled analysis of two Swedish cohorts of 17,202 infants. *Radiat Res*, 151:626-632.
- Lunk KH, Petersen JH (2006). Migration of formaldehyde and melamine monomers from kitchen- and tableware made of melamine plastic. *Food Addit Contam*, 23:948-955.
- Lyons TR, Schedin PJ, Borges VF (2009). Pregnancy and breast cancer: When they collide. *J Mamm Gland Biol Neoplasia*, 14:87-98.
- Ma H, Hill C, Bernstein L, Ursin G (2008). Low-dose medical radiation exposure and breast cancer risk in women under age 50 years overall and by estrogen and progesterone receptor status: Results from a case-control and a case-case comparison. *Breast Cancer Res Treat*, 109:77-90.
- MacKenzie I (1965). Breast cancer following multiple fluoroscopies. *Br J Cancer*, 19:1-8.
- Maffini M, Calabro JM, Soto AM, *et al.* (2005). Stromal regulation of neoplastic development: Age dependent normalization of neoplastic mammary cells by mammary stroma. *Int J Pathol*, 167:1405-1410.
- Maffini MV, Rubin BS, Sonnenschein C, *et al.* (2006). Endocrine disruptors and reproductive health: The case of bisphenol-A. *Mol Cell Endocrinol*, 254-255:179-186.
- Magnusson C, Baron JA, Correia N, *et al.* (1999). Breast-cancer risk following long-term oestrogen and oestrogen-progestin replacement therapy. *Int J Cancer*, 81:339-344.
- Mahadevan B, Keshava C, Musafia-Jeknic T, *et al.* (2005). Altered gene expression patterns in MCF-7 cells induced by the urban dust particulate complex mixture standard reference material 1649a. *Cancer Res*, 65:1251-1258.
- Manz A, Berger J, Dwyer JH, *et al.* (1991). Cancer mortality among workers in chemical plant contaminated with dioxin. *Lancet*, 338:959-964.
- Marcus PM, Newman B, Millikan RC, *et al.* (2000). The associations of adolescent cigarette smoking, alcoholic beverage consumption, environmental tobacco smoke, and ionizing radiation with subsequent breast cancer risk (United States). *Cancer Causes Control*, 11:271-278.
- Markey CM, Luque EH, Munoz-de-Toro M, *et al.* (2001). In utero exposure to bisphenol A alters the development and tissue organization of the mouse mammary gland. *Biol Reprod*, 65:1215-1223.
- Martin MB, Reiter R, Pham T, *et al.* (2003). Estrogen-like activity of metals in MCF-7 breast cancer cells. *Endocrinology*, 144:2425-2436.
- Maskarinec G, Zhang Y, Takata Y, *et al.* (2006). Trends of breast cancer incidence and risk factor prevalence over 25 years. *Breast Cancer Res Treat*, 98:45-54.
- Massart F, Harrell JC, Frederico G, *et al.* (2005). Human breast milk and xenoestrogen exposure: A possible impact on human health. *J Perinatol*, 25:282-288.
- Massart F, Meucci V, Saggese G, Soldani G (2008). High growth rate of girls with precocious puberty exposed to estrogenic mycotoxins. *J Pediatr*, 152:690-695.
- Matanoski GM, Breyse PN, Elliott EA (1991). Electromagnetic field exposure and male breast cancer. *Lancet*, 337:737.
- Mathelin C, Annane K, Treisser A, *et al.* (2008). Pregnancy and post-partum breast cancer: A prospective study. *Anticancer Res*, 28:2447-2452.
- Matsumoto H, Adachi S, Suzuki Y (2005). Bisphenol A in ambient air particulates responsible for the proliferation of MCF-7 human breast cells and its concentration changes over 6 months. *Arch Environ Contam Toxicol*, 48:459-466.
- Mattsson A, Ruden BI, Palmgren J, *et al.* (1995). Dose-and time-response for breast cancer risk after radiation therapy for benign breast disease. *Br J Cancer*, 72:1054-1061.
- McCarty KM, Santella RM, Steck SE, *et al.* (2009). PAH-DNA adducts, cigarette smoking, GST polymorphisms and breast cancer risk. *Environ Health Perspect*, 117:552-555.
- McElroy JA, Egan KM, Titus-Ernstoff L, *et al.* (2007). Occupational exposure to electromagnetic field and breast cancer risk in a large, population-based, case-control study in the United States. *J Occup Environ Med*, 49:266-274.
- McElroy JA, Shafer MM, Trentham-Dietz A, *et al.* (2006). Cadmium exposure and breast cancer risk. *J Natl Cancer Inst*, 98:869-873.
- McElvinney DM, Darnton AJ, Hodson JT, *et al.* (2001). Cancer among current and former workers at National Semiconductor (UK) LTD, Greenock: Results of an investigation by the Health and Safety Executive. Norwich, UK: Her Majesty's Stationary Office.
- McKelvey W, Brody JG, Aschengrau A, Swartz CH (2004). Association between residence on Cape Cod, Massachusetts, and breast cancer. *Ann Epidemiol*, 14:89-94.
- Medgal SP, Kroenke CH, Laden F, Pukkala E, Schernhammer ES (2005). Night work and breast cancer risk: A systematic review and meta-analysis. *Eur J Cancer*, 41:2023-2032.
- Medina D (2007). Chemical carcinogenesis of rat and mouse mammary glands. *Breast Disease*, 28:63-68.
- Medina-Ramon M, Zock JP, Kogevinas M, *et al.* (2005). Asthma, chronic bronchitis, and exposure to irritant agents in occupational domestic cleaning: a nested case-control study. *Occup Environ Med*, 62:598-606.
- Meeker JD, Sathyanarayana S, Swan SH (2009). Phthalates and other additives in plastics: human exposure and associated health outcomes. *Philos Trans Royal Soc*, 364:2097-2113.
- Meerts I, Letcher RJ, Hoving S, *et al.* (2001). In vitro estrogenicity of polybrominated diphenyl ethers, hydroxylated PBDEs, and polybrominated bisphenol A compounds. *Environ Health Perspect*, 109:399-407.
- Mei J, Hu H, McEntee M, *et al.* (2003). Transformation of non-cancerous human breast epithelial cell line MCF10A by the tobacco-specific carcinogen NNK. *Breast Cancer Res Treat*, 79:95-105.
- Mellemkjaer L, Friis S, Olsen JH, *et al.* (2006). Risk of second cancer among women with breast cancer. *Int J Cancer*, 118:2285-2292.
- Melnick RL, Sills RC, Portier CJ, *et al.* (1999). Multiple organ carcinogenicity of inhaled chloroprene (2-chloro-1,3-butadiene) in F344/N rats and B6C3F1 mice and comparison of dose-response with 1,3-butadiene in mice. *Carcinogenesis*, 20:867-878.
- Mense SM, Hei TK, Ganju R, Bhat HK (2008). Phytoestrogens and breast cancer prevention: Possible mechanisms of action. *Environ Health Perspect*, 116:426-433.
- Messina M, Wu AH (2009). Perspectives on the soy-breast cancer relation. *Am Soc Nutr*, 89:1673S-1679S.
- Michels KB, Mohllajee AP, Roset-Bahmanyar ER, *et al.* (2007). Diet and breast cancer. *Cancer*, 109 (Suppl 12):2712-2749.
- Miki Y, Suzuki T, Tazawa C, *et al.* (2007). Aromatase localization in human breast cancer tissues: possible interactions between intratumoral stromal

and parenchymal cells. *Am Assoc Cancer Res*, 67:3945-54.

Milham S (2004). A cluster of male breast cancer in office workers. *Am J Ind Med*, 46:86-87.

Miller MD, Marty MA, Broadwin R, *et al.* (2007). The association between exposure to environmental tobacco smoke and breast cancer: A review by the California environmental protection agency. *Prev Med*, 44:93-106.

Miller S, Sweet C, Depinto J, *et al.* (2000). Atrazine and nutrients in precipitation from the Lake Michigan mass balance study. *Environ Sci Technol*, 34:55-61.

Millikan R, DeVoto E, Duell EJ *et al.* (2000). Dichlorodiphenyldichloroethene, polychlorinated biphenyls and breast cancer among African-American and white women in North Carolina. *Cancer Epidemiol Biomarkers Prev*, 9:1233-1240.

Millikan RC, Player JS, deCotret AR, *et al.* (2005). Polymorphisms in DNA repair genes, medical exposure to ionizing radiation, and breast cancer risk. *Cancer Epidemiol Biomarkers Prev*, 14:2326-2334.

Mills PK, Yang R (2005). Breast cancer risk in Hispanic agricultural workers in California. *Int J Occup Environ Health*, 11:123-131.

Mirocha CJ, Schauerhamer B, Christensen M, *et al.* (1979). Incidence of zearalenol (Fusarium mycotoxin) in animal feed. *Appl Environ Microbiol*, 38:749-750.

Mohai P, Lantz PM, Morenoff J, *et al.* (2009). Racial and socioeconomic disparities in residential proximity to polluting industrial facilities: Evidence from the Americans' Changing Lives Study. *Am J Public Health*, 99: S649-S656.

Moon HJ, Han SY, Shin JH, *et al.* (2007). Gestational exposure to nonylphenol causes precocious mammary gland development in female rat offspring. *J Reprod Dev*, 53:333-344.

Moore CJ. (2008). Synthetic polymers in the marine environment: A rapidly increasing long-term threat. *Environ Res*, 108: 131-139.

Morabia A, Bernstein M, Heritier S, *et al.* (1996). Relation of breast cancer to active and passive exposure to tobacco smoke. *Am J Epidemiol*, 143:918-928.

Moral R, Wang R, Russo IH, *et al.* (2007). The plasticizer butyl benzyl phthalate induces genomic changes in rat mammary gland after neonatal/prepubertal exposure. *BMC Genomics*, 8:453.

Moral R, Wang R, Russo IH, *et al.* (2008). Effect of prenatal exposure to the endocrine disruptor bisphenol A on mammary gland morphology and gene expression signatures. *J Endocrinol*, 196:101-112.

Morello-Frosch R, Brody JG, Brown P, *et al.* (2009). Toxic ignorance and right-to-know in biomonitoring results communication: a survey of scientists and study participants. *Environ Health*, 8:6 doi:10.1186/1476-069X-8-6.

Morgan WF (2003). Non-targeted and delayed effects of exposure to ionizing radiation: II. Radiation-induced genomic instability and bystander effects in vivo, clastogenic factors and transgenerational effects. *Radiat Res*, 159:581-596.

Morin-Doody M, Freedman DM, Alexandre BH, *et al.* (2006). Breast cancer incidence in U.S. radiologic technologists. *Cancer*, 106:2707-2715.

Morin-Doody M, Lonstein JE, Stovall M, *et al.* (2000). Breast cancer mortality after diagnostic radiography: Findings from the U.S. Scoliosis Cohort Study. *Spine*, 25:2052-2063.

Muñoz-de-Toro M, Markey CM, Wadia PR, *et al.* (2005). Perinatal exposure to bisphenol-A alters peripubertal mammary gland development in mice. *Endocrinology*, 146:4138-4147.

Murata M, Midorikawa K, Koh M, *et al.* (2004). Genistein and daidzein induce cell proliferation and their metabolites cause oxidative DNA damage in relation to isoflavone-induced cancer of estrogen-sensitive organs. *Biochem*, 43:2569-2577.

Murray TJ, Maffini MV, Ucci AA, *et al.* (2007a). Induction of mammary gland ductal hyperplasias and carcinoma in situ following fetal bisphenol A exposure. *Reprod Toxicol*, 23:383-390.

Murray D, McEwan AJ (2007b). Radiobiology of systemic radiation therapy. *Cancer Biother Radiopharm*, 22:1-22.

Muscat JE, Britton JA, Djordjevic MV, *et al.* (2003). Adipose concentrations of organochlorine compounds and breast cancer recurrence in Long Island, New York. *Cancer Epidemiol Biomarkers Prev*, 12:1474-78.

MWSC: Million Women Study Collaborators (2003). Breast cancer and hormone-replacement therapy in the Million Women Study. *Lancet*, 362:419-427.

N

Narod SA, Dube MP, Klign J, *et al.* (2002). Oral contraceptives and the risk of breast cancer in *BRCA1* and *BRCA2* mutation carriers. *J Natl Cancer Inst*, 94:1773-1779.

NAS: National Academy of Sciences (2008). Phthalates and Cumulative Risk Assessment: The Tasks Ahead. Washington, DC: The National Academies Press.

NCRP: National Council on Radiation Prediction and Measurements (2009). Ionizing Radiation Exposure of the Population of the United States (Report No.160).

Nelson CM, Bissell MJ (2006). Of extracellular matrix, scaffolds, and signaling: Tissue architecture regulates development, homeostasis and cancer. *Ann Rev Cell Dev Biol*, 22:287-309.

Nelson H, Tyne K, Naik A, *et al.* (2009). Screening for breast cancer: an update for the U.S. preventive services task force. *Ann Intern Med*, 151:727-737.

Newcomer LM, Newcomb PA, Trentham-Dietz A, *et al.* (2003). Oral contraceptive use and risk of breast cancer by histologic type. *Int J Cancer*, 106:961-964.

NHGRI: National Human Genome Research Institute. (2010). Genome-wide association studies. www.genome.gov/20019523 (7/12/2010).

Nickerson K (2006). Environmental contaminants in human milk. *J Midwifery Womens Health*, 51:26-34.

Nie J, Beyea J, Bonner MR, *et al.* (2007). Exposure to traffic emissions throughout life and risk of breast cancer: the western New York exposures and breast cancer (web) study. *Cancer Causes Control*, 18:947-955.

NIEHS (1998). Working Group Report: Assessment of health effects from exposure to power-line frequency electric and magnetic fields. National Institute of Environmental Health Sciences of the National Institutes of Health.

NIEHS: National Institute of Environmental Health Sciences (2009): NIEHS awards Recovery Act funds to address bisphenol A research gaps. www.niehs.nih.gov/news/releases/2009/bisphenol-research.cfm (7/12/2010).

Nikaido Y, Danbara N, Tsujita-Kyutoku M, *et al.* (2005). Effects of prepubertal exposure to xenoestrogen on development of estrogen target organs in female CD-1 mice. *In Vivo*, 19: 487-494.

Nordman IC, Dalley DN (2008). Breast cancer in men: should aromatase inhibitors become first-line hormonal treatment? *Breast J*, 14:562-569.

NPIC: National Pesticide Information Center (2010). Active ingredient fact sheets. <http://npic.orst.edu/npicfact.htm> (7/12/2010).

NRPB: National Radiological Protection Board (Britain) (1995). Risk of radiation-induced cancer at low doses and low-dose rates for radiation protection purposes. *Documents of the NRPB*, 6:25.

NRC: National Research Council (2005). Biologic effects of ionizing radiation VII: Health risks from exposure to low levels of ionizing radiation. National Academy of Science, Washington DC.

NRC: National Research Council (2009). Science and Decisions: Advancing Risk Assessment. National Academies Press: Washington, D.C.

NTP: National Toxicology Program U.S. Department of Health and Human Services (1993). Toxicology and Carcinogenesis studies of 1,3-butadiene (CAS No. 106-99-0) in B6C3F1 mice (inhalation studies). NTP TR 434, NIH Pub. No. 93-3165. Research Triangle Park, NC.

NTP: National Toxicology Program (2002). Tenth Report on Carcinogens. National Institute of Environmental Health Sciences. National Institutes of Health.

NTP: National Toxicology Program (2003). Chemicals associated with site-specific tumor induction in mammary gland. <http://ntp.niehs.nih.gov/index.cfm?objectid=E1D18034-123F-7908-7B2C2AE41B1F3778> (7/12/2010).

NTP: National Toxicology Program (2005a). Vinyl chloride. Eleventh report on carcinogens. National Institute of Environmental Health Sciences. National Institutes of Health. <http://ntp.niehs.nih.gov/ntp/roc/eleventh/profiles/s186vinyl.pdf> (7/12/2010).

NTP: National Toxicology Program (2005b). Ethylene oxide. Eleventh report on carcinogens. National Institute of Environmental Health Sciences. National Institutes of Health. <http://ntp.niehs.nih.gov/ntp/roc/eleventh/profiles/s085ethy.pdf> (7/12/2010).

NTP: National Toxicology Program (2005c). Benzene. Eleventh report on carcinogens. National Institute of Environmental Health Sciences. National Institutes of Health. <http://ntp.niehs.nih.gov/ntp/roc/eleventh/profiles/s019benz.pdf> (7/12/2010).

NTP: National Toxicology Program (2005d). o-Toluidine and o-Toluidine hydrochloride. Eleventh report on carcinogens. National Institute of Environmental Health Sciences. National Institutes of Health. <http://ntp.niehs.nih.gov/ntp/roc/eleventh/profiles/s178otol.pdf> (7/12/2010).

NTP-CERHR (2008). NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Bisphenol A. Research. NIH Publication No. 08-5994. <http://cerhr.niehs.nih.gov/chemicals/bisphenol/bisphenol.pdf> (7/27/10).

NTP: National Toxicology Program (2009). Report on carcinogens, Eleventh edition. U.S. Department of Health and Human Services, Public Health Service. <http://ntp.niehs.nih.gov/index.cfm?objectid=32BA9724-F1F6-975E-7FCE50709CB4C932> (7/12/2010).

O

O'Connor JC, Plowchalk DR, Van Pelt CS, *et al.* (2000). Role of prolactin in chloro-S-triazine rat mammary tumorigenesis. *Drug Chem Toxicol*, 23:575-601.

Oehlmann J, Schulte-Oehlmann U, Kloas W, *et al.* (2009). A critical analysis of the biological impacts of plasticizers on wildlife. *Phil Trans Royal Soc*, 364:2047-2062.

Oh MJ, Paul S, Kim SJ, *et al.* (2009). Comparative analysis of gene expression pattern after exposure to nonylphenol in human cell lines. *Biochip J*, 2:261-268.

Oldenburg RA, Meijers-Heijboer H, Cornelisse CJ, Devilee, P (2007). Genetic susceptibility for breast cancer: How many more genes to be found? *Crit Rev Oncol/Hematol*, 63:125-149.

Olivier M, Hainaut P (2001). TP53 mutation patterns in breast cancers: searching for clues of environmental carcinogenesis. *Cancer Biol* 11: 353-360.

Onami S, Ozaki M, Mortimer JE, Pal SK (2010). Male breast cancer: An update in diagnosis treatment and molecular profiling. *Maturitas*, 65:308-314.

Orgeas CC, Sanner K, Hall P, *et al.* (2009). Breast cancer incidence after hormonal infertility treatment in Sweden: A cohort study. *Am J Obstet Gynecol*, 200:72.e1-72.e7.

Outwater JL, Nicholson A, Barnard N (1997). Dairy products and breast cancer: the IGF-1, estrogen and bGH hypothesis. *Med Hypotheses*, 48:453-461.

P

Padmanabhan V, Siefert K, Ransom S, *et al.* (2008). Maternal bisphenol-A levels at delivery: A looming problem? *J Perinatol*, 28:258-263.

Palli D, Masala G, Mariani-Costantini R, *et al.* (2004). A gene-environment interaction between occupation and BRCA1/BRCA2 mutations in male breast cancer? *Eur J Cancer*, 40:2474-2479.

Palmer JR, Wise LA, Hatch EE, *et al.* (2006). Prenatal diethylstilbestrol exposure and risk of breast cancer. *Cancer Epidemiol Biomarkers Prev*, 15:1509-1514.

Palmer JR, Wise LA, Horton NJ, *et al.* (2003). Dual effect of parity on breast cancer risk in African-American women. *J Natl Cancer Inst*, 95:478-483.

PAN: Pesticide Action Network (2000-2010). Pesticides database: chemicals. www.pesticideinfo.org/Search_Chemicals.jsp (7/12/2010).

Park SK, Kang D, McGlynn KA, *et al.* (2008). Intrauterine environments and breast cancer risk: meta-analysis and systematic review. *Breast Cancer Res*, 10: doi: 10.1186/bcr1850.

Parkin DM, Bray F, Ferlay J, Pisani P (2005). Global cancer statistics, 2002. *Cancer*, 55:74-108.

Parkin DM, Fernandez LMG (2006). Use of statistics to assess the global burden of breast cancer. *Breast J*, 12:S70-S80.

Parveen M, Zhu Y, Kiyama R (2009). Expression profiling of the genes responding to zearalenone and its analogues using estrogen-responsive genes. *FEBS Lett*, 583: 2377-2384.

Pasanisi P, Hedelin G, Berrino J, *et al.* (2009). Oral contraceptive use and BRCA penetrance: A case-only study. *Cancer Epidemiol Biomarkers Prev*, 18:2107-2113.

Patterson DG, Wong LY, Turner WE, *et al.* (2008). Levels in the U.S. population of those persistent organic pollutants (2003-2004) included in the Stockholm convention or in other long-range transboundary air pollution agreements. *Environ Sci Technol*, 43:1211-1218.

PCP: President's Cancer Panel (2008). Meeting Summary. Environmental Factors in Cancer. Charleston, SC.

Peplonska B, Stewart P, Szeszenia-Dabrowska N, *et al.* (2007). Occupation and breast cancer risk in Polish women: A population-based case-control study. *Am J Ind Med*, 50:97-111.

Perera FP, Rauh V, Whyatt RM, *et al.* (2005). A summary of recent findings on birth outcomes and developmental effects of prenatal ETS, PAH, and pesticide exposures. *Neurotoxicology*, 26:573-587.

Perlin SA, Wong D, Sexton K. (2001). Residential proximity to industrial sources of air pollution: Interrelationships among race, poverty, and age. *J Air Waste Manag Assoc*, 51:406-421.

Perrone MG, Gualtieri M, Ferrero L, *et al.* (2010). Seasonal variations in chemical composition and in vitro biological effects of fine PM from Milan. *Chemosphere*, 78:1368-1377.

Perou CM, Sørle T, Eisen MB, *et al.* (2000). Molecular portraits of human breast tumors. *Nature*, 406:747-752.

Pervez S, Khan H (2007). Infiltrating ductal carcinoma breast with central necrosis closely mimicking ductal carcinoma in situ (comedo type): a case series. *J Med Case Rep*, 1:83.

Pesatori AC, Consonni D, Rubagotti M, *et al.* (2009). Cancer incidence in the population exposed to dioxin after the "Seveso accident": Twenty years of follow-up. *Environ Health*, 8:39. doi:10.1186/1476-069X-8-39.

Peters R (2005). Man-made chemicals in maternal and cord blood. Greenpeace and World Wildlife Fund UK. www.greenpeace.org/raw/content/nederland-old/reports/man-made-chemicals-in-maternal.pdf (7/12/2010).

Peterson JL, Vallow LA, Hines SL, Buskirk SJ (2009). Ductal carcinoma in situ of the breast. *Oncol Rev*, 3:237-246.

Petralia SA, Chow W-H, McLaughlin J, *et al.* (1998). Occupational risk factors for breast cancer among women in Shanghai. *Am J Ind Med*, 34:477-483.

Petralia SA, Vena JE, Freudenheim, *et al.* (1999). Risk of premenopausal breast cancer in association with occupational exposure to polycyclic aromatic hydrocarbons and benzene. *Scand J Work Environ Health*, 25:215-221.

Phillips LS, Millikan RC, Schroeder JC, *et al.* (2009). Reproductive and hormonal risk factors for ductal carcinoma in situ of the breast. *Cancer Epidemiol Biomarkers Prev*, 18:1507-1514.

Pierce DA, Shimizu Y, Preston DL (1996). Studies of the mortality of atomic bomb survivors. Report 12, Part I. Cancer: 1950-1990. *Radiat Res*, 146:1-27.

Pliskova M, Vondracek J, Vojtesek B, *et al.* (2005). Deregulation of cell proliferation by polycyclic aromatic hydrocarbons in human breast carcinoma MCF-7 cells reflects both genotoxic and nongenotoxic events. *Toxicol Sci*, 83:246-246.

Preston DL, Mattsson A, Holmberg E, *et al.* (2002). Radiation effects on breast cancer risk: A pooled analysis of eight cohorts. *Radiat Res*, 158:220-235

Pugazhendhi D, Sadler AJ, Darbre PD (2007). Comparison of the global gene expression profiles produced by methylparaben, n-butylparaben and 17B-oestradiol in mcf7 human breast cancer cells. *J Appl Toxicol*, 27:67-77.

Pujol P, Hilsenbeck SG, Chamness GC, *et al.* (1994). Rising levels of estrogen receptor in breast cancer over 2 decades. *Cancer*, 74:1601-1606.

Pukkala E, Kesminiemi A, Poliakov S, *et al.* (2006). Breast cancer in Belarus and Ukraine after the Chernobyl accident. *Int J Cancer*, 119:651-658.

Q

Quach T, Nguyen K-D, Doan-Billings P-A, *et al.* (2008). A preliminary study of Vietnamese nail salon workers in Alameda County, California. *J Community Health*, 33:336-343.

R

Rajapakse N, Ong D, Kortenkamp A (2001). Defining the impact of weakly estrogenic chemicals on the action of steroidal chemicals. *Toxicol Sci*, 60:296-304.

Rajapakse N, Silva E, Kortenkamp A (2002). Combining xenoestrogens at levels below individual no-observed-effect concentrations dramatically enhances steroid hormone action. *Environ Health Perspect*, 110:917-921.

Ralston SL, Coffing SL, Seidel A, *et al.* (1997). Stereoselective activation of dibenzo[a,l]pyrene and its trans-11,12-dihydrodiol to fjord region 11,12-diol 13,14-epoxides in a human mammary carcinoma MCF-7 cell-mediated V79 cell mutation assay. *Chem Res Toxicol*, 10:687-693.

Ramamoorthy K, Wang F, Chen IC, *et al.* (1998). Potency of combined estrogenic pesticides: Synergism between synthetic estrogens? *Science*, 275:405-406.

Rastogi SC, Schouten A, Dekruijf N, *et al.* (1995). Contents of methylparaben, ethylparaben, propylparaben, butylparaben and benzylparaben in cosmetic products. *Contact Derm*, 32:28-30.

Ravdin PM, Cronin KA, Howlader N, *et al.* (2007). The decrease in breast cancer incidence in 2003 in the United States. *New England J Med*, 356:1670-1674.

Raynor JL, Enoch RR, Fenton SE (2005). Adverse effects of prenatal exposure to atrazine during a critical period of mammary gland growth. *Toxicol Sci*, 87:255-266.

Redberg (2009). Cancer risks and radiation exposure from computed tomographic scans. How can we be sure that the benefits outweigh the risks? *Arch Intern Med*, 169:2049-2050.

Reeves GK, Beral V, Green J, *et al.* (2006). Hormonal therapy for menopause and breast-cancer risk by histological type: a cohort study and meta-analysis. *Lancet Oncol*, 7:910-918.

Rennix CP, Quinn MM, Amoroso PJ, *et al.* (2005). Risk of breast cancer among enlisted army women occupationally exposed to volatile organic compounds. *Am J Ind Med*, 48:157-167.

Rennstam K, Hedenfalk I (2006). Molecular signatures of progression from benign epithelium to metastatic breast cancer *Breast Cancer Res*, 8:213 (doi:10.1186/bcr1528).

Reynolds, JD (1997). International pesticide trade: Is there any hope for the effective regulation of controlled substances? *J Land Use & Environ Law*, 131. www.law.fsu.edu/journals/landuse/Vol131/REYN.HTML (7/12/2010).

Reynolds P, Hurley S, Goldberg DE, *et al.* (2004). Active smoking, household passive smoking, and breast cancer: Evidence from the California Teachers Study. *J Natl Cancer Inst*, 96:29-37.

Rice S, Whitehead SA (2006). Phytoestrogens and breast cancer: promoters or protectors? *Endocr Relat Cancer*, 13:995-1015.

Richter CA, Birnbaum LS, Farabollini F, *et al.* (2007). In vivo effects of bisphenol A in laboratory rodent studies. *Reprod Toxicol*, 24:199-224.

Rivas A, Lacroix M, Olea-Serrano F, *et al.* (2002). Estrogenic effect of a series of bisphenol analogues on gene and protein expression in MCF-7 breast cancer cells. *J Steroid Biochem Mol Biol*, 82:45-53.

Robbins AS, Clarke CA (2007). Regional changes in hormone therapy use and breast cancer incidence in California from 2001 to 2004. *J Clin Oncol*, 25:3437-3439.

Robinson PE, Mack GA, Remmers J, *et al.* (1990). Trends of PCB, hexachlorobenzene, and benzene hexachloride levels in the adipose tissue of the U.S. population. *Environ Res*, 53:175-192.

Rodriguez-Mozaz S, Lopez de Alda M, Barcelo D (2005). Analysis of bisphenol A in natural waters by means of an optical immunosensor. *Water Res*, 39:5071-5079.

Rogan WJ (1996). Pollutants in breast milk. *Arch Pediatr Adolesc Med*, 150:81-90.

Rohr JR, McCoy KA (2009). A qualitative meta-analysis reveals consistent effects of atrazine on freshwater fish and amphibians. *Environ Health Perspect*, 118:20-32.

Ron E, Ikeda T, Preston DL, *et al.* (2005). Male breast cancer incidence among atomic bomb survivors. *J Natl Cancer Inst*, 97:603-605.

Roseboom T, de Rooij S, Painter R (2006). The Dutch famine and its long-term consequences for adult health. *Early Human Devel*, 82:485-491.

Rosenberg L, Zhang Y, Coogan PF, *et al.* (2009). A case-control study of oral contraceptive use and incident breast cancer. *Am J Epidemiol*, 169:473-479.

Ross RK, Paganini-Hill A, Wan PC, Pike MC (2000). Effect of hormone replacement therapy on breast cancer risk: estrogen versus estrogen plus progestin. *J Natl Cancer Ins*, 92:328-332.

Rossouw JE, Anderson GL, Prentice RL, *et al.* (2002). Risks and benefits of estrogen plus progestin in healthy postmenopausal women. *J Am Med Assoc*, 288(3):321-333.

Routledge EJ, Parker J, Odum J, *et al.* (1998). Some alkyl hydroxy benzoate preservatives (parabens) are estrogenic. *Toxicol Appl Pharmacol*, 153:12-19.

- Roychoudhuri R, Evans H, Robinson D, *et al.* (2004). Radiation-induced malignancies following radiotherapy for breast cancer. *Br J Cancer*, 91:868-872.
- Rudel RA, Geno P, Melly SJ, *et al.* (1998). Identification of alkylphenols and other estrogenic phenolic compounds in wastewater, septage, and groundwater on Cape Cod, Massachusetts. *Environ Sci Technol*, 32:861-69.
- Rudel RA, Brody JG, Spengler JD, *et al.* (2001). Methods to detect selected potential mammary carcinogens and endocrine disruptors in commercial and residential air and dust samples. *J Air Water Manag Assoc*, 51:499-513.
- Rudel RA, Camann DE, Spengler JD, *et al.* (2003). Phthalates, alkylphenols, pesticides, polybrominated diphenyl ethers, and other endocrine-disrupting compounds in indoor air and dust. *Environ Sci Technol*, 37:4543-4553.
- Rudel RA, Attfield KA, Schifano JN, *et al.* (2007). Chemicals causing mammary gland tumors in animals signal new directions for epidemiological chemicals testing, and risk assessment for breast cancer prevention. *Cancer*, 109 (Suppl 12):2635-2666.
- Rudel RA, Perovich LJ (2009a). Endocrine disrupting chemicals in indoor and outdoor air. *Atmospheric Environ*, 43:170-181.
- Rudel RA, Fenton S (2009b). Report to funders: Mammary gland evaluation and risk assessment workshop, November 16-17, 2009. www.silent-spring.org/pdf/our_research/MammaryGlandEvaluationandRiskAssessmentWorkshop_Summary.pdf (7/12/2010).
- Rundle A, Tang D, Hibshoosh H, *et al.* (2000). The relationship between genetic damage from polycyclic aromatic hydrocarbons in breast tissue and breast cancer. *Carcinogenesis*, 21:1281-1289.
- Russo J, Hu YF, Silva IDCG, Russo IH (2001). Cancer risk related to mammary gland structure and development. *Microsc Res Tech*, 52:204-223.
- Russo J, Russo I (2004). Ch. 4: The role of estrogen in breast cancer. In: *Molecular Basis of Breast Cancer*, Berlin: Springer-Verlag.
- Russo J, Moral R, Wang R, *et al.* (2008). Effect of prenatal exposure to the endocrine disruptor bisphenol A on mammary gland morphology and gene expression signature. *J Endocrinol*, 196: 101-112.
- Ryan BC, Hotchkiss AK, Crofton KM, Gray LE. (2010) In utero and lactational exposure to bisphenol A, in contrast to ethinyl estradiol, does not alter sexually dimorphic behavior, puberty, fertility, and anatomy of female LE rats. *Toxicol Sci*, 114:133-148.
- Sadler AJ, Pugazhendhi D, Darbre PD (2009). Use of global gene expression patterns in mechanistic studies of oestrogen action in MCF-7 human breast cancer cells. *J Steroid Biochem Mol Biol*, 114:21-32.
- Saeed M, Rogan E, Cavalieri E (2009). Mechanism of metabolic activation and DNA adduct formation by the human carcinogen diethylstilbestrol: The defining link to natural estrogens. *Int J Cancer*, 124:1276-1284.
- Sagiv SK, Gaudet MM, Eng SM, *et al.* (2009). Polycyclic aromatic hydrocarbon-DNA adducts and survival among women with breast cancer. *Environ Res*, 109:287-291.
- Sakamoto T, Horiguchi H, Oguma E, Kayama F (2009). Effects of diverse dietary phytoestrogens on cell growth, cell cycle and apoptosis in estrogen-receptor-positive breast cancer cells. *J Nutr Biochem*, doi: 10.1016/j.jnutbio.2009.06.010.
- Salehi F, Turner MC, Phillips KP, *et al.* (2008). Review of the etiology of breast cancer with special attention to organochlorines as potential endocrine disruptors. *J Toxicol Environ Health*, 11:276-300.
- Sanderson JT, Letcher RJ, Heneweer M, *et al.* (2001). Effects of chloro-S-triazine herbicides and metabolites on aromatase activity in various human cell lines and on vitellogenin production in male carp hepatocytes. *Environ Health Perspect*, 109:1027-1031.
- Santodonato J (1997). Review of the estrogenic and antiestrogenic activity of polycyclic aromatic hydrocarbons: relationship to carcinogenicity. *Chemosphere*, 34:835-848.
- Sathyanarayana S, Karr CJ, Lozano P, *et al.* (2008). Baby care products: Possible sources of infant phthalate exposure. *Pediatrics*, 121:e260-e268.
- Saxena S, Copas AJ, Mercer C, *et al.* (2006). Ethnic variations in sexual activity and contraceptive use: national cross-sectional study. *Contraception*, 74:224-233.
- Schairer C, Lubin J, Troisi R, *et al.* (2000). Menopausal estrogen and estrogen/progestin replacement therapy and breast cancer risk. *J Am Med Assoc*, 283:485-491.
- Schecter A, Birnbaum L, Ryan JJ, Constable JD (2006). Dioxins: An overview. *Environ Res*, 101: 419-428.
- Schellong G (1998). Pediatric Hodgkin's disease: Treatment in the late 1990s. *Annals Oncol*, 9:S115-S119.
- Schettler T (2005). Human exposure to phthalates via consumer products. *Int J Androl*, 29:134-139.
- Schlumpf M, Cotton B, Conscience M, *et al.* (2001). In vitro and in vivo estrogenicity of UV screens. *Environ Health Perspect*, 109:239-244.
- Schonfelder G, Wittfoht W, Hopp H, *et al.* (2002). Parent Bisphenol A accumulation in the human maternal-fetal-placental unit. *Environ Health Perspect*, 110:A703-707.
- Schootman M, Jeffe DB, Lian M, *et al.* (2009). The role of poverty rate and racial distribution in the geographic clustering of breast cancer survival among older women: A geographic and multilevel analysis. *Am J Epidemiol*, 169:554-561.
- Schuetz F, Diel IJ, Püeschel M, *et al.* (2007). Reduced incidence of distant metastases and lower mortality in 1072 patients with breast cancer with a history of hormone replacement therapy. *Am J Obstet Gynecol*, 196:e1-9.
- Scribner JD, Mottet NK (1981). DDT acceleration of mammary gland tumors induced in the male Sprague-Dawley rat by 2-acetamidophenanthrene. *Carcinogenesis*, 2:1235-1239.
- SEER: Surveillance Epidemiology and End Results. Cancer of the breast: SEER stat fact sheets. www.seer.cancer.gov/statfacts/html/breast.html (7/12/2010).
- SDA: Soap and Detergent Association (2007). Keep kids safe while cleaning house. www.cleaninginstitute.org/assets/1/AssetManager/CleaningMattersMarApr07.pdf (7/12/2010).
- Segaloff A, Maxfield WS (1971). The synergism between radiation and estrogen in the production of mammary cancer in the rat. *Cancer Res*, 31:166-168.
- Seifert A, Helge T, Homback-Klonisch S, *et al.* (2009). TCDD mediates inhibition of p53 and activation of Era signaling in MCF-7 cells at moderate hypoxic conditions. *Int J Oncol*, 35:417-424.
- Shaham J, Gurvich R, Gorat A, *et al.* (2006). The risk of breast cancer in relation to health habits and occupational exposures. *Am J Ind Med*, 49:1021-1030.
- Shaner, H (2002). Guidelines for optimizing waste segregation. From HCWH: Health Care Without Harm. (2002). Going green: A resource kit for pollution prevention in health care. www.noharm.org/lib/downloads/waste/Guidelines_Waste_Segregation.pdf (7/12/2010).
- Shantakumar S, Terry MB, Paykin A, *et al.* (2007a). Age and menopausal effects of hormonal birth control and hormone replacement therapy in relation to breast cancer risk. *Am J Epidemiol*, 165:1187-1198.
- Shantakumar S, Terry MB, Teitelbaum SL, *et al.* (2007b). Reproductive factors and breast cancer

- risk among older women. *Breast Cancer Res Treat*, 102:365-374.
- Sheffield LG, Welsch CW (1985). Zeranone (B-resorcylic acid lactone), a common residuous component of natural foodstuffs, stimulates developmental growth of the mouse mammary gland. *Cancer Lett*, 28:77-83.
- Shen H, Main KM, Virtanen HE, *et al.* (2007). From mother to child: Investigation of prenatal and postnatal exposure to persistent bioaccumulating toxicants using breast milk and placenta biomonitoring. *Chemosphere*, 67:S236-S262.
- Shen L, Worrell E, Patel M (2009). Present and future development in plastics from biomass. *Biofuel Bioprod Bior*, 4:25-40.
- Shore RE, Hildreth N, Woodard E, *et al.* (1986). Breast neoplasms in women given X-ray therapy for acute postpartum mastitis. *J Natl Cancer Inst*, 77:689-696.
- Shoushtari AN, Michalowska AM, Green JE (2007). Comparing genetically engineered mouse mammary cancer models with human breast cancer by expression profiling. *Breast Disease*, 28:39-51.
- Shu XO, Zheng Y, Cai H, *et al.* (2009). Soy food intake and breast cancer survival. *J Am Med Assoc*, 302:2437-2443.
- Sibbald B, Roland M (1998). Understanding controlled trials: why are randomised controlled trials important? *Br Med J*, 316:201.
- Siddiqui MKJ, Anand M, Mehrotra PK, *et al.* (2005). Biomonitoring of organochlorines in women with benign and malignant breast disease. *Environ Res*, 98:250-257.
- Siegel BZ (1995). Pesticide hazard assessment project 1981-1984. Honolulu, HI: Pacific Biomedical Research Center, University of Hawaii.
- Sigurdson AJ, Doody MM, Rao RS, *et al.* (2003). Cancer incidence in the U.S. Radiologic Technologists Health Study, 1983-1998. *Cancer*, 97:3080-3089.
- Sigurdson AJ, Bhatti P, Chang S-C, *et al.* (2009). Polymorphisms in estrogen biosynthesis and metabolism-related genes, ionizing radiation exposure, and risk of breast cancer among U.S. radiologic technologists. *Breast Cancer Res Treat*, 118:177-184.
- Silva SN, Moita R, Azevedo AP, *et al.* (2007a). Menopausal age and XRCC1 gene polymorphisms: Role in breast cancer risk. *Cancer Detect Prev*, 31:303-309.
- Silva E, Scholze M, Kortenkamp A (2007b). Activity of xenoestrogens at nanomolar concentrations in the E-screen assay. *Environ Health Perspect*, 115 (Suppl 1):91-97.
- Silver SR, Whelan EA, Daddens JA, *et al.* (2009). Occupational exposure to polychlorinated biphenyls and risk of breast cancer. *Environ Health Perspect*, 117:276-282.
- Simcox NJ, Fenske RA, Wolz SA, *et al.* (1995). Pesticides in household dust and soil: Exposure pathways for children of agricultural families. *Environ Health Perspect*, 103:1126-1134.
- Simon SL, Weinstock RM, Doody MM, *et al.* (2006). Estimating historical radiation doses to a cohort of U.S. radiologic technologists. *Radiat Res*, 166:174-192.
- Sims AH (2009). Bioinformatics and breast cancer: What can high-throughput genomic approaches actually tell us? *J Clin Pathol*, 62:879-885.
- Siriwardhana N, Choudhary S, Wang H-CR (2008). Precancerous model of human breast epithelial cells induced by NNK for prevention. *Breast Cancer Res Treat*, 109:427-441.
- Skinner MK, Manikkam M, Guerrero-Bosagna C (2010). Epigenetic transgenerational actions of environmental factors in disease etiology. *Trends Endocrinol Metab*, 21:214-222.
- Slack RJ, Gronow JR, Voulvoulis N (2005). Household hazardous waste in municipal landfills: Contaminants in leachate. *Sci Total Environ*, 337:119-137.
- Smigal C, Jemal A, Ward E, Cokkinides V, *et al.* (2006). Trends in breast cancer by race and ethnicity: Update 2006. *Cancer*, 56:168-183.
- Smith R and Lourie B (2009). *Slow Death by Rubber Duck*. Toronto: Knopf Canada.
- Smith-Bindman R, Lipson J, Marcus R, *et al.* (2009). Radiation dose associated with common computed tomography examinations and the associated lifetime attributable risk of cancer. *Arch Intern Med*, 169:2078-2086.
- Soler D, Pampalona J, Tusell L, Genesca A (2009). Radiation sensitivity increases with proliferation-associated telomere dysfunction in nontransformed human epithelial cells. *Aging Cell*, 8:414-425.
- Sonnenschein C, Soto A (2000). The somatic mutation theory of carcinogenesis: Why it should be dropped and replaced. *Mol Carcinogenesis*, 29:1-7.
- Sørlie T, Tibshirani R, Parker J, *et al.* (2003). Repeated observation of breast tumor subtypes in independent gene expression data sets. *Proc Nat Acad Sci*, 100: 8418-8423.
- Soto AM, Justicia H, Wray JW, Sonnenschein C (1991). p-Nonyl-phenol: An estrogenic xenobiotic released from "modified" polystyrene. *Environ Health Perspect*, 92:167-173.
- Soto AM, Chung KL, Sonnenschein C (1994). The pesticides endosulfan, toxaphene, and dieldrin have estrogenic effects on human estrogen-sensitive cells. *Environ Health Perspect*, 102:380-383.
- Soto AM, Sonnenschein C, Chung KL, *et al.* (1995). The E-SCREEN assay as a tool to identify estrogens: An update on estrogenic environmental pollutants. *Environ Health Perspect*, 103 (Suppl 7): 113-122.
- Soto AM, Sonnenschein C (2004). The somatic mutation theory of cancer: Growing problems with the paradigm? *BioEssays*, 26:1097-1107.
- Soto AM, Maffini MV, Schaeberle CM, Sonnenschein C (2006). Strengths and weaknesses of in vitro assays for estrogenic and androgenic activity. *Best Pract Res Clin Endocrinol Metab*, 20:15-33.
- Soto AM, Maffini M, Sonnenschein C (2008a). Neoplasia as development gone awry: the role of endocrine disruptors. *Int J Androl*, 31:288-293.
- Soto AM, Vandenberg LN, Maffini MV, Sonnenschein C (2008b). Does breast cancer start in the womb? *Basic Clin Pharmacol Toxicol*, 102:125-133.
- Stahlhut RW, Welshons WV, Swan SH (2009). Bisphenol A data in NHANES suggest longer than expected half-life, substantial non-food exposure, or both. *Environ Health Perspect*, 117:784-789.
- Stanford JL, Herrinton LJ, Schwartz SM (1995). Breast cancer incidence in Asian migrants to the United States and their descendants. *Epidemiology*, 6:181-183.
- Steck SE, Gaudet MM, Eng SM, *et al.* (2007). Cooked meat and risk of breast cancer: Lifetime versus recent dietary intake. *Epidemiology*, 18:373-382.
- Steenland K, Whelan E, Daddens J, *et al.* (2003). Ethylene oxide and breast cancer incidence in a cohort study of 7,576 women. *Cancer Causes Control*, 14:531-539.
- Steingraber S. (2007). *The Falling Age of Puberty in U.S. Girls: What We Know, What We Need to Know*. San Francisco: Breast Cancer Fund.
- Stevens RG (2009). Working against our endogenous circadian clock: Breast cancer and electric lighting in the modern world. *Mutat Res*, 680:106-108.
- Stuebe AM, Willett WC, Xue F, Michels KB (2009). Lactation and incidence of premenopausal breast cancer: a longitudinal study. *Arch Intern Med*, 169:1364-1371.
- Sugiura-Ogasawara M, Ozaki Y, Sonta S, Makino T, Suzumori K. (2005). Exposure to bisphenol A is associated with recurrent miscarriage. *Human Reprod*, 20:2325-2429.

Sukocheva OA, Yang Y, Gierthy JF, *et al.* (2005). Methyl mercury influences growth-related signaling in MCF-7 breast cancer cells. *Environ Toxicol*, 20:32-44.

Sutherland L, Easthope T, Sattler B, *et al.* (2008). Guide to choosing safer products and chemicals: Implementing chemicals policy in health care. www.noharm.org/lib/downloads/chemicals/Guide_to_Safer_Chems.pdf (7/12/2010).

Swan SH, Main KM, Liu F, *et al.* (2005). Decrease in anogenital distance among male infants with prenatal phthalate exposure. *Environ Health Perspect*, 113:1056-1061.

Swartz CH, Reddy S, Benotti MJ, *et al.* (2006). Steroid estrogens, nonylphenol ethoxylate metabolites, and other wastewater contaminants in groundwater affected by a residential septic system on Cape Cod, MA. *Environ Sci Technol*, 40:4894-4902.

Sweeney C, Giuliano AR, Baumgartner KB, *et al.* (2007). Oral, injected and implanted contraceptives and breast cancer risk among U.S. Hispanic and non-Hispanic white women. *Int J Cancer*, 121:2517-2523.

T

Talsness CE (2008). Overview of toxicological aspects of polybrominated diphenyl ethers: A flame-retardant additive in several consumer products. *Environ Res*, 108:158-167.

Teitelbaum SL, Britton JA, Gammon MD, *et al.* (2003). Occupation and breast cancer in women 20-44 years of age (United States). *Cancer Causes Control*, 14:627-637.

Thomas P, Dong J (2006). Binding and activation of the seven-transmembrane estrogen receptor GPR30 by environmental estrogens: A potential novel mechanism of endocrine disruption. *J Steroid Biochem Mol Biol*, 102:175-179.

Thompson PA, DeMarini DM, Kadlubar FF, *et al.* (2002). Evidence for the presence of mutagenic arylamines in human breast milk and DNA adducts in exfoliated breast ductal epithelial cells. *Environ Mol Mutagenesis*, 39:134-142.

Thompson D, Kriebel D, Quinn MQ, Wegman DH, Eisen EA (2005). Occupational exposure to metalworking fluids and risk of breast cancer among female autoworkers. *Am J Indust Med*, 47:153-160.

Titus-Ernstoff L, Hatch EE, Hoover RN, *et al.* (2001). Long-term cancer risk in women given diethylstilbestrol (DES) during pregnancy. *Br J Cancer*, 84:126-133.

Tiway CM (1998). Premature sexual development in children following the use of estrogen- or placenta- containing hair products. *Clin Pediatr*, 37:733-739.

Tiway CM, Ward JA (2003). Use of hair products containing hormone or placenta by U.S. military personnel. *J Pediatr Endocrinol Metab*, 16:1025-1032.

Tokunaga M, Land CE, Tokuoka S, *et al.* (1994). Incidence of female breast cancer among atomic bomb survivors, 1950-1985. *Radiat Res*, 138:209-223.

Toppiari J, Juul A (2010). Trends in pubertal timing in humans and environmental modifiers. *Mol Cell Endocrinol*, 324:39-44.

Touillaud MS, Thiebaut ACM, Fournier A, *et al.* (2007). Dietary lignan intake and postmenopausal breast cancer risk by estrogen and progesterone receptor status. *J Natl Cancer Inst*, 99:475-86.

Travis RC, Allen NE, Appleby PN, *et al.* (2008). A prospective study of vegetarianism and isoflavone intake in relation to breast cancer risk in British women. *Int J Cancer*, 122:705-710.

Troisi R, Potischman N, Roberts J, *et al.* (2003). Associations of maternal and umbilical cord hormone concentrations with maternal, gestational and neonatal factors (United States). *Cancer Causes Control*, 14:347-355.

Troisi R, Hatch EE, Titus-Ernstoff L, *et al.* (2007). Cancer risk in women prenatally exposed to diethylstilbestrol. *Int J Cancer*, 121:356-360.

Tsai KK, Chuang EY, Little JB, *et al.* (2005). Cellular mechanisms for low-dose ionizing radiation-induced perturbation of the breast tissue microenvironment. *Cancer Res*, 65:6734-6744.

Tsigionia A, Lagoudi A, Chandriou S, *et al.* (2010). Indoor air in beauty salons and occupational health exposure of cosmetologists to chemical substances. *Int J Environ Res Public Health*, 7:314-324.

Turesky RJ (2007). Formation and biochemistry of carcinogenic heterocyclic aromatic amines in cooked meats. *Toxicol Lett*, 168:219-227.

Turnbull C, Mirugaesu N, Eeles R (2006). Radiotherapy and genetic predisposition to breast cancer. *Clin Oncol*, 18:257-267.

Tward JD, Wendland MM, Shrieve DC, *et al.* (2006). The risk of secondary malignancies over 30 years after the treatment of non-Hodgkin lymphoma. *Cancer*, 107:108-115.

Tynes T, Andersen A, Langmark F (1992). Incidence of cancer in Norwegian workers potentially exposed to electromagnetic fields. *Am J Epidemiol*, 136:81-88.

U

USPSTF: U.S. Preventive Services Task Force (2009). Screening for breast cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*, 151:716-727.

Ueda M, Imai T, Takizawa T, *et al.* (2005). Possible enhancing effects of atrazine on growth of 7, 12-dimethylbenz(a) anthracene-induced mammary tumors in ovariectomized Sprague-dawley rats. *Cancer Sci*, 96:19-25.

Updike MS, Sawdy JC, Wang L, *et al.* (2007). Primary cultured human breast epithelial cells up-regulate protein disulfide isomerase in response to zeranol. *Anticancer Res*, 27:407-410.

V

Valeron PF, Pestano JJ, Luzardo OP, *et al.* (2009). Differential effects exerted on human mammary epithelial cells by environmentally relevant organochlorine pesticides either individually or in combination. *Chem-Biol Interact*, 180:485-491.

Vandenberg LN, Maffini MV, Schaeberle CM, *et al.* (2008). Perinatal exposure to the xenoestrogen bisphenol-A induces mammary intraductal hyperplasias in adult CD01 mice. *Reprod Toxicol*, 26:210-219.

Vandenberg LN, Maffini MV, Wadia PH, *et al.* (2007). Exposure to environmentally relevant doses of the xenoestrogen bisphenol-A alters development of the fetal mouse mammary gland. *Endocrinology*, 148:116-127.

Vandenberg LN, Wadia PR, Schaeberle, *et al.* (2006). The mammary gland response to estradiol: Monotonic at the cellular level, non-monotonic at the tissue level of organization? *J Steroid Biochem Molec Biol*, 101:263-274.

van Meeuwen JA, ter Burg W, Piersma A, *et al.* (2007). Mixture effects of estrogenic compounds on proliferation and pS2 expression of MCF-7 human breast cancer cells. *Food Chem Toxicol*, 45:2319-2330.

Verkooijen HM, Bouchardy C, Vinh-Hung V, *et al.* (2009). The incidence of breast cancer and changes in the use of hormone replacement therapy: A review of the evidence. *Maturitas*, 64:80-85.

Veronesi U, Luini A, Del Vecchio M, *et al.* (1993). Radiotherapy after breast-preserving surgery in women with localized cancer of the breast. *New England J Med*, 328:1587-1591.

Verschaeve L, Koppen G, Van Gorp U, *et al.* (2007). Seasonal variations in spontaneous levels of DNA damage; implication in the risk assessment of environmental chemicals. *J Appl Toxicol*, 27: 612-620.

Vessey M, Painter R (2006). Oral contraceptive use and cancer: Findings in a large cohort study, 1968-2004. *Br J Cancer*, 95:385-389.

Villanueva CM, Durand G, Coutté MB, *et al.* (2005). Atrazine in municipal drinking water and risk of low birth weight, preterm delivery, and small-for-gestational-age status. *Occup Environ Med*, 62:400-405.

Viney P, Khan AE, Valaanderen J, Vermeulen R (2009). The impact of new research technologies on our understanding of environmental causes of disease: The concept of clinical vulnerability. *Environ Health*, 8:54-64.

vom Saal FS, Hughes C (2005). An extensive literature concerning low-dose effects of bisphenol A show the need for a new risk assessment. *Environ Health Perspect*, 113:926-933.

vom Saal FS, Akingbemi BT, Belcher SM, *et al.* (2007). Chapel Hill bisphenol A expert panel consensus statement: Integration of mechanisms, effects in animals and potential to impact human health at current levels of exposure. *Reprod Toxicol*, 24:131-138.

vom Saal FS, Akingbemi BT, Belcher SM, *et al.* (2010). Flawed experimental design reveals the need for guidelines requiring appropriate positive controls in endocrine disruption research. *Toxicol Sci*, 115:612-613.

Vorderstrasse BA, Fenton SE, Bohn AA, *et al.* (2004). A novel effect of dioxin: Exposure during pregnancy severely impairs mammary gland differentiation. *Toxicol Sci*, 78:248-257.

W

Wadia PR, Vandenberg LN, Schaeberle CM, *et al.* (2007). Perinatal bisphenol A exposure increases estrogen sensitivity of the mammary gland in diverse mouse species. *Environ Health Perspect*, 115:80-86.

Wahner-Roedler DL, Petersen IA (2004). Risk of breast cancer and breast cancer characteristics in women after treatment for Hodgkin lymphoma. *Drugs Today*, 40:865-79.

Walrath J, Li FP, Hoar SK, *et al.* (1985). Causes of death among female chemists. *Am J Public Health*, 75:883-885.

Wang FI, Kuo ML, Shun CT, *et al.* (2002). Chronic toxicity of a mixture of chlorinated alkanes and alkenes in ICR mice. *J Toxicol Environ Health*, 65:279-291.

Warnberg F, Yuen J, Holmberg L (2000). Risk of subsequent invasive cancer after breast cancer in situ. *Lancet*, 355:724-725.

Warner MB, Eskanazi B, Mocarelli P, *et al.* (2002). Serum dioxin concentrations and breast cancer risk in the Seveso Women's Health Study. *Environ Health Perspect*, 110:625-628.

Warri A, Saarinen NM, Makela S, Hilakivi-Clarke L (2008). The role of early life genistein exposures in modifying breast cancer risk. *Br J Cancer*, 98:1485-1493.

Watson CS, Bulayeva NN, Wozniak AL, *et al.* (2005). Signaling from the membrane via membrane estrogen receptor-alpha: Estrogens, xenoestrogens, and phytoestrogens. *Steroids*, 70:364-371.

Weiderpass E, Pukkala E, Kauppinen T, *et al.* (1999). Breast cancer and occupational exposures in women in Finland. *Am J Ind Med*, 36:48-53.

Weinstein S (2010). NJIT patent may be able to replace BPA; Make consumer products safer. www.njit.edu/news/2010/2010-053.php (7/12/2010).

Weise, Elizabeth (2004). "Growth hormones in veal spark debate." *USA Today*, April 1, 2004.

Weiss JR, Moysich KB, Swede H (2005). Epidemiology of male breast cancer. *Cancer Epidemiol Biomarkers Prev*, 14:20-26.

Welshons WV, Nagel SC, vom Saal FS (2006). Large effects from small exposures. III. Endocrine mechanisms mediating effects of bisphenol A at levels of human exposure. *Endocrinology*, 147:S56-S69.

Wennborg H, Yuen J, Axelsson G, *et al.* (1999). Mortality and cancer incidence in biomedical laboratory personnel in Sweden. *Am J Ind Med*, 35:382-389.

Weschler CJ (2009). Changes in indoor pollutants since the 1950s. *Atmospheric Environ*, 43:153-169.

Westerhoff P, Yoon Y, Snyder S, *et al.* (2005). Fate of endocrine disruptor, pharmaceutical, and personal care product chemicals during simulated drinking water treatment processes. *Environ Sci Technol*, 39:6649-6663.

WHO: World Health Organization (1996). Levels of PCBs, PCDDs, and PCDFs in human milk. WHO European Centre for Environment and Health.

WHO: World Health Organization Global Malaria Programme (2007). The use of DDT in Malaria vector control: WHO position statement. www.who.int/ipcs/capacity_building/who_statement.pdf

Wigle DT, Arbuckle TE, Turner MC, Berube A, Yang Q, *et al.* (2008). Epidemiologic evidence of relationships between reproductive and child health outcomes and environmental chemical contaminants. *J Toxicol Environ Health*, 11:373-517.

Willson HR (2009). Pesticide regulations. In *Radcliffe's IPM World Textbook*. The Regents of the University of Minnesota. <http://ipmworld.umn.edu/chapters/willson.htm> (7/12/2010).

Windham GC, Pinney SM, Sjodin A, *et al.* (2010). Body burdens of brominated flame retardants and other persistent organo-halogenated compounds and their descriptors in U.S. girls. *Environ Res*, doi:10.1016/j.envres.2010.01.004.

Wittassek M, Angerer J, Kolossa-Gehring M, *et al.* (2009). Fetal exposure to phthalates: a pilot study. *Int J Hyg Environ Health*, 212:492-498.

Wolff MS (1983). Occupationally derived chemicals in breast milk. *Am J Ind Med*, 4:259-281.

Wolff MS, Teitelbaum SL, Windham G, *et al.* (2007). Pilot study of urinary biomarkers of phytoestrogens, phthalates, and phenols, in girls. *Environ Health Perspect*, 115:116-121.

Wolff MS, Teitelbaum SL, Pinney SM, *et al.* (2010). Investigation of relationships between urinary biomarkers of phytoestrogens, phthalates, and phenols, and pubertal stages in girls. *Environ Health Perspect*, 118:1039-1046.

Woodruff TJ, Parker JD, Kyle AD, *et al.* (2003). Disparities in exposure to air pollution during pregnancy. *Environ Health Perspect*, 111: 942-946.

Woolcott CG, Aronson KJ, Hanna WM, *et al.* (2001). Organochlorines and breast cancer risk by receptor status, tumor size and grade (Canada). *Cancer Causes Control*, 12:395-404.

Wozniak AL, Bulayeva NN, Watson CS (2005). Xenoestrogens at picomolar to nanomolar concentrations trigger membrane estrogen receptor-alpha-mediated Ca²⁺ fluxes and prolactin release in GH3/B6 pituitary tumor cells. *Environ Health Perspect*, 113:431-9.

Wright EG (2004). Radiation-induced genomic instability: Manifestations and mechanisms. *Int J Low Radiat*, 1:231-241.

WSPPN: Western Sustainability and Pollution Prevention Network (1999). Carcinogens and reproductive toxins found in cleaning products. <http://wsppn.org/Janitorial/factsheets.cfm> (7/12/2010).

Wu AH, Yu MC, Tseng CC, Pike MC (2008). Epidemiology of soy exposures and breast cancer risk. *Br J Cancer*, 98:9-14.

Wu HDI, Chou SY, Chen DR, *et al.* (2006). Differentiation of serum levels of trace elements in normal and malignant breast patients. *Biol Trace Elem Res*, 113:9-18.

WVE: Women's Voices for the Earth (2007). Household hazards: Potential hazards of home cleaning products. www.womenandenvironment.org/campaignsandprograms/SafeCleaning/folder.2010-03-10.7450668740/HazardsReport.pdf (7/12/2010).

X

Xian C (1995). Degradation of IGF-1 in the adult rat gastrointestinal tract is limited by a specific antiserum or the dietary protein casein. *J Endocrinol*, 146:215.

Xie L, Thrippleton K, Irwin MA, *et al.* (2005). Evaluation of estrogenic activities of aquatic herbicides and surfactants using a rainbow trout vitellogenin assay. *Toxicol Sci*, 87:391-398.

Xu J, Wu Laosheng, Chen, W, *et al.* (2009a). Pharmaceuticals and personal care products (PPCPs), and endocrine disrupting compounds (EDCs) in runoff from a potato field irrigated with treated wastewater in southern California. *J Health Sci*, 55:306-310.

Xu P, Ye W, Jen R, *et al.* (2009b). Mitogenic activity of zeranol in human breast cancer cells is enhanced by leptin and suppressed by gossypol. *Anticancer Res*, 29:4621-4628.

Y

Ye W, Pingping X, Threlfall WR, *et al.* (2009). Zeranol enhances the proliferation of pre-adipocytes in beef heifers. *Anticancer Res*, 29:5045-5052.

Ye X, Bishop AM, Reidy JA, *et al.* (2006a). Parabens as urinary biomarkers of exposure in humans. *Environ Health Perspect*, 114: 1843-1846.

Ye X, Kuklenyik Z, Needham LL, Calafat AM (2006b). Measuring environmental phenols and chlorinated organic chemicals in breast milk using automated on-line column-switching-high performance liquid chromatography-isotope dilution tandem mass spectrometry. *J Chromatog*, 831:110-115.

Ye X, Pierik FH, Angerer J, *et al.* (2009). Levels of metabolites of organophosphate pesticides, phthalates, and bisphenol A in pooled urine specimens from pregnant women participating in the Norwegian mother and child cohort study (MoBa). *Int J Hyg Environ Health*, 212:481-491.

Ying MWL, Agrawal A, Cheung K-L (2005). The 'other half' of breast cancer: a review of male breast cancer. *J Men's Health Gender*, 2:406-414.

Yu CP, Chu KH (2009a). Occurrence of pharmaceuticals and personal care products along the West Prong Little Pigeon River in east Tennessee, USA. *Chemosphere*, 75:1281-1286.

Yu L, Zhan P (2009b). Molecular mechanisms underlying proliferation and apoptosis in breast cancer MCF-7 cells induced by pentabrominated diphenyl ethers. *Toxicol Environ Chem*, 91:665-670.

Yuri T, Nikaido Y, Shimano N, *et al.* (2004). Effects of prepubertal zeranol exposure on estrogen target organs and N-methyl-N-nitrosourea-induced mammary tumorigenesis in female Sprague-Dawley rats. *In Vivo*, 18:755-762.

Z

Zarbl H (2007). Toxicogenomic analyses of genetic susceptibility to mammary gland carcinogenesis, in rodents: Implications for human breast cancer. *Breast Disease*, 28:87-105.

Zhang M, Yang H, Holman CD (2009). Dietary intake of isoflavones and breast cancer risk by estrogen and progesterone receptor status. *Breast Cancer Res Treat*, 118:553-563.

Zheng T, Holford T, Mayne S, *et al.* (1999). DDE and DDT in breast adipose tissue and risk of female breast cancer. *Am J Epidemiol*, 150:453-458.

Zheng T, Holford TR, Taylor Mayne S, *et al.* (2002). A case-control study of occupation and breast cancer risk in Connecticut. *J Cancer Epidemiol Prev*, 7:3-11.

Zhu Y, Stevens RG, Leaderer D, *et al.* (2008). Non-synonymous polymorphisms in the circadian gene NPAS2 and breast cancer. *Breast Cancer Res Treat*, 107:421-425.

Ziegler RG, Hoover RN, Pike MC, *et al.* (1993). Migration patterns and breast cancer risk in Asian American women. *J Nat Cancer Inst*, 85:1819-27.

Ziegler RG (2000). Phytoestrogens and breast cancer. *Am J Clin Nutr*, 79:183-184.

Zimmerman LI, Lima R, Pietrobon R, Marcozzi D (2008). The effects of seasonal variation on hazardous chemical releases. *J Hazard Mater*, 151:232-238.

Zota A, Rudel RA, Morello-Frosch R, Brody JG (2008). Elevated house dust and serum concentrations of PBDEs in California: unintended consequences of furniture flammability standards? *Environ Sci Technol*, 42:8158-8164.

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