Concerns about the Safety of Soyfoods without Scientific Foundation. By, Mark Messina, PhD, MS

For centuries foods made from soybeans have been an important part of the cuisines of many East Asian countries and have been consumed for decades by Western vegetarians and health-conscious individuals. Soyfoods are best known for the quantity and quality of protein they protein. In addition to its high quality,[1] soy protein directly lowers blood cholesterol levels,[2] an attribute formally recognized by the US Food and Drug Administration (FDA) when it approved a health claim for soyfoods and coronary heart disease.[3] Other health agencies have also endorsed soyfoods. For example, the American Heart Association emphasizes the role soyfoods can play in reducing risk of heart disease because of their fiber and high polyunsaturated fat content.[4] More recently, soyfoods were prominently featured in the 2020-2025 US Dietary Guidelines, being included in the protein group and vegetable subgroup; plus, soymilk and soy-based yogurt, were the only plant-based dairy alternatives identified as suitable replacements for milk and yogurt.[5]

Over the past 30 years, soyfoods have been rigorously investigated for their potential health benefits independent of their nutrient content. Proposed benefits include protection against osteoporosis,[6,7] coronary heart disease[8] and certain types of cancer.[9,10] Much of the research interest in soy is because it is a uniquely rich source of isoflavones. Isoflavones are naturally occurring plant compounds commonly classified as phytoestrogens, although they differ from the hormone estrogen. More than 1,000 scientific papers are published on isoflavones annually.

Despite their proposed benefits, the high isoflavone content of soyfoods has led to concerns that soy could adversely affect some individuals. However, with few exceptions, these concerns are based on the results of animal studies. Animal studies are a legitimate part of the scientific literature but because of well-accepted limitations, they carry much less weight within the scientific community than human studies.[11] Animal studies are used primarily for hypothesis generation, not as a basis for reaching conclusions about health effects in humans. Furthermore, because rodents metabolize isoflavones differently than humans, they are not particularly useful for providing insight about these soybean constituents.[12,13]

Over the past decade, the safety of soyfood consumption has been confirmed by the results of both observational and clinical research. This research has led to independent scientific organizations, such as the American Cancer Society[14] and the FDA,[15] along with many others, rejecting concerns about the safety of soy.

Isoflavones

Isoflavones are widely distributed within the plant, but among commonly consumed foods, soybeans and traditional Asian soyfoods are uniquely rich sources.[16] This point is illustrated by the average isoflavone intake among older Japanese, which is about 40 mg/day,[17,18] whereas in Europe and the United States, intake is <3 mg/day.[19-23] In traditional soyfoods, each gram of soy protein is associated with approximately 3.5 mg isoflavones[17] whereas because of losses during processing, the isoflavone content of concentrated sources of soy protein, such as soy protein isolate (~90% protein) and soy protein concentrate (~65% protein), is greatly reduced.[24] The

three isoflavones in soybeans are genistein, daidzein and glycitein, which comprise roughly 50%, 40% and 10% of total isoflavone content, respectively.[24]

Isoflavones have a chemical structure similar to the hormone estrogen, which allows them to bind to estrogen receptors and exert estrogen-like effects under certain experimental conditions. For this reason, isoflavones are commonly classified as phytoestrogens (plant estrogens). However, isoflavones differ from the hormone estrogen at the molecular level and clinically. In fact, isoflavones are more accurately classified as selective estrogen receptor modulators (SERMS) than as phytoestrogens.[25] SERMS have tissue-selective effects; that is, in some tissues they function as estrogen agonists, in other tissues as estrogen antagonists (anti-estrogens), and in many tissues affected by the hormone estrogen, they may have no effects at all.

To understand how two molecules with similar chemical structures can have different, and even opposite, physiological effects, it is instructive to consider the case of cholesterol (found in animal products) and phytosterols (found in plants). These two compounds have almost identical chemical structures, and yet, dietary cholesterol can modestly increase blood cholesterol[26] whereas phytosterols markedly decrease it.[27] The ability of isoflavones to function as SERMS is attributed to their preference for binding to and activating estrogen receptor-beta in comparison with estrogen receptor-alpha.[25] When activated, these two receptors have different and sometimes opposite physiological effects. In contrast to isoflavones, the hormone estrogen binds with equal affinity to each estrogen receptor.

Finally, it is important to recognize not only that isoflavones differ from the hormone estrogen, but that soyfoods contain hundreds of biologically active components. Therefore, the health effects of soy protein and soyfoods, may not necessarily be predicted from research involving isolated isoflavones.

Breast cancer

For the past 30 years, the role of soy in breast cancer prevention has been rigorously investigated.[28,29] This effort was fueled in part by the historically low breast cancer incidence rates in soyfood-consuming countries.[30,31] More informative however, are Asian population studies, which show that women who regularly consume soy are less likely to develop breast cancer than women who infrequently consume soy.[9] Nevertheless, research in mice utilizing one specific model, that began to be published in the late 1990s, raised concern that the isoflavones in soy could increase risk of breast cancer in high-risk women and worsen the prognosis of breast cancer survivors.[32]

However, extensive clinical research supports the safety of soy, even when intake greatly exceeds typical Japanese intake. Neither soy nor isoflavone intake affects established markers of breast cancer risk, including mammographic density[33-35] and most importantly, in vivo breast cell proliferation. Cells that replicate more quickly are more likely to be transformed into cancer cells. None of the 6 studies that evaluated the impact of soy or isoflavones on breast cell proliferation found an effect.[36-41] These studies require taking breast biopsies. In contrast to the lack of effect of isoflavones, combined hormone therapy (estrogen plus progestin), which

increases breast cancer risk,[42] increases breast cell proliferation 4-10-fold within just 12 weeks.[43,44]

The observational data are not only supportive of safety, but suggestive of benefit. That is, post-diagnosis soy intake is associated with reduced recurrence and improved survival. Five studies, 3 from China and 2 from the United States, have evaluated the effects of consuming soy after a diagnosis of breast cancer. The results of these studies, which include over 11,000 women with breast cancer, were statistically analyzed by Chinese researchers.[45] When comparing high versus low soy intake, risk of recurrence was reduced by 26% and mortality by 16%, both findings were statistically significant. The American Cancer Society,[14] the American Institute for Cancer Research,[46] the World Cancer Research Fund International[47] and the Canadian Cancer Society[48] have all concluded that women with breast cancer can safely consume soyfoods. In addition, the European Food Safety Authority[49] and the Permanent Senate Commission on Food Safety of the German Research Foundation[50] concluded that isoflavone supplements (soyfoods were not evaluated) do not adversely affect breast tissue.

Male feminization and reproduction function

The estrogen-like effects of isoflavones underlie concerns that soyfoods feminize men. Two case reports, describing single individuals, added to this concern. One of these reports described a 60-year-old man who developed gynecomastia,[51] and the other, described a 19-year-old vegan who experienced loss of libido and low testosterone levels.[52] In both cases, the cause was alleged to be soy intake. However, each of these men consumed 360 mg of isoflavones daily, approximately 9 times more isoflavones than consumed by the typical older Japanese man.[17] Excessive intake of nearly any food can be expected to have negative effects on health, especially in the context of an unbalance diet, which was the case for these two men. In contrast to these case-reports, clinical data definitively refute concerns about feminization.

In 2021, researchers published a statistical analysis of clinical studies that examined the effect of soy and isoflavone intake on hormone levels in men. A total of 41 studies were included in the analysis.[53] Total testosterone and free testosterone (biological active form) levels were assessed in 1,753 and 752 men, respectively; estradiol and estrone levels were measured in 1,000 and 239 men, respectively. Estrogen was measured because although this hormone is viewed as the primary female reproductive hormone, older men produce more estrogen than older women.[54] Regardless of the statistical model, no significant effects of soy protein or isoflavone intake on any of the hormones measured were found. Sub-analysis of the data according to isoflavone dose and study duration also showed no effect.

One pilot cross-sectional study found that soy intake was associated with low sperm concentration (sperm count was not affected).[55] However, much of that effect was because soy intake was associated with an increased ejaculate volume, a finding which is biologically implausible. Furthermore, follow-up research by these investigators showed soy did not impact fertility.[56] More importantly, none of the 3 intervention studies that examined the effects of soy or isoflavones on sperm and semen parameters found any adverse effects.[57-59] Finally, neither of the two clinical studies to examine gynecomastia found any adverse effects.[60,61] One of these studies is especially notable because it was 3 years in duration, involved about 300 men, and intervened with 100 mg of isoflavones daily, which is at the high end of dietary intake range.[60]

Thyroid function

There is a long history of investigation of the effects of soy on thyroid function.[62] Animal research published more than 20 years raised concerns that isoflavones could impair the functioning of this organ.[63,64] However, in 2006, a narrative review that included 14 clinical studies concluded neither soy nor isoflavones affect thyroid function in healthy individuals.[65] More recently, the first statistical analysis of the effects of soy on thyroid hormones was published.[66] It found no effect on the two main thyroid hormones, thyronine (T4) and triiodothyronine (T3). The European Food Safety Authority[49] and the Permanent Senate Commission on Food Safety of the German Research Foundation[50] concluded isoflavones do not affect thyroid function.

Research also suggests that even if iodine intake is marginal, isoflavones will not exacerbate thyroid function.[67] Finally, one study found that in subclinical hypothyroid patients, isoflavones increased the likelihood of progressing to overt hypothyroidism.[68] However, a follow up study by this research group involving a larger dose of isoflavones found no adverse effects.[69] Soyfoods and soy protein may inhibit the absorption of thyroid medication, but this is true for food in general and many herbs and supplements, which is why thyroid medication is taken on an empty stomach.[70]

Cognitive function

Concern about soy impairing cognitive function began with the results of the Honolulu-Asia Aging Study, which found higher midlife tofu consumption was independently associated with indicators of cognitive impairment in late life.[71] However, there were major limitations to this this observational study, one of which is that it was designed to investigate heart disease, not cognition. In 2014, a comprehensive review of the clinical, epidemiologic, and animal data concluded that the evidence was insufficient to draw conclusions about the association between dietary intake of soy isoflavones and cognition in older adults.[72] However, one year later, a meta-analysis of 10 placebo-controlled randomized trials of soy isoflavone supplementation, involving 1,024 postmenopausal women, found isoflavones favorably affected cognitive function and visual memory.[73] In agreement, a subsequently published analysis found that supplementation with soy isoflavones improved executive function and memory domains of cognitively normal older adults in half of the included studies.[74] Finally, a statistical analysis of 16 trials (1386 participants, mean age, 60 years) published in 2020, found soy isoflavones improved overall cognitive function and memory.[75] At this point, while it may be premature to conclude isoflavones improve cognition, the evidence refutes concerns that isoflavones or soy impair cognitive function.

Puberty onset

Soy consumption begins early in life in Asian populations. Japanese infants begin to consume soy products such as tofu and miso soup, which are common baby foods, between 6 and 12 months of age.[76] Several studies have documented the amount of soy consumed by Japanese[77] and Chinese[78,79] children. With respect to health effects, 2 clinical studies evaluated the impact of soy[80] or isoflavone[81] intake on hormone levels in children; neither study reported any effects.

Despite these findings and the historical precedent of Asian childhood soy consumption, the possible impact of soy on puberty onset is a relationship that has garnered attention.

This attention is due at least in part because pubertal characteristics are occurring at an earlier age in children throughout the world as evidenced by several changes including the advance in the age at which menarche occurs.[82-93] However, puberty is occurring earlier in life in countries that consume soy as well as those that do not.[82]

To examine the relationship between soy intake and menses onset, researchers from Loma Linda University in California, enrolled 327 Seventh-day Adventist (SDA) girls in a retrospective study.[94] Because about 40% of SDAs practice some form of vegetarianism,[95] their soy consumption is much higher than the general US population.[96] The mean age of menses onset of all girls in the study was 12.5 years. No relationship was found between age of menses onset and soy intake.[94]

A similarly designed study involving SDA boys was published four years later.[97] In this case, the measure of puberty onset was the first onset of pubic hair (Tanner stage 2). Among the 248 SDA boys, moderate and high total soy isoflavone intake was associated with a slightly earlier age at pubarche; however, no significant associations were noted between isoflavone intake and facial hair onset, which was used as a secondary measure of puberty onset. Also, it is notable that even among high-soy-consuming boys, puberty onset was later than is typical for US boys.[98] Thus, the evidence that soy intake advances age of puberty in either girls or boys is unimpressive.

Prenatal soy intake

Asian women consume soy during pregnancy as they do throughout other periods of life.[99-101] As a result, the fetus is exposed to isoflavones. However, the concentration of estrogen in the womb[102-105] is decidedly higher than the concentration of isoflavones in soyfood-consuming women.[106-108] Furthermore, the hormone estrogen is a much more potent than isoflavones.[109] Based on the greater potency and concentration of estrogen in comparison to isoflavones, and the historical precedent of prenatal soy consumption, evidence suggests the fetus is unlikely to be adversely affected by isoflavones.

Allergy

In 2004, the US Congress passed the Food Allergen Labeling and Consumer Protection Act (FALCPA), which mandates that the label of a food containing an ingredient that is or is derived protein from a "major food allergen" must declare the presence of the allergen in the manner described by the law. Eight allergenic foods, commonly referred to as the “Big 8,” fall under the FALCPA. The Big 8 foods that must be declared on product labels are milk/dairy, eggs, fish, crustacean shellfish, tree nuts, peanuts, wheat, and soy. (Recent developments indicate sesame seen will soon be added to this list). These foods account for 90% of the food allergic reactions among Americans.

However, the prevalence of allergy for each of these foods varies markedly. In fact, surveys show that among the Big 8, the prevalence of soy allergy is lowest. Based on the results of

surveys published within the past 15 years, a reasonable estimate is that approximately 3 out of every 1,000 adults are allergic to soy protein.[110] In Europe, soy is one of the Big 14, but again, research indicates the prevalence of soy allergy is low in that continent. In fact, it is lower than foods not included in the Big 14.[111] Finally, although children tend to have more food allergies than adults, about 70% of children with soy allergy outgrow their allergy by age 10.[112]

Mineral absorption

As is the case for all legumes and whole grains, soybeans contain compounds that can inhibit the absorption of minerals such as calcium and iron.[113] However, despite containing phytate and oxalate, two inhibitors of calcium absorption, calcium absorption from calcium-fortified soymilk[114,115] and calcium-set tofu,[116] is comparable to the absorption of calcium from cow's milk. In soybeans, the main inhibitor of iron absorption is phytate. However, studies suggest that the absorption of iron is much better than originally thought because much of the iron in soy is in a form that is resistant to inhibitors of iron absorption.[117,118] Furthermore, research shows that in response to the chronic consumption of a high-phytate diet, the inhibitory effect of phytate on iron absorption is greatly reduced.[119]

Fermented versus unfermented soyfoods

Most soy consumed throughout the world is unfermented because the ethnic Chinese consume little in the way of fermented soyfoods (excluding soy sauce, which is a condiment, not a food).[17] In South Korea, about 70% of soy consumed is in unfermented form[120] whereas in Japan, about 50% is unfermented.[121] Fermented and unfermented soyfoods have similar protein and isoflavone contents, although in fermented foods, the isoflavones are in a slightly different form than in unfermented foods. Fermentation can reduce the protease inhibitor content of soybeans,[122] but since soy protein from unfermented soyfoods is highly digestible, this reduction is likely of little consequence.[1,123] Fermentation can also reduce phytate content, but it is not clear this reduction will significantly affect mineral absorption.[122] Finally, Asian observational studies generally show both unfermented and fermented soyfoods are beneficial, although some studies have found one type is more beneficial than the other, but no clear pattern emerges. Overall, the evidence indicates that both forms of soy can make important contributions to a healthy diet.

Safe intake levels

There is a considerable range of soyfood intake among Asian countries. In Japan and some urban areas of China, average consumption is around 1½ to 2 servings per day, but older people with more traditional diets may consume as many as 3 servings per day.[17] In terms of protein, average intake in Japan is about 8 to 10 grams daily, whereas in Shanghai, it may be as high as 12 grams per day.[124] About 5% of Shanghainese consume about 25 grams per day.[124] Vegans in the United States consume about 13 grams soy protein per day.[96] When the US FDA approved a health claim for soyfoods and coronary heart disease based on the cholesterol-lowering effect of soy protein, it established 25 grams per day as the threshold intake for cholesterol reduction.[3] However, many clinical studies have intervened with as much as 40 grams of soy protein without reporting any adverse effects. Based on clinical research, an upper limit to isoflavone intake

should be about 100 mg per day. Exceeding this amount has not been shown to be harmful, but there is no historical precedent for doing so. Also, 100 mg isoflavones is provided by about 4 servings of traditional soyfoods. Eating more than four servings of soy per day is inconsistent with the principles of variety and moderation as no food should place too large a role in the diet, no matter how healthy it may be.

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