BREAST CANCER & THE ENVIRONMENT RESEARCH CENTERS

Early Life Exposure to Phenols and Breast Cancer Risk in Later Years

FACT SHEET on PHENOLS

Abstract

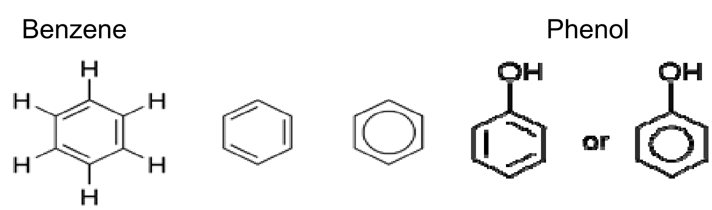
Phenols or phenolics are a manufactured class of weakly acidic water-soluble chemical compounds related to the organic chemical compound phenol naturally present in most foods. Phenol is used as a slimicide, a disinfectant, in medical products, and as a reagent in research laboratories and as a precursor or intermediate during the manufacture of phenolic resins, bisphenol A, caprolactam, adipic acid, alkylphenols, aniline, and chlorinated phenols. Phenol ranks in the top 50 chemical volumes produced in the United States. Phenols are readily absorbed following inhalation, ingestion or skin contact, and are widely distributed in the body, can cross the placenta, and have been found in human breast milk. Some phenols are weak endocrine disrupters. Epidemiological studies are needed to determine the association between phenol exposure and human breast cancer risk. Research studies investigating the association of phenols with breast cancer risk, sources of exposures, effects on puberty, and general effects in the body are ongoing. The International Agency for Research on Cancer (IARC) classification for phenols is Group 3, not classifiable with regard to its carcinogenicity to humans (1,2,3).

This fact sheet provides information about nine phenolic compounds being measured and examined by the Breast Cancer and the Environment Research Centers (BCERC) epidemiology studies, sources of exposures, effects on puberty, effects in the body, and research studies looking at phenols as being associated with breast cancer risk. Phenols are nonessential chemical compounds.

What are phenols?

Phenols, sometimes called **phenolics**, are a class of aromatic organic compounds consisting of one or more hydroxyl groups attached to an aromatic hydrocarbon group (4). Phenol is a benzene derivative and is the simplest member of the phenolic chemical. Its chemical formula is C_6H_5OH and its structure is that of a hydroxyl group (-OH) bonded to a phenyl ring (Fig. 1). Synonyms for phenol include carbolic acid, benzophenol, and hydroxybenzene.

Figure 1:



Phenol is produced naturally and synthesized as a manufactured chemical. Naturally, it is a constituent of coal tar and creosote, decomposing organic material, human and animal wastes, and as a compound found in many non-foods and foods. For example, salicylic acid is a natural phenolic compound found in willow bark. Salicylic acid is also synthesized from phenol as an intermediate in the industrial production of aspirin. Phenol is also formed during forest fires, and by atmospheric degradation of benzene in the presence of light. In addition, phenol is produced by the body and excreted as a metabolic product independent of external exposure or intake.

Phenol is a high volume chemical with production exceeding 3-billion pounds annually in the United States and 6-billion pounds worldwide. It ranks in the top 50 in production volumes for chemicals produced in the United States with the housing and construction industries accounting for about half of the phenol used (8). Manufacture of phenolic resins is the largest single use of phenol, reported to be 1.188 billion pounds in 1988 (33). Phenol is usually sold commercially as a thick liquid.

The three major uses of manufactured phenol are as chemical intermediates to produce:

1. phenolic resins (human made polymers consisting of phenol) used in plywood adhesive, construction, automotive, and appliance industries
2. bisphenol A which is used primarily in the manufacture polycarbonate plastics, epoxy resins and non-polymer additives to other synthetic polymers
3. caprolactam which is used in the manufacture of nylon 6 and other synthetic fibers

Phenol is also used as an antiseptic, a general disinfectant, and a slimicide (chemicals that kill bacteria and fungi in slimes), in medical preparations including lotions, ointments, mouthwashes, salves. Phenol is also the active ingredient in some over-the-counter oral anesthetics sprays used as a treatment for sore throats. Minor uses of phenol include the manufacture of paint and varnish removers, lacquers, paints, rubber, ink, illuminating gases, tanning dyes, perfumes, soaps and toys (6,7).

How are humans exposed to phenols?

Exposures to phenol can occur in the workplace, from environmental media, from contaminated drinking water or foodstuffs, or from use of consumer products containing phenol (ATSDR). Phenol is readily absorbed following inhalation, ingestion, and skin contact.

Very small amounts of phenol is produced endogenously as a breakdown product of protein metabolism by the action of bacteria on normal constituents of the diet in the gut and excreted independent of external exposure to the compound.

Inhalation

- **Indoor air and house dust**

Exposure to phenol through inhalation is a less probable route than oral and dermal. Phenol can be released during the combustion of wood, fuel emissions and tobacco. It has been found that the smoke of 1 nonfilter cigarette contains 60–140 μg of phenol, 19–35 μg for a filter-tipped cigarette, and 24–107 μg in cigars (IARC 1986; NCI 1998), and smoking these products indoors produces a measurable amount of phenol (Guerin et al. 1992). If children are present in indoor environments polluted with tobacco smoke, they may be exposed to low levels of phenol.

Ingestion

- **Water**

Ingestion of contaminated water

- **Food**

Free and bound phenol compounds are found naturally in foods. High phenol foods include tomatoes, apples, peanuts, bananas, oranges, cocoa, red grapes, colored fruits (e.g., cranberries), and milk. These compounds may also be a contaminant in packaged foods, as these compounds are used in can liners and foil wraps. The "phenol" category contains quite a few subgroups, both food and non-food. For example, a non-food is salicylate a natural chemical made by many plants is a subgroup of phenol.

Skin Contact

Phenol compounds are found in dental sealants, sunscreen, lotions, hand soap, and toothpaste. Topically applied these compounds are a skin irritant.

The nine phenolic compounds and exposure sources examined by the BCERC epidemiology studies are listed in Table 1. Below the table each compound exposure source is further described.

Table 1. Phenolic compounds, their parent compounds, and examples of environmental sources. (9)

	Chemical name or common synonym	Abbreviation	Parent Compound, if applicable	Additives, commercial and personal product exposure sources
1	Bisphenol A	BPA		Polycarbonate containers and coatings (cans, cups), dental sealant
2	Benzophenone-3(2-hydroxy-4-methoxy-benzophenone), (oxybenzone)	BP3		Sunscreen agent, photostabilizer for synthetic resins
3, 4, 5	2,4-Dichlorophenol and trichlorophenols (chlorinated phenols)	24DCP, 245TCP, 246TCP	Phenoxy- and other derivatives (245, 246 TCP are metabolites of Hexachlorobenzene and Hexachlorocyclohexane.)	Herbicides (organochlorine pesticides)
6	2,5-Dichlorophenol	25DCP	4-dichlorobenzene (metabolite of p-DCB)	Mothballs
7	ortho-Phenylphenol	o-PP		Fungicide
8	4-tert-Octylphenol	4-t-OP		Detergent surfactant
9	Triclosan [5-chloro-2-(2,4-dichlorophenoxy)phenol]	TRCS		Microbicide in home cleaning and personal care products

1. Bisphenol A (BPA)

Bisphenol A belongs to the phenol class of aromatic organic compounds and is a chemical compound containing two phenol functional groups. It was first synthesized over 100 years ago and during the 1930's BPA was investigated as an estrogen drug. Beginning in the 1950's BPA has primarily been used to manufacture polycarbonate plastic. It is also found in epoxy resins used to line metal food and drink cans, as a polymer additive to polyvinyl chloride plastic (e.g. plastic cling wraps and plastic pipes), and some dental sealants. Bisphenol A is also used during the manufacture of specialty resins and flame retardants, such as tetrabromobisphenol A. The recycling code 7 on the bottom of some plastic containers, such as large water bottles used in water dispensers, often indicates that the plastic is made of polycarbonate. There are many synonyms for bisphenol A (10).

Human exposure is primarily through ingestion.

Ingestion sources of BPA include:

- **Contaminated Foods and Beverages**
  - BPA can migrate from **polycarbonate plastic bottles or food storage containers** into foods or beverages especially once the container has been heated to high temperatures (e.g. boiling water)
  - BPA can migrate from the **epoxy resin inner lining of some metal food and drink cans** into the food or liquid containing the food
  - BPA may also migrate from **polycarbonate plastic in some clear plastic spill-proof cups and cutlery** (forks, knives, and spoons) into hot or fatty foods

- **Oral exposure from dental procedures**
  - Several studies have shown that some dental sealants and composite materials used to fill cavities can release BPA

The US EPA has set a safe human intake dose of 50 micrograms per kilogram of body weight per day for **bisphenol A.**

2. Benzophenone-3(2-hydroxy-4-methoxy-benzophenone)[oxybenzone] (BP3)
BP3 (oxybenzone) is an ultraviolet (UV) filter and is used in the manufacture of sunscreens, as a photostabilizer for synthetic resins, many personal care, and household products. A listing of products containing BP3 can be found at: http://householdproducts.nlm.nih.gov/cgi-bin/household/brands?tbl=chem&id=240. Use of the term "sunscreen" or similar sun protection terminology in a product's labeling generally causes the product to be subject to regulation as a drug (11). There are many synonyms for BP3 (25).

Humans can be exposed through skin absorption, inhalation, and ingestion.

3-5. 2,4-Dichlorophenol and trichlorophenols (24DCP, 245TCP, 246TCP)
2,4-Dichlorophenol and trichlorophenols (24DCP, 245TCP, 246TCP) are chlorinated phenols and are primarily used to manufacture herbicides.

245TCP and 246TCP are metabolites of several organochlorine chemicals, including hexachlorobenzene and hexachlorocyclohexane. Trichlorophenols are no longer intentionally manufactured, but they may be produced as byproducts of the manufacture of other chlorinated aromatic compounds. Small amounts of trichlorophenols can be produced during combustion of natural materials and from the chlorination of waste water that contains phenols. IARC classifies polychlorophenols (including trichlorophenols) as possibly carcinogenic to humans, and NTP classifies 246TCP as reasonably anticipated to be a human carcinogen.

The general population may be exposed to 246TCP through ingestion of contaminated food or water and inhalation of contaminated air (12).

Exposure is primarily through ingestion of contaminated water, inhalation, and skin contact.

6. 2,5-Dichlorophenol (25DCP)
2,5-Dichlorophenol (25DCP), an aromatic chemical compound, is a metabolite of paradichlorobenzene. It is primarily used to manufacture mothballs. 25DCP replaced the more traditional naphthalene. P-dichlorobenzene is the parent compound(13). Trade names for p-DCB include *Paramoth*, *Para crystals*, and *Paracide* reflecting its widespread use as a pesticide to kill moths, molds, and mildew. p-DCB is also used as a precursor in the production of the polymer poly(p-phenylene sulfide) used in urinal deodorant blocks to deodorize restrooms and waste containers.

Exposure is primarily through inhalation and skin contact.

7. ortho-Phenylphenol (o-PP) Fungicide
Ortho-Phenylphenol (o-PP) is primarily used to manufacture fungicides.

Exposure is primarily through inhalation and skin contact.

8. 4-tert-Octylphenol (4-t-OP)
4- tert octylphenol (4-t-OP) is a chemical used primarily to manufacture phenolic resins (98%), with the remainder converted into ethoxylates to produce detergent surfactants. Octylphenol belongs to a larger family of chemicals called alkylphenols (APs). The most commercially important alkylphenols are nonylphenol (NP) and octylphenol (OP). They exist in different forms, or "isomers", and are used to make nonylphenol ethoxylates (NPEs) and octylphenol

ethoxylates (OPEs). APs are high production volume man–made chemicals that are reacted with ethylene oxide primarily to manufacture surfactant products called alkylphenol ethoxylates (APEs). APEs are made from and break down into alkylphenols, which are used as antioxidants in plastics and rubber products. The most common APEs are nonylphenol ethoxylates (NPEs).

Alkylphenol ethoxylates (APEs) are synthetic surfactants used in some detergents and cleaning products. APES and/or other alkyphenol derivatives are also used in pesticides, lube oil, hair dyes and other hair care products, and as nonoxynol-9 in spermicides. APs and APEs have been in use for over 50 years and are important to a number of industrial processes, including pulp and paper, textiles, coatings, agricultural pesticides, lube oils and fuels, metals and plastics used in food storage.

Exposure is primarily through skin contact.

9. Triclosan [5-chloro-2-(2,4-dichlorophenoxy)phenol] (TRCS)

Tricolosan **(TRCS)** is an anti-bacterial (microbicide) ingredient that can be found in a wide variety of home care products such as detergents and dish soaps, personal care products such as anti-acne cleansers, deodorants, hand soaps, cosmetics, lotions, creams, toothpastes, mouthwashes, and first aid creams. Microban is another trade name for this compound.

Exposure is primarily through ingestion and skin contact. Oral exposure is primarily through consumer medical products, such as mouthwashes, throat lozenges, and toothpastes.

How does phenol work in the human body?

Phenol is well absorbed from the gastrointestinal tract and through the skin of both animals and humans. It is metabolized principally by conjugation (by sulfation and glucuronidation) with a minor oxidation pathway leading to quinone-related reactive intermediates which bind covalently to protein and are detoxified by conjugation with glutathione. Most of the absorbed phenol and its metabolites are excreted in the urine, with trace amounts of excreted in expired air and the feces.

In addition, very small amounts of phenol is produced endogenously as a breakdown product of protein metabolism by the action of bacteria on normal constituents of the diet in the gut and excreted independent of external exposure to the compound. Some of this internally-produced phenol may be eliminated in the feces and some may pass to the blood.

[To be added: specifics for how each of the nine phenol compounds work in the human body.]

Are phenols endocrine disruptors?

Some. It is certain that some phenols are endocrine disruptors, and it is likely that some phenolic compounds will not have endocrine disrupting activity.

The two phenols that have been characterized as acting as endocrine disruptors are bisphenol A and alkylphenol (octylphenol and nonylphenol isomers). Bisphenol A (BPA) is an estrogenic compound and may also act as a disruptor of androgen action. Two research labs have shown on multiple occasions that BPA causes altered mammary gland development in animal models following early life exposure (26). Nonylphenol exposure during pregnancy has also been shown to disrupt normal mammary gland development in rats (Moon, Kim, Fenton et al., 2007).

According to EPA, an endocrine disrupter is an exogenous agent that interferes with the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body that are responsible for the maintenance of *homeostasis* (biological stability), reproduction, development and/or behavior (27).

Does phenol exposure influence onset of puberty in girls?
Unknown. BCERC's biology and epidemiology studies are investigating this question.

Several animal studies reveal low-dose exposure to BPA (2.4 and 50 ppb per day) can affect the timing of the onset of sexual maturation in females (14,15,16). A multi-generation reproductive toxicity study conducted by the drinking-water route in rats reported delayed puberty, as evidenced by increased age at vaginal opening, and decreases in absolute and relative uterine weights (29).

There is a lack of studies concerning the developmental or reproductive effects of phenol in humans. The National Toxicology Program (NTP) Center for the Evaluation of Risks to Human Reproduction (CERHR) expert panel in August 2007 expressed some concern that exposure to Bisphenol A causes neural and behavioral effect, and minimal concern that exposure potentially causes accelerations in puberty (24).

The BCERC epidemiology study entitled "Environmental and Genetic Determinants of Puberty" completed a small pilot study in November 2006 and measured phenols in young girls urine. The pilot study completed in November 2006 examined urinary biomarkers in ninety peripubertal Asian, Black, Hispanic and White girls to determine exposures to three chemical families known or likely to possess hormonal activity that may be estrogen agonistic or antagonistic (phytoestrogens, phthalate acids, and phenolic compounds). Nine phenols were sampled. Phenols had the lowest concentrations of the three chemical families, and only 3 (BPA, BP3, and 25DCP) of the 9 were detected in > 94% of the samples collected. The highest individual measurement was for benzophenone-3 (BP3; 26,700 µg/L). BP3 was higher in whites and 2,5-dichlorophenol (25DCP) was higher in blacks. BP3 was higher in samples collected in summer (9). *O*-Desmethylangolensin (*O*-DMA), 25DCP, and 2,4-dichlorophenol (24DCP) levels differed across the three study sites included in this study. The highest median concentrations for individual analytes in each chemical family were for the phytoestrogen enterolactone (298 µg/L), phthalate acid monoethylphthalate (MEP; 83.2 µg/L), and phenolic compound benzophenone-3 (BP3; 14.7 µg/L) (9). This small pilot data set will guide future expanded cohort studies.

Do phenols cross the placenta?
Yes.

Are phenols found to be present in breast milk?
Yes.

In addition to a number of previous studies, a recent study of 20 breast milk samples eight phenolic compounds: bisphenol A (BPA), 4-tert-octylphenol (4-tOP), ortho-phenylphenol (OPP), 2,4-dichlorophenol, 2,5-dichlorophenol, 2,4,5-trichlorophenol, 2,4,6-trichlorophenol, and 2-hydroxy-4-metoxybenzophenone (BP-3), BPA, OPP, and BP-3 were detected in more than 60% of the samples tested (17).

Chemical components (PAHs, cresol, phenols) of cal tar creosote may be stored in body fat, they may be found in breast milk and could pass to nursing infants (18).

Are concentration levels of phenols the same in men and women?
No. The concentration level depends on the exposure compound. Males have higher occupational exposure to phenols manufactured for use in construction industries.

Are there medical tests for phenol exposure?
Yes.

Phenol can be detected in urine. This test can be used to determine whether a person has recently been exposed to phenol or to substances that are changed to phenol in the body. However, no test will tell whether a person has been exposed only to phenol, because many substances are changed to phenol in the body. Most of the phenol that enters the body is excreted in the urine within 24 hours. There are tests that measure presence of substances converted to phenol in the body in blood, however, they are less common.

Urine Tests

Urine can be tested for the presence of substances converted to phenol in the body recently, usually within one or two days of exposure (19). For example, the most common urine test measures a breakdown product of p-DCB called 2,5-dichlorophenol(25DCP) to measure for exposure to p-DCB.

Measurement of phenol in urine requires special laboratory equipment and techniques that are not routinely available in most hospitals or clinics. However, urine samples can be taken at a doctor's office and can be sent to specialized laboratories for analysis.

The normal range of phenol in the urine of unexposed individuals is 0.5–80 milligrams of phenol per liter of urine (mg/L); normal concentrations in urine generally do not exceed 20 mg/L (ACGIH 2001).This test can be used to determine if the urine has a higher than normal concentration of phenol, thus suggesting recent exposure to phenol or to substances that are converted to phenol in the body (e.g., benzene). However, health effects associated with any level of phenolic exposures are not known.

In in vitro studies, what is the association between phenol exposure and breast cancer risk? [An experiment in a test tube or cell culture system is an in vitro experiment.]
Unknown.

In in vivo studies, what is the association between phenol exposure and breast cancer risk? [An experiment in an animal model is referred to as an in vivo experiment.]
BCERC's laboratory-based biology research project entitled, "Environmental Effects on the Molecular Architecture and Function of the Mammary Gland across the Lifespan," is investigating this question. However, it is apparent that BPA has significant effects on both mammary gland development and tumor susceptibility in rodent models. Female offspring of timed-pregnant Wistar rats exposed to 25 pg/kg body weight/day demonstrated precocious mammary epithelial development, and chemical carcinogen exposure further induced increased ductal hyperplasia and development of neoplastic lesions compared to controls (30). Offspring of pregnant BPA-exposed mice demonstrate similar morphological changes (31)..

In epidemiological studies, what is the association between phenol exposure and breast cancer risk? [Studies of diseases in populations of humans or other animals.]

There have been "virtually no" studies of direct effects of phenols in humans. Epidemiological studies are needed to determine the association between phenol exposure and human breast cancer risk.

Bisphenol A is known to mimic the endogenous hormone estradiol and there is a growing body of scientific research that is raising concerns about exposures to low doses of BPA during development resulting to adverse effects on health later in life. Specific examples include breast and prostate cancers and obesity.

Were phenols included in the National Report on Human Exposure to Environmental Chemicals biomonitoring measurements from the 1999-2002 National Health and Nutrition Examination Survey (NHANES) Third Report?

Yes. There were seven phenols followed and reported in selected participants. Four environmental phenols, Bisphenol A, 2-Hydroxy-4-methoxybenzophenone (Benzophenone-3), 4-tert-Octyl phenol and 2,4,4'-Trichloro-2'-hydroxyphenyl ether (Triclosan), and three organchlorine pesticides, Pentachlorophenol, 2,4,5-Trichlorophenol, 2,4,6-Trichlorophenol. Reported for the first time in the Third Report are the four environmental phenols.

Below is a summary of three of the phenols monitored in children aged 6-11 that are also being biomonitored in the BCERC pilot epidemiology study. No data is available in children for certain phenols, including bisphenol A (BPA), a chemical with hormonal activity relevant to pubertal development (28), however, CDC has analyzed urine samples from a nationally representative group of people for the presence of bisphenol A in the NHANES **2003-2004 survey.** Calfat, Ye, Wong, Reidy, and Needham in October 2007 has evaluated this data in a recently published scientific journal (33).

3-5. 2,4-Dichlorophenol and trichlorophenols (24DCP, 245TCP, 246TCP)
Geometric mean levels of urinary 2,4,6-TCP were slightly higher for children aged 6-11 years than for either groups aged 12-19 or 20-59 years, and the group aged 12-19 had higher levels than the group aged 20-59 years. It is unknown whether these differences associated with age represent differences in exposure, pharmacokinetics, or the relationship of dose per body weight.

The *Third Report* released in July 2005 by the US Centers for Disease Control (CDC) presents first-time exposure data for 38 of the 148 chemical compounds and their breakdown products found in consumer goods and manufacturing byproducts in a representative cross section of 2,400 Americans. The *Report* also includes the data from the *Second Report*; that is, data for 1999-2000. The *National Report on Human Exposure to Environmental Chemicals* provides an ongoing assessment of the U.S. population's exposure to environmental chemicals using biomonitoring. Biomonitoring is the assessment of human exposure to chemicals by measuring the chemicals or their metabolites in human specimens such as blood or urine (20). Since 1999, the US Centers for Disease Control and Prevention (CDC) has conducted the National Health and Nutrition Examination Survey (NHANES) to assess the health and nutritional status of adults and children in the United States. The survey, which currently examines about 5,000 people each year, includes a detailed interview and a range of physical examinations. The survey is designed to produce information that is representative of the US population aged 2 months and older (32).

CDC as yet has no optimal biomarker for nonylphenol (21).

What has the IARC determined about phenols and carcinogenesis?

The International Agency for Research on Cancer (IARC) classification for phenols is Group 3, not classifiable with regard to its carcinogenicity to humans. The IARC is part of the World Health Organization.

Has the federal government made recommendations to protect human health?

The federal government develops regulations and recommendations to protect public health. Regulations *can* be enforced by law. The EPA, the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA) are some federal agencies that develop regulations for toxic substances. **Recommendations** provide valuable guidelines to protect public health, **but *cannot* be enforced by law.** The Agency for Toxic

Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH) are two federal organizations that develop recommendations for toxic substances.

Environmental Protection Agency (EPA)

EPA has classified phenol as a Group D, not classifiable as to human carcinogenicity, based on a lack of data concerning carcinogenic effects in humans and animals (22,23).

EPA has determined that the level of phenol in ambient water (lakes, streams) should be limited to 21 mg/L in order to protect human health from the potential toxic effects of exposure to phenol through ingestion of water and contaminated aquatic organisms. EPA requires that spills of 1,000 pounds of phenol or more to the environment be reported to the Agency. The EPA lifetime health advisory for phenol in water is 2 mg/L.

FDA

Phenol is listed on the FDA's Everything Added to Foods in the United States (EAFUS) List and is approved as a component of food packaging materials.

National Toxicology Program (NTP) (NTP a division of the Department of Human Health Services within the National Institutes of Environmental Health Sciences (NIEHS); National Institute of Health (NIH))

The NTP Center for the Evaluation of Risks to Human Reproduction (CERHR) convened an expert panel of 12 independent scientists in August 2007 to review and assess scientific studies on the potential reproductive and developmental hazards of bisphenol A (BPA). From scientific studies on rats and mice, the report determined that for pregnant woman and fetuses, infants and children exposure to BPA in utero potentially causes neural and behavioral effects and accelerations in puberty, and for the general population, exposure to BPA was categorized as negligible concern for adverse reproductive effects. For highly exposed subgroups, such as occupationally exposed populations, the level of concern was elevated to minimal (24). There is no data in women and fetuses, infants and children.

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http://www.bcerc.org/cotc.htm

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For more information on the Breast Cancer and the Environment Research Centers, go to http://www.bcerc.org.

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