

## BREAST CANCER & THE ENVIRONMENT RESEARCH CENTERS

Early Life Exposure to the Phytoestrogen Daidzein and Breast Cancer Risk in Later Years

### FACT SHEET on the PHYTOESTROGEN DAIDZEIN

#### Abstract

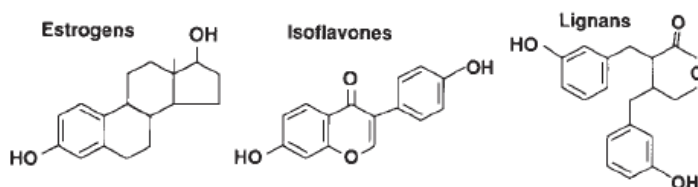
**Daidzein** is a phytoestrogen (estrogen-like chemical compound present in plants) that binds to estrogen receptors and has both weak estrogenic and weak anti-estrogenic effects. There are three major classes of phytoestrogens that have estrogen-like actions in the human body. They are lignans, isoflavones, and coumestans. Daidzein is an isoflavone. Exposure to daidzein occurs principally through foods made with soybeans and soy protein. In a proportion of the population, daidzein is metabolized by intestinal bacteria to produce equol and O-DMA, metabolites that are more estrogenic than daidzein. Daidzein can cross the placenta and has been found in breast milk. It is unknown whether daidzein influences early onset of puberty in girls. Exposure to daidzein can be measured using a blood or urine test; however levels vary widely in each person due to considerable variability in the metabolism of daidzein. *In vitro* and *in vivo* studies have found that daidzein stimulates the growth of estrogen-sensitive breast cancer cells. Epidemiologic studies have found conflicting evidence; some studies have found an association between soy exposure and decreased breast cancer risk while others have found no association. Some epidemiological evidence indicates that soy intake may be more protective when the exposure occurs prior to puberty. More research needs to be conducted on the association between breast cancer risk and daidzein specifically before conclusions can be drawn. The International Agency for Research on Cancer (IARC) has not determined whether phytoestrogens are carcinogenic to humans.

This fact sheet provides information about daidzein, one of three phytoestrogens 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 daidzein as being associated with breast cancer risk.

#### What is daidzein?

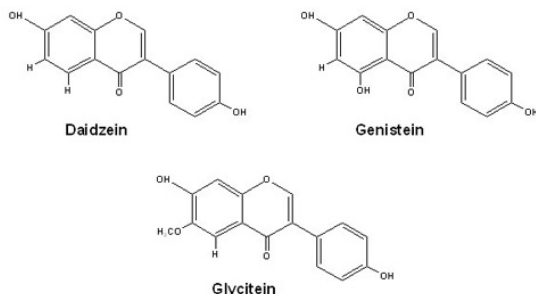
**Daidzein** is a phytoestrogen (estrogen-like chemical compound present in plants) that is derived from certain plant precursors by human metabolism. Phytoestrogens are naturally occurring chemical constituents that may interact with estrogen receptors in humans to produce weak estrogenic or anti-estrogenic effects. They are composed of a wide group of nonsteroidal compounds similar in structure and function to human estrogens (1). A conspicuous feature of the chemical structure of phytoestrogens is the presence of a phenolic ring that, with few exceptions, is a prerequisite for binding to the estrogen receptor (Fig. 1). For this reason, phytoestrogens can act as weak estrogen agonists, partial agonists, or as antagonists to endogenous estrogens (such as estradiol) and xenoestrogens (including phytoestrogens) at estrogen receptors in both animals and humans. Therefore, working as estrogen mimics, phytoestrogens may either have the same effects as estrogen or block estrogen's effects (24, 25, 26). There are three major classes of plant chemical compounds that have estrogen-like actions in the body. They are lignans (enterolactone, enterodiol), isoflavones (genistein, daidzein, biochanin A), and coumestans. The two major chemical classes of phytoestrogens found in people's diets are lignans (enterodiol and enterolactone) and isoflavones (daidzein, genistein, and glycitein). Lignans are the main class of phytoestrogens present in Western diets. Daidzein is an isoflavone.

Figure 1:



Isoflavones are a subgroup of flavinoids. Among commonly consumed foods, isoflavones are found in dietary-relevant amounts only in the soybean. The two primary isoflavones in soybeans are daidzein and genistein and their respective glucosides genistin and daidzin (Fig. 2). Soy foods typically contain more genistein than daidzein, although this ratio varies among different soy products.

Figure 2:



The terms “soy” and “soybean” are commonly used for the leguminous Asian plant *Glycine max*. Soybean is also used to designate the edible seed of this plant. In this fact sheet, the term “soy” is used as an adjective to denote products derived from the edible seed (e.g., soy milk, soy formula, soy meal) and soybean is used to refer to the edible seed itself.

The common biological roles of phytoestrogens are to protect plants from stress and to act as part of a plant’s defense mechanism. Some ecologists postulate that phytoestrogens may have evolved to protect the plants by interfering with the reproductive ability of grazing animals (2).

### **How are humans exposed to daidzein?**

Ingestion is the source of human exposure to daidzein. Exposure occurs principally through food, infant formulas, and/or dietary supplements made with soybeans and soy protein, but not soy oils. All soybean foods and proteins currently available for human consumption contain significant amounts of the isoflavones genistein and daidzein, either as the aglycone (unconjugated form) or as different types of glycoside conjugates.

### **Ingestion**

- **Food**

Leguminous plant foods contain daidzein. Soybeans, a cholesterol-free, high protein legume, contain the most daidzein. Daidzein can be found in many food products containing soy such as soy-based infant formulas, tofu, soymilk, soy flour, textured soy protein, soy protein isolates, tempeh, and miso, as well as over-the-counter dietary supplements. Often, soy flour is used for fortification of other flours, including wheat, rice, and corn. The daidzein content of these products is quite variable.

Soy flour contains 53% soy protein. Textured Soy Protein (TSP), a meat substitute made from defatted soy found in hamburgers, sausages, hot dogs, meatballs, meat loafs, can contain 50% to 70% soy protein, depending on the starting soy material used. Soy Protein Isolates (SPI), used in the preparation of specialty nutrition foods such as infant formulas, sports drinks, bodybuilding beverages, energy bars, and special diets for the very sick, contain 90% soy protein. Soy oil and soy sauce contain little to zero daidzein.

Total Isoflavone, Daidzein and Genistein Aglycone Content of Selected Foods				
Food	Serving	Total Isoflavones (mg)	Daidzein (mg)	Genistein (mg)
Soy protein concentrate, aqueous washed	3.5 oz	102	43	56
Soy protein concentrate, alcohol washed	3.5 oz	12	7	5
Miso	½ cup	59	22	34
Soybeans, boiled	½ cup	47	23	24
Tempeh	3 ounces	37	15	21
Soybeans, dry roasted	1 ounce	37	15	19
Soy milk	1 cup	30	12	17
Tofu yogurt	½ cup	21	7	12
Tofu	3 ounces	20	8	12
Soybeans, green, boiled (Edamame)	½ cup	12	6	6
Meatless (soy) hot dog	1 hot dog	11	3	6
Meatless (soy) sausage	3 links	3	0.6	2
Soy cheese, mozzarella	1 oz	2	0.3	1

Source: <http://lpi.oregonstate.edu/infocenter/phytochemicals/soyiso/index.html#source>

Daidzein and daidzin are also found in *Radix puerariae* (RP), an herbal medicine prepared from the root of the legume *Pueraria labata* (also known as kudzu). RP has been used for centuries in traditional Chinese medicine to treat a variety of disorders, including alcohol-dependency in people who abuse alcohol. It is thought that the “anti-drinking” effect of RP is due to daidzein and daidzin (3).

- **Infant Formulas**

Soy-based infant formulas have been commercially available since the mid 1960s (4). The formulas are made from soy protein isolate (SPI) and contain significant amounts of soy isoflavones. In 1997, the total isoflavone content of soy-based infant formulas commercially available in the US ranged from 32-47 mg/liter (~ 34 fluid ounces) (5).

Total Isoflavone, Daidzein and Genistein Aglycone Content of Selected Soy-based Infant Formulas				
Soy-based Formula	Serving	Total isoflavones (mg)	Daidzein (mg)	Genistein (mg)
Mead Johnson Prosoabee, ready to feed	8 fl oz	9.4	4.1	5.3
Ross Isomil, ready to feed	8 fl oz	10.2	4.7	5.5
Wyeth-Ayerst Nursoy, ready to feed	8 fl oz	6.4	1.8	3.9

Source: <http://lpi.oregonstate.edu/infocenter/phytochemicals/soyiso/index.html#sources>

Infants are able to absorb isoflavones, and infants fed soy formula were demonstrated to have plasma isoflavone blood levels exceeding those of Japanese adults several-fold (6). Soy-based infant formula can result in plasma concentrations of isoflavones in infants that are 13,000 - 22,000 times higher than endogenous estrogen concentrations in infants (7).

- **Dietary Supplements**

Dietary supplements containing daidzein are available in the US without a prescription. These products are not standardized, and the amounts of soy isoflavones they provide may vary considerably. For example, in an analysis of soy supplements purchased at a local health food store containing daidzein, the daidzein content measured was 8.9 mg/tablet; the value represented 84% of the daidzein level listed on the product label (8).

Daidzein is mainly present in the form of its beta-glucoside, daidzin in supplements. A standard soy isoflavone supplement is usually comprised of approximately 38% daidzin, 50% genistin, and 12% glycitin (3). A typical daily dose (50 mg) of soy isoflavone supplement delivers approximately 19 mg of daidzin, 25 mg of genistin and about 6 mg of



glycitin. Smaller amounts of daidzein are also contained in some red clover supplement preparations.

Women with estrogen receptor-positive tumors are advised to exercise caution in the use of daidzein/daidzin supplements and should only use them if they are recommended and monitored by a physician (3).

- **Water**

Not a significant route of exposure. Daidzein is a solid substance that is practically insoluble in water.

**Inhalation**

Not a significant route of exposure.

**Intravenous**

Not a significant route of exposure.

**Skin Absorption**

Not a significant route of exposure.

***How does daidzein work in the human body?***

Daidzein is an isoflavone aglycone and is produced in the body from plant isoflavones. Isoflavones are contained in soybean or soy foods in two chemical forms, i.e., aglycones (unconjugated form) and glucosides (bound to a sugar molecule). The main dietary source of daidzein is the biologically active glucoside daidzin. Fermentation or digestion of soybeans or soy products results in the release of the sugar molecule from the isoflavone glycoside, daidzin, leaving the isoflavone aglycone, daidzein (9). Before daidzein can act it first needs to be released from daidzin. This normally happens in the stomach (acid hydrolysis) and intestine (action of bacterial enzymes).

After daidzein is released from daidzin, it may be absorbed into the blood or it may be further metabolized by intestinal bacteria into the metabolites equol and O-desmethylangolensin (O-DMA) (3, 10). The extent of this metabolism appears to be highly variable among individuals and is influenced by the specific bacteria present in the intestine and other components of the diet. After consuming soy or daidzein, approximately 30%-50% of the population produces equol, and approximately 80%-90% produces O-DMA (10).

Daidzein inhibits the class I isoenzymes of human alcohol dehydrogenase (ADH) and the human mitochondrial aldehyde dehydrogenase (ALDH-2). Inhibition of both class I ADH and ALDH-2 may suppress alcohol consumption in humans (3). Both daidzein and daidzin significantly reduced free-choice alcohol intake by more than 50% in hamsters (11).

Daidzein is also an antioxidant. It is thought that daidzein is a less potent antioxidant than genistein; however, there are few studies comparing the antioxidant activity of the two isoflavones (12, 13). Equol is a more potent antioxidant than daidzein (10).

***Is daidzein an endocrine disruptor?***

Perhaps.

Endocrine disruptors are exogenous synthetic or natural chemicals that can mimic or modify the action of endogenous hormones. Isoflavones bind to both estrogen receptors (ER  $\alpha$  and ER  $\beta$ ), however, they preferentially bind to and activate ER  $\beta$  (14). For this reason, they are sometimes classified as selective estrogen receptor modulators (SERMs). Daidzein has been found to have both weak estrogenic and weak anti-estrogenic effects (3, 24). In vivo, daidzein's estrogenic activity is one-fourth that of genistein (15). The metabolites of **daidzein**, equol and O-DMA, have been shown to bind to human estrogen receptors with a greater affinity than daidzein (10).

### ***Does daidzein exposure influence onset of puberty in girls?***

Unknown. BCERC's biology and epidemiology studies are investigating this question.

*In vivo* research investigating the association of daidzein exposure with mammary tissue development and onset of menarche is ongoing.

The BCERC epidemiology study entitled "Environmental and Genetic Determinants of Puberty" completed a small pilot study in November 2006 and measured daidzein in young girls urine. The pilot study 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). Phytoestrogens as a group had the highest concentrations (16). All six phytoestrogens (Enterolactone, Genistein, Daidzein, Equol, Enterodiol, O-DMA) were detected in >98% of samples collected. The levels of phytoestrogen metabolites were similar to those reported in the NHANES 2001–2002 children (7). The exposures varied by characteristics that may be relevant to development (7). 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) (16). This small pilot data set will guide future expanded cohort studies.

### ***Does daidzein cross the placenta?***

Yes.

By measuring the levels of daidzein at birth in human newborns and umbilical cords, studies have shown that daidzein can be transferred from mother to fetus (17, 18). In the US, typical diets are low in soy products, and the fetus is thus hypothesized to be exposed to low levels of daidzein. In Asian cultures consuming soy products, the fetus is exposed to daidzein as a result of maternal soy product intake.

Pregnant women are advised to avoid the use of daidzein/daidzin-containing supplements pending long-term safety studies (3).

### ***Is daidzein found to be present in breast milk?***

Yes.

Despite the potential for daidzein exposure, breast milk remains the best and most complete nutritional source for young infants. Nursing mothers are advised to avoid the use of daidzein/daidzin-containing supplements pending long-term safety studies (3).

### ***Are concentration levels of daidzein the same in men and women?***

Yes.

A recent study of 1414 adults from 9 European countries found that plasma concentrations of daidzein did not differ significantly in men and women; the mean concentration for men was 0.89 mg/L and the mean concentration for women was 0.80 mg/L (19). In the National Health and Nutrition Examination Survey (NHANES) 2001-2002, females and males also had similar urinary levels of daidzein; the mean concentration for males was 49.8 µg/L and the mean concentration for females was 53.6 µg/L (7).

### ***Are there medical tests for daidzein exposure?***

Yes.

### **Blood Tests**

Phytoestrogens persist in plasma for about 24 hours. The plasma half-life of genistein and daidzein, measured from their plasma appearance and disappearance curves to be 7.9 hours in adults; peak concentrations occur 6-8 hours after ingestion. Consequently, adherence to a soy-containing diet will ultimately lead to high steady-state plasma concentrations. Plasma concentrations of 50-800 ng/mL are achieved for daidzein, genistein and equol in adults



consuming modest quantities of soy-foods containing in the region of 50 mg/day of total isoflavones. These values are similar to those of Japanese consuming their traditional diet (20).

### **Urine Tests**

Most studies of the metabolism of isoflavones have focused on urinary excretion. This is partly because of the high concentrations found in urine after soy intake and the methodologic difficulties encountered in measuring the lower concentrations in other biological fluids. Few studies have measured circulating concentrations of isoflavones; this reflects the greater difficulty of measurement in plasma compared with urine.

Isoflavones have short-half lives (approximately 8 hours), and nearly all ingested isoflavones are excreted within 24 hours in both urine and feces (21). There is considerable interindividual variation in gut bacterial metabolism of daidzein which leads to markedly different urinary concentrations of daidzein and its metabolites in different individuals (14). In NHANES 2001-2002, the mean urine concentration for daidzein in the total population age 6 and older was 48.6 µg/L. The range from the 50th percentile to the 95th percentile was 48.5-957.0 µg/L (7).

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

*In vitro* studies of daidzein and breast cancer risk are limited. One recent study found that both daidzein and equol stimulated the growth of estrogen-dependent breast cancer cells at concentrations between 0.001 and 50 µM (22, 26).

### ***In in vivo studies, what is the association between daidzein exposure and breast cancer risk?*** [An experiment in an animal model is referred to as an in vivo experiment.]

*In vivo* studies of daidzein and breast cancer risk are limited. One recent study found that dietary daidzein stimulated the growth of estrogen-dependent mammary tumors in mice, but dietary equol did not (22). Another study demonstrated that daidzein in the diet had no effect on chemically-induced mammary cancer in rats (23).

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

There is no evidence that dietary intake of plant isoflavones is associated with breast cancer risk. Evidence from epidemiological studies is conflicting for soy and total phytoestrogen intake. Some case-control and cohort studies have found a protective effect and some have not found any effect. One recent meta-analysis of 18 epidemiologic studies concluded that soy intake may be associated with a small reduction in breast cancer risk (27). In the studies that stratified by menopausal status, the reduction in breast cancer risk was somewhat stronger among premenopausal women. However, the authors also noted that there were methodological problems with many of the studies included in the meta-analysis.

Some epidemiological evidence indicates that soy intake may be more protective when the exposure occurs prior to puberty. One study of Chinese women found that intake of soyfood during adolescence reduced breast cancer risk in a dose-dependent manner (28). The highest quintile of intake reduced risk by 49%.

There are a limited number of epidemiological studies that have examined the relationship between daidzein specifically and breast cancer. One 2007 Dutch study found high plasma levels of daidzein, O-DMA, and equol were associated with a 17%, 17% and 23% reduction in risk, respectively; however, none of these associations were statistically significant (13). The same study also found that high plasma levels of genistein were associated with a 32% reduction in breast cancer risk, and this association was statistically significant.

## **Was daidzein included in biomonitoring measurements from the 1999-2002 National Health and Nutrition Examination Survey (NHANES) Third Report?**

Yes.

Urinary levels of phytoestrogens were measured in a subsample of NHANES participants aged 6 years and older (7). Participants were selected within the specified age range to be a representative sample of the U.S. population. In general, the concentrations observed in the NHANES 1999-2000 and 2000-2001 subsamples reflect a diet lower in isoflavones than lignans, consistent with consumption of a Western diet in which whole grains and cereals rather than soybean products contribute the bulk of phytoestrogens. Enterolactone levels were highest followed by daidzein, genistein, enterodiol, equol, and O-desmethylangolensin. Isoflavone levels at the higher percentiles may reflect dietary supplementation with soy products.

In NHANES 2001-2002, both urinary genistein and daidzein levels were higher in the group aged 6 – 11 years than in either of the groups aged 12-19 years or 20 years and older. Females and males had similar urinary levels of daidzein.

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.

## **What has the IARC determined about daidzein and carcinogenesis?**

The International Agency for Research on Cancer (IARC) has not determined phytoestrogens to be carcinogenic to humans. The IARC is part of the World Health Organization (WHO).

## **Has the federal government made recommendations to protect human health?**

Yes.

### **FDA**

In October 1999, FDA approved a health claim that can be used on labels of soy-based foods to tout their heart-healthy benefits. The agency reviewed research from 27 studies that showed soy protein's value in lowering levels of total cholesterol and low-density lipoprotein (LDL, or "bad" cholesterol).

Since 1999, food marketers can now use the following claim, or a reasonable variation, on their products: "Diets low in saturated fat and cholesterol that include 25 grams of soy protein a day may reduce the risk of heart disease. One serving of (name of food) provides \_\_\_ grams of soy protein."

To qualify for the claim foods must contain per serving:

- 6.25 grams of soy protein
- low fat (less than 3 grams)
- low saturated fat (less than 1 gram)
- low cholesterol (less than 20 milligrams)
- sodium value of less than 480 milligrams for individual foods, less than 720 milligrams if considered a main dish, and less than 960 milligrams if considered a meal.

Foods made with the whole soybean, such as tofu, may qualify for the claim if they have no fat other than that naturally present in the whole bean.



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This publication was carried out as part of the NIEHS/NCI Breast Cancer and the Environment Research Centers, four centers with transdisciplinary research collaborations integrated across biologic, epidemiologic, and community outreach cores. Funding was provided by grant numbers ES/CA 012770, 012771, 012800, and 012801 from the National Institute of Environmental Health Sciences (NIEHS) and the National Cancer Institute (NCI), NIH, DHHS. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIEHS or NCI, NIH.





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