

BREAST CANCER & THE ENVIRONMENT RESEARCH CENTERS

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

FACT SHEET on the PHYTOESTROGEN ENTEROLACTONE

Abstract

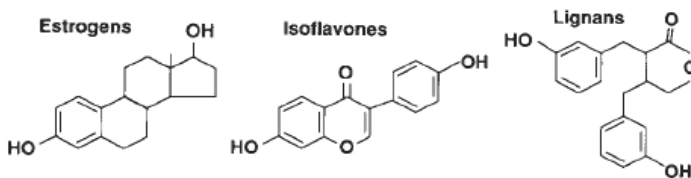
Enterolactone (ENL) is a phytoestrogen (estrogen-like chemical compound present in plants) that binds to estrogen receptors and has both weak estrogenic and weak anti-estrogenic effects. There are three major classes of phytoestrogens that have estrogen-like actions in the human body. They are lignans, isoflavones, and coumestans. Enterolactone is a lignan. Enterolactone is produced when the plant lignan matairesinol is acted upon by the action of bacterial flora in the colon of humans or animals. Exposure to enterolactone primarily occurs through ingesting whole grain products, seeds, and some fruits and vegetables. No studies were found showing that enterolactone crosses the placenta or that it is found in breast milk. It is unknown whether enterolactone influences early onset of puberty in girls. Exposure to enterolactone can be measured using a blood or urine test; however levels vary widely in each person due to considerable variability in the metabolism of enterolactone. *In vitro*, *in vivo* and epidemiologic studies are limited and inconclusive. A few *in vivo* studies have found high consumption of flax seeds to reduce breast tumors. The few epidemiologic studies looking at enterolactone have found little evidence that dietary intake of plant lignans is significantly associated with breast cancer risk. More research needs to be conducted on the association between breast cancer risk and enterolactone 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 enterolactone, 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 enterolactone as being associated with breast cancer risk.

What is enterolactone?

Enterolactone is a phytoestrogen (estrogen-like chemical compound present in plants) that is derived from certain plant precursors by the action of human colonic bacteria. Phytoestrogens are naturally occurring chemical constituents that may interact with estrogen receptors to produce estrogenic or anti-estrogenic effects and are composed of a wide group of nonsteroidal compounds similar in structure and function to human estrogens (1,2,3). 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 and xenoestrogens with estrogen receptors in both animals and humans (4,5). Therefore, working as estrogen mimics, phytoestrogens may either have the same effects as estrogen or block estrogen's effects (1). 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. Enterolactone is a lignan.

Figure 1:



A plant lignan, referred to as a mammalian precursor, is acted upon (metabolized) by human intestinal microflora (bacteria) in the colon to produce the mammalian lignans enterolactone and enterodiol. The lignan precursors that have been identified in the human diet include pinoresinol, lariciresinol, secoisolariciresinol, matairesinol, and others. Matairesinol and secoisolariciresinol were among the first lignan precursors identified in the human diet and are therefore, the most extensively studied. Matairesinol is metabolized into the biologically active mammalian lignan enterolactone; secoisolariciresinol is metabolized into the biologically active mammalian lignan enterodiol. Enterodiol can be converted to enterolactone, but not the reverse.

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 (5).

How are humans exposed to enterolactone?

Ingestion is the source of human exposure to the mammalian lignan enterolactone. Exposure to enterolactone primarily occurs through ingesting whole grain products, seeds, and some fruits and vegetables. Ground flaxseed is the richest known dietary source of enterolactone. The principal lignan precursor found in flaxseed is secoisolariciresinol diglucoside (SDG).

Ingestion

- **Food**

When you eat lignans, bacteria in the digestive tract convert them to enterodiol and enterolactone. Seeds (ground flax, sesame, pumpkin, and sunflower), cereals and grains (oatmeal, rye meal), cereal bran (rye and oats), legumes (peanut and soybean), fruits (apricots, blackberry, cranberry, strawberry, red current), and vegetables (asparagus, brussell sprouts, broccoli, cabbage, curly kale) all contain lignans.

Ground flaxseed is the richest known dietary source. Whole flaxseeds that are consumed pass through the digestive system undigested, and do not produce a significant amount of lignans. Flaxseed oil lacks lignans, but some processors add them to their oil.

Total Lignan Content of Selected Foods		
Food	Serving	Total Lignans (mg)
Flaxseeds (ground)	1 oz	85.5
Sesame seeds	1 oz	11.2
Curly kale	½ cup, chopped	0.8
Broccoli	½ cup, chopped	0.6
Apricots	½ cup, sliced	0.4
Cabbage	½ cup, chopped	0.3
Brussels sprouts	½ cup, chopped	0.3
Strawberries	½ cup	0.2
Tofu	¼ block (4 oz)	0.2
Dark rye bread	1 slice	0.1

Source: <http://pi.oregonstate.edu/infocenter/phytochemicals/lignans/>

- **Infant Formulas**

None known to contain enterolactone.

- **Dietary Supplements**

Dietary supplements containing lignans derived from flaxseed are available in the U.S. without a prescription. One supplement can provide 50 mg of secoisolariciresinol diglycoside (SDG) per capsule. The appropriate lignan dosage has yet to be determined, but a range of 10 mg to 30 mg daily dose of SDG may be sufficient to deliver the health benefits associated with flax lignans.

- **Water**

Enterolactone is a solid substance that is practically insoluble in water.



Inhalation

Not a significant route of exposure. Lignans are present in high concentration in Norwegian spruce bark (*Picea abies*).

Intravenous

Not a significant route of exposure.

Skin absorption

Not a significant route of exposure.

How does enterolactone work in the human body?

Enterolactone is produced in the human body from plant lignans. When plant lignans are ingested, they can be metabolized by gut flora (intestinal bacteria) in the large intestine into the mammalian lignans, enterodiol and enterolactone. Enterodiol can also be converted to enterolactone by intestinal bacteria (6). Enterodiol and enterolactone have two metabolic fates. One, they can be excreted directly in the feces; or two, after being absorbed from the gut, they can be secreted into the bile and be reabsorbed from the intestine, and eventually excreted in the urine in conjugated form.

The metabolism of lignans in animals and humans is complex and involves both mammalian and gut microbial processes. There is considerable individual variation in the absorption and metabolism of ingested lignans. Mammalian lignans differ from plant lignans. Once mammalian lignans are produced in the colon, they are absorbed, transported to the liver, and secreted in bile. A portion reaches the kidney and eventually is excreted in the urine (7).

Is enterolactone an endocrine disruptor?

Yes.

Endocrine disruptors are exogenous synthetic or natural chemicals that can mimic or modify the action of endogenous hormones. Enterolactone binds to estrogen receptors found on sex hormone-binding globulin (SHBG). When enterolactone attaches to these receptors, estrogen (and testosterone) cannot, and as such can compete with estrogen for binding sites may help to reduce the growth of certain types of cancers.

Phytoestrogens eaten at sufficiently high concentrations can cause them to be active as estrogens (8).

Does enterolactone exposure influence onset of puberty in girls?

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

The BCERC epidemiology study entitled "Environmental and Genetic Determinants of Puberty" completed a small pilot study in November 2006 and measured enterolactone 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 (9). All six phytoestrogens (Enterolactone, Genistein, Daidzein, Equol, Enterodiol, O-DMA) were detected in > 98% of the samples collected. The highest median concentration of the six phytoestrogens was for enterolactone. Enterolactone was higher among girls with body mass index < 85th reference percentile than those at or above the 85th percentile (9). The levels of phytoestrogen metabolites were similar to those reported in the NHANES 2001–2002 children(9). 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.

Does enterolactone cross the placenta?

Unknown.

Is enterolactone found to be present in breast milk?

Unknown.

Despite the potential for enterolactone exposure, breast milk remains the best and most complete nutritional source for young infants.

Are concentration levels of enterolactone the same in men and women?

No.

Levels of enterolactone are diet dependent. Some studies have shown men to have higher levels.

Are there medical tests for enterolactone exposure?

Yes. Concentration levels of enterolactone can be detected by blood and urine tests. Enterolactone levels measured in either **blood** or **urine** reflect an increase in a dose dependent manner related to dietary intake of plant lignans and to the activity of intestinal bacteria. Vegetarians have high plasma and urinary concentrations of lignans.

Blood Tests

Phytoestrogens persist in **blood plasma** for about 24 hours. The concentration of enterodiol and enterolactone can be detected in blood serum.

Urine Tests

The concentration of enterodiol and **enterolactone** can be detected in urine. The relationship between the dose and urinary excretion is linear for many phytoestrogens.

Lignans have short half-lives. Because excretory half-lives are reported to be in the range of 3-10 hours, urinary concentrations reflect recent consumption.

In in vitro studies, what is the association between enterolactone 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 enterolactone 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 the association between enterolactone exposure and breast cancer risk.

Some animal studies, when fed high amounts of flaxseeds, have been shown to cause developmental abnormalities as well as a decrease in breast and lung tumors. However, there have been no studies showing a direct effect. Flaxseed supplies alpha-linolenic acid. Alpha-linolenic acid (omega 3 fat) has been shown in animal studies to be protective for cancer, while omega 6 fats (linoleic acid, arachidonic acid) have been found to be cancer promoting. Lignans can act as antioxidants in the test tube, but the significance of such antioxidant activity in humans is not clear because lignans are rapidly and extensively metabolized (2,15).

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

There is no evidence that dietary intake of plant lignans is associated with breast cancer risk. Two prospective cohort studies and two case-control studies that examined plant lignan intake and breast cancer risk found them not to be related (10,11,12,13). An inverse association between a

high enterolactone concentration in both urine and serum, and the risk of breast cancer suggests a chemopreventive action for enterolactone.

Was enterolactone 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 (14). 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 higher in lignans and lower in isoflavones, consistent with consumption of a Western diet in which whole grains and cereals rather than soybean products contribute the bulk of phytoestrogens. For lignans, enterolactone levels were highest. Vegetarian women in Boston, men and women consuming experimental cruciferous diet, and Boston women consuming a macrobiotic diet excreted significantly higher levels of these lignans (14).

In NHANES 2001-2002, urinary enterolactone levels were higher in the group aged 6-11 years than in the group aged 12-19 years. Levels of the lignans previously have been reported to differ by race and in an NHANES III statistical analysis, to differ by income, gender, and age. Males had higher urinary levels of enterolactone in the both the 1999-2000 and 2001-2002 subsamples (14).

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 enterolactone 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?

Unknown.



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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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