



Soyfoods Safety Issues

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Traditional soyfoods have played an important role in East Asian diets for centuries, and have been consumed by health-conscious individuals in Western countries for decades. More recently, soyfoods have become increasingly popular among mainstream consumers in the West, largely because of research suggesting they offer health benefits independent of the nutrients they provide. Possible health benefits include reducing risk of coronary heart disease,¹⁻³ osteoporosis⁴⁻⁶ and some forms of cancer.⁷ Many of the proposed benefits of soyfoods are attributed to their being essentially unique dietary sources of isoflavones, a group of diphenolic molecules with estrogen-like properties. However, it is precisely for this reason that questions about the potential adverse effects of soyfoods have been raised.

In 1999, as part of the process for approving the health claim for soy protein and coronary heart disease, the U.S. Food and Drug Administration (FDA) reviewed the scientific literature and concluded that soyfoods were safe.⁸ During the past decade, considerably more research has been conducted although most of the concerns being raised today were previously considered by the FDA. In 2005, the Agency for Healthcare Research and Quality identified only minor problems associated with the intake of large amounts of soy, such as mild gastrointestinal disturbances, although most of the research they evaluated wasn't designed to specifically address safety issues.⁹ However, a similar conclusion was reached by Austrian researchers in a just-published meta-analysis, which was undertaken to specifically address the safety of phytoestrogen supplements.¹⁰ Nevertheless, discussions about the safety of soy continue to appear in the scientific literature and popular media.

Considerations in Evaluating Soy Research

Most scientists can probably agree that there is a legitimate basis for discussion about potential adverse effects of soy consumption in some individuals under certain circumstances. Some types of in vitro and animal studies have raised concern, but this is hardly surprising given the sheer volume of research conducted. Almost 2,000 soy-related scientific papers are published annually.

Unfortunately, sensationalized media stories – and especially online articles lacking editorial oversight – often focus on a tiny minority of studies unrepresentative of the overall scientific literature.

The relevance of in vitro and animal studies to humans is always a matter of debate. Clearly, in vitro conditions cannot duplicate the complexity of living organisms, human or otherwise. Further, by necessity, these studies typically examine the effects of isolated compounds, which may be quite different from effects seen when these compounds are examined in their natural milieu. The biological impact of one nutrient or non-nutrient in a food can be dependent upon the presence of others.^{11, 12}

Studies in rats and mice, while certainly part of the scientific literature, often have limited value for predicting effects in humans because of the many physiological and anatomical differences between rodents and humans. In the case of soy, there is an additional caveat; most animals, including rodents and non-human primates, metabolize isoflavones very differently than humans.¹³⁻¹⁷ Therefore, one may derive, at most, only very limited insight about the possible effects of soyfoods in humans based on the results from studies in which rodents are fed isoflavone-rich soy protein or mixed isoflavones as exist in soybeans.

The FDA concluded that soyfoods are safe in its review when approving the health claim for soy protein and coronary heart disease.

It is also important to recognize that many highly investigated foods and food components have been linked with adverse effects in at least some studies and this includes foods that are recommended by most nutritionists for their roles as part of a healthy diet. For example, whole grains contain phytate (as do soyfoods), which can decrease mineral absorption.¹⁸ Nevertheless, the nutrition community recommends the intake of whole grains because the overwhelming preponderance of evidence indicates that they are nutritionally beneficial. The obvious point is that when evaluating any food—including soy—it is necessary to not only evaluate the totality of the evidence but to carefully consider the strengths and weaknesses of study designs.

One serving of a traditional soyfood, such as 3 to 4 ounces of tofu or 1 cup of soymilk, provides about 25 mg of isoflavones.



The vast majority of the data show that soyfoods and isoflavones are safe.

Evaluating the Evidence:

Hormonal Balance

Isoflavones bind to and transactivate estrogen receptors and can potentially influence steroid hormone synthesis and metabolism via their effects on enzymes involved in a variety of metabolic pathways.^{19,20} Not surprisingly, there has been considerable investigation into the effects of isoflavone-rich soy products and isoflavone supplements on hormone levels in both men and women. Some of this research was aimed at determining whether decreases in testosterone and estrogen levels might account for the proposed role of soy in reducing risk of prostate and breast cancer, respectively.

However, according to the conclusions of two recently published meta-analyses, the purported chemopreventive effects of soyfoods are unlikely to be related to their effects on blood hormone concentrations. The vast majority of studies have shown no effects on circulating reproductive hormone levels in men^{21,22} or women²³⁻²⁵ in response to the intake of soy protein or isoflavones. One meta-analysis, which included 32 studies and 36 treatment groups, evaluated the effects of soy products on total and free testosterone in men.²⁶ The other, which included 47 studies, evaluated the effects of soy products on levels of estradiol and other reproductive hormones in pre- and postmenopausal women.

Fertility

Given the large populations of Asian countries that consume soy, it is somewhat ironic and almost nonsensical that concerns that soy intake impairs fertility have been raised. On the other hand, in many respects the biological effects of isoflavones first came to the attention of the scientific community in the 1940s because of breeding problems experienced by female sheep in Western Australia grazing on a type of clover rich in isoflavones.²⁷⁻²⁹ Furthermore, two decades ago it was established that isoflavone-rich soy, which was part of the standard diet of cheetahs in North American zoos, was a factor in the decline of fertility in these animals.³⁰ However, problems in the latter arose because felines are only poorly able to glucuronidate phenolic compounds, a major step in the bodily elimination of isoflavones – a good example of differences in isoflavone metabolism between animals and humans.³¹⁻³³ In the case of the sheep, serum levels of equol – a bacterially synthesized metabolite of the soybean isoflavone daidzein, far exceeded anything approaching human levels simply because daily isoflavone intake was estimated to be several grams³⁴ – versus the 40 mg common to Asian populations.³⁵

In women, soyfoods do appear to increase the length of the menstrual cycle. However, ovulation is not prevented, but is simply delayed by one day.³⁶ Interestingly, longer cycles are associated with a decreased breast cancer risk.³⁷ In men, a small pilot epidemiologic study found that soy consumption was associated with lower sperm concentration but there were many weaknesses to this study. In fact, much of the decreased sperm concentration occurred because there was an increase in ejaculate volume in men consuming higher amounts of soy.³⁸ Furthermore, in contrast to this one epidemiologic study, all three of the clinical studies conducted show that isoflavones have no effect on sperm concentration or quality.³⁸⁻⁴⁰ Interestingly, a case report actually noted that isoflavones increased sperm count. Daily isoflavone



Fast Facts about Isoflavones

- Isoflavones are one of five chemical classes of anticarcinogens found in soy.
- Soyfoods are the only significant natural dietary source of isoflavones.
- Research shows isoflavones may prevent the onset of osteoporosis and may protect against various forms of cancer.

supplementation for six months in the male partner of an infertile couple with initially low sperm count led to normalization of sperm quality and quantity and allowed the couple to conceive.⁴¹

Soy, Isoflavones and Thyroid Function

The first animal studies investigating the effects of soy intake on thyroid function were published 70 years ago.⁴²⁻⁴⁴ Concerns about the anti-thyroid effects of soy are based primarily on in vitro research^{45,46} and studies in rodents administered isolated isoflavones.^{47,48} Although several cases of goiter were attributed to the use of soy infant formula, this problem was eliminated in the mid-1960s with the advent of iodine fortification of the formula.^{42,43,49}

A comprehensive review published in 2006 that included 14 clinical trials concluded there was little evidence that soyfoods or isoflavones adversely affect thyroid function in healthy men or women.⁵⁰ Studies published since this review are supportive of this conclusion.⁵¹⁻⁵⁴ One of these is a three-year study that included more than 200 postmenopausal women who were given isoflavone supplements at either 80 or 120 mg/day (personal communication, Lee Alekel, Iowa State University).

Although soy has no effect on thyroid function in euthyroid individuals, soyfoods may increase the amount of thyroid medication needed by hypothyroid patients, not because of an effect on the thyroid but rather because soy protein may interfere to some extent with the absorption of the medication.⁵⁵⁻⁵⁸ Soy is not alone in this regard as many herbs, drugs and fiber supplements have similar effects.⁵⁹⁻⁶⁷ In any event, it is not necessary for

thyroid patients (with the exception of infants with congenital hypothyroidism) to avoid soyfoods since thyroid medication is taken on an empty stomach and dosages can easily be adjusted to compensate for any effects of soy.

Finally, there are two clinical situations in which the relationship between soy intake and thyroid function have not been explored that warrant consideration. One involves individuals with subclinical hypothyroidism, which represents about five percent of the general adult population but a higher percentage among individuals over the age of 60 years.⁶⁸ This condition is defined as having normal levels of the two primary thyroid hormones, thyroxine and triiodothyronine, but elevated levels of thyroid stimulating hormone.⁶⁹ There is no evidence that soyfoods pose a problem for subclinical hypothyroid patients but research specifically addressing this issue has not been conducted. The second situation involves individuals whose iodine intake is marginal or inadequate. In the United States, iodine intake is generally quite good.⁷⁰ In any event, when an individual whose iodine intake is suboptimal, the appropriate recommendation is to increase iodine intake, not to avoid soyfoods.

Soyfoods and Breast Cancer Risk

The estrogen-like effects of isoflavones form the theoretical basis for concern that soyfoods might be contraindicated for women at increased risk of breast cancer and for breast cancer patients with estrogen-sensitive tumors.⁷¹⁻⁷⁵ Isoflavones bind to estrogen receptors, stimulate the growth of human estrogen receptor positive breast cancer cells in vitro and, in certain types of experimental rodent models, stimulate the growth of existing estrogen-responsive mammary tumors.^{76,77} However, not all rodent models show that soy stimulates the growth of existing mammary tumors⁷⁸ and even in rodent models where stimulation occurs, minimally processed soyfoods do not have this effect.⁷⁹ More importantly, the human data suggest that isoflavones, regardless of the source, do not exert stimulatory effects on breast tissue.

In none of the four clinical trials, three involving postmenopausal and one involving premenopausal women in which researchers took breast tissue biopsies before and after exposure to isoflavones, were effects on cell proliferation noted.^{23,80-82} Increased cell proliferation is generally regarded as a risk factor for cancer. Isoflavone exposure also has no effect on breast tissue density (increased density is a marker of cancer risk).⁸³⁻⁸⁶ In contrast to the lack of effects of isoflavones, estrogen plus progestin hormone therapy, which increases breast cancer risk,⁸⁷ increases breast tissue density and breast cell proliferation.^{88,89}

The American Cancer Society states that breast cancer patients can safely consume up to three servings of traditional soyfoods daily.

Finally, three prospective epidemiologic studies provide important insight into the soy and breast cancer relationship. The findings from these studies are reassuring in regard to safety and even suggestive of benefit. In one, neither soy nor isoflavone intake was related to the disease-free survival of Chinese breast cancer patients over the 5.2 year follow-up period.⁹⁰ In this study, of the 1,001 patients for whom data on receptor status were available, approximately 63 percent were estrogen receptor-positive. The limitation of this study is that soy intake was assessed prior to diagnosis.

Isoflavone Content of Soyfoods

One serving of a traditional soyfood provides about 20 to 35 mg of isoflavones.

Soyfood	Serving size	Total (mg) isoflavone/ serving
Miso	1 Tbsp	7
Soybeans, Green, Cooked	1/2 cup	50
Soybeans, Black, Cooked	1/2 cup	40
Soybeans, Yellow, Cooked	1/2 cup	78
Soybeans, Roasted, Plain	1/4 cup	78
Soymilk, Plain, Unfortified	1 cup	10
Soymilk, Plain, Fortified	1 cup	43
Soy Flour, Defatted	1/4 cup	42
Soy Flour, Full-Fat	1/4 cup	33
Soy Flour, Low-Fat	1/4 cup	50
Soy Crumbles	1/2 cup	9
Soy Protein Isolate Powder, Plain	1/3 cup	53
Textured Soy Protein, Dry	1/4 cup	33
Tempeh	1/2 cup	53
Tofu	1/2 cup	25

In the second study, data from the Shanghai Breast Cancer Survival Study, a population-based cohort study of breast cancer survivors, were analyzed to investigate the effect of soy intake after diagnosis on breast cancer prognosis.⁹¹ During the median follow-up period of approximately 3.9 years, the hazard ratio associated with the highest quartile of soy protein intake was 0.71 for total mortality and 0.68 for recurrence compared with the lowest quartile of intake. In fact, in this study, high soy intake was as protective as tamoxifen use. In an editorial accompanying the *Journal of the American Medical Association* article, researchers from the National Cancer Institute and Fred Hutchinson Research Center in Seattle remarked that, "Patients with breast cancer can be assured that enjoying a soy latte or indulging in pad thai with tofu causes no harm and, when consumed in plentiful amounts, may reduce risk of disease recurrence."⁹²

A third study, which was conducted in the United States, involved 1,954 breast cancer survivors who were followed for 6.3 years. During this time, there were 282 breast cancer recurrences. Suggestive trends for a reduced risk of cancer recurrence were observed with increasing quintiles of isoflavone intake compared to no intake among postmenopausal women and among tamoxifen users.⁹³ Interestingly, the benefit of soyfood intake on survival was more pronounced among women with estrogen receptor positive breast cancer.

The clinical and epidemiologic findings described above are certainly consistent with the position of the American Cancer Society that breast cancer patients can safely consume up to three servings of traditional soyfoods daily.⁹⁴ However, because none of the data can be considered definitive, breast cancer patients should always discuss any dietary changes with their healthcare provider.



Effects of Soy on Mineral Status

Soyfoods are frequently used in place of animal foods, many of which are good sources of iron, zinc and, in the case of dairy foods, calcium. Relatively little red meat is needed to meet daily iron and zinc requirements, so questions about the effects of soy on the status of these two minerals pertains mostly to those eating a predominately plant-based diet.⁹⁵

As noted previously, soybeans, like other legumes and whole grains, are high in phytate,⁹⁶ which reduces the absorption of some minerals, including zinc and iron.⁹⁷ Zinc absorption from soyfoods is only modestly lower than that from other sources. However, because soybeans contain relatively little zinc, unfortified soyfoods are not particularly good sources of this mineral.⁹⁸⁻¹⁰¹ Zinc status is difficult to assess^{102, 103} so those consuming a plant-based diet are advised to identify good plant sources of zinc in their diet or to take a zinc supplement.¹⁰⁴⁻¹⁰⁸

In contrast to zinc, soyfoods are relatively high in iron.¹⁰⁹ Until recently, it was believed that the iron in essentially all plant foods, including soyfoods, was poorly absorbed. However, new research utilizing improved methodology indicates that iron absorption from soy may be higher than previously thought because most of the iron in soy is in the form of ferritin. Although there is debate about the bioavailability of ferritin iron, two important recently conducted

Recent research shows that only about 1 out of 2,500 American adults are allergic to soy protein.

clinical studies in which subjects were fed soyfoods show it to be highly bioavailable.^{110, 111} Clinical studies support these findings by showing that incorporating soy into the diet does not negatively impact iron status.

In fact, a recently presented study, designed specifically to examine the effect of soyfoods on mineral status, provides very reassuring results. In the study, young premenopausal women consumed either 2-3 servings of soyfoods daily or non-soyfoods matched for type of food (i.e., soy burgers in place of hamburgers, soy milk in place of cow's milk). Results showed there were no statistically significant effects of soy on urinary and serum zinc, serum hemoglobin and iron, or transferrin saturation (see reference for a description of this study).⁴⁰

In addition to phytate, soybeans are also high in oxalate – another compound that binds calcium and reduces its absorption.¹⁰ Oxalate is one reason that spinach, despite being high in calcium, is not a good source of this mineral. However, despite the presence of both phytate and oxalate, calcium absorption from soy is surprisingly good.¹¹³ Bioavailability of calcium from calcium-fortified soy products, such as soymilk, depends to some extent on the type of supplemental calcium used.¹¹⁴ When calcium carbonate is used as the fortificant in soymilk, absorption is similar to that seen with cow's milk.¹¹⁵ In contrast, calcium absorption from soymilk fortified with tricalcium phosphate is about 25 percent lower than from cow's milk.¹¹⁶ However, because of the high amounts of tricalcium phosphate added, the amount of calcium available to the body from both types of calcium-fortified soymilk is similar to that from cow's milk.¹¹⁵

Allergies

Soy protein, as is the case for essentially all food proteins, can cause allergic reactions in sensitive individuals. Soy protein is one of the eight foods responsible for approximately 90 percent of all food-induced allergic reactions in the United States.¹¹⁸ But, these foods are not equally allergenic and allergy to soy protein is relatively rare.¹¹⁹ A recent nationally representative telephone survey found that only approximately one out of 2,500 adults reported having a doctor-diagnosed allergy to soy protein.¹²⁰ The rate is undoubtedly higher in children, as children are more likely to have food allergies. However, most children outgrow soy allergies early in life.¹²¹

A Word about Processing

Tofu and miso are the most commonly consumed soyfoods in Japan and China, whereas in the United States, many people choose more processed forms of soy such as meat analogs and energy bars.¹²² Numerous human studies demonstrate that processed soy products provide the same high-quality protein as traditional soyfoods.¹²³

Depending on processing methods, however, the isoflavone content of these foods can be markedly reduced.¹²⁴ The isoflavone content of a large number of soy-containing foods can be found in an online database created by Iowa State University and the United States Department of Agriculture at: <http://www.nal.usda.gov/fnic/foodcomp/Data/isoflav/isoflav.html>.

Many traditional soyfoods such as miso, tempeh and natto undergo fermentation. While mineral absorption may be very slightly improved with fermentation and may give rise to other possibly beneficial compounds, there is little evidence that these foods are superior to unfermented ones. In fact, several epidemiologic studies show protective effects of non-fermented but not fermented soyfoods. Non-fermented soyfoods have been consumed in Japan¹²⁵ and China¹²⁶ for at least 500 and 1,000 years, respectively. In Japan, where many fermented foods are quite popular, at least half of the total soy consumed comes from foods that are not fermented.^{127, 128}

Summary and Conclusions

When evaluating the safety of soyfoods, it is imperative to consider the totality of the scientific research. This research indicates that soyfoods can be safely incorporated into the diets of essentially all healthy individuals with the exception of those allergic to soy protein. Nevertheless, because all foods have the potential to cause undesirable effects in some individuals, people with specific health concerns should consult their healthcare provider regarding unique nutritional needs.

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The United Soybean Board (USB) is a farmer-led organization comprised of 68 farmer-directors. Working with independent academic researchers affiliated with the National Institutes of Health (NIH) and academic institutions, USB has invested millions of dollars into health and nutrition research related to soy. Soybean farmers take pride in producing one of the healthiest food crops in the world. To access healthy soy recipes and more nutrition information, please visit SoyConnection.com.