SOY MYTHS & FACTS

SOY CONSUMPTION	ENDOCRINE EFFECTS	BREAST CANCER
MINERAL STATUS	ALLERGIES	SOY INFANT FORMULA

Soyfoods are common in Asian and many health-conscious western diets, thus it is pertinent to explore the safety of soy as documented in the body of accumulated research. Consumers can be encouraged to continue feeding their families soyfoods for generations to come.

Introduction

Traditional soyfoods have played an important role in Asian diets for centuries and been consumed by health-conscious individuals in Western countries for many decades. Soyfoods have become increasingly popular among mainstream consumers in the West. Nevertheless, soyfoods are not without controversy. Concerns have arisen that soy may exert adverse effects in some individuals.

The FDA concluded that soyfoods are safe for all, except those who are allergic to soy protein.

Many of the concerns can be attributed to the uniquely rich isoflavone content of soybeans and studies conducted in animals. However, the totality of the clinical and epidemiologic research shows these concerns are without scientific merit – as discussed in the text below. Health agencies and academic groups that have reviewed the data are in support of this conclusion.

In 1999, as part of the process for approving the soy protein and coronary heart disease-health claim, the U.S. Food and Drug Administration (FDA) concluded that soyfoods are safe for all, except those who are allergic to soy protein.[1]

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.[2]

In 2009, a meta-analysis conducted by Austrian researchers, which was undertaken specifically to address the safety of isoflavone supplements, concluded they have a safe side-effect profile.[3]

In 2012, the American Cancer Society[4] and the American Institute for Cancer Research[5] concluded that women with breast cancer can safely consume soyfoods.

In 2015, Health Canada approved a health claim for soy protein and coronary heart disease similar to the 1999 U.S. claim. After extensively reviewing the scientific literature, Health Canada concluded that soy consumption was associated with only minor side effects, mostly gastrointestinal in nature.[6]

In 2015, the European Food Safety Authority concluded that isoflavones do not exert adverse effects on the three tissues evaluated, the breast, uterus and thyroid.[7]

In 2017, as part of its reevaluation of the soy protein health claim, the FDA reconfirmed its position that soy protein is safe.[8]

In 2018, in a joint report, the American Institute for Cancer Research and the World Cancer Research Fund concluded post-diagnosis soy intake may improve the survival of women with breast cancer.[9]

Soy Consumption

Many Asian dietary surveys have been published over the past 25 years, some involving thousands of individuals that have included detailed questions about soy consumption. These surveys make several clear, important points. The first being that soy consumption among Asian countries varies quite markedly. Japan is at the high-end of the spectrum whereas Hong Kong is at the low-end. The second point is that most soy consumed throughout the world is unfermented.[10]

The best indicators of soyfood intake are the amount of soy protein and isoflavones consumed. Because there are approximately 3.5 mg isoflavones per gram protein in traditional soyfoods, soy protein intake can be estimated from isoflavone intake and visa versa. This ratio will not apply to some refined soy products because the processing used in their making can cause as much as 80 percent of the isoflavone content to be lost.

In Japan, the daily intake of soy protein by older individuals is approximately eight to 10 g, which represents about 10 percent of their total protein intake.[10] Isoflavone intake ranges from about 30 to 50 milligrams per day (mg/d).[11] Chinese soy intake varies markedly among regions.[12] Large studies from Shanghai, a high-soy-consuming area, indicate men consume anywhere from about nine to as much as 13 g of soy protein per day,[13] the latter figure representing about 15 percent of total protein intake.[14] Shanghainese women consume about 9 g soy protein per day.[15] Individuals in the upper quarter of intake consume about 15 to 20 g soy protein daily. Approximately 1.5 servings of a traditional soyfood provides about 10 g soy protein since one serving provides about 7 g protein, although some soyfoods can provide considerably more than this amount. In Korea, the national survey, which involved over 11,000 healthy adults ≥19 y, revealed that mean isoflavone intake was approximately 24 mg/d.[16]

In Japan, approximately half of the soy consumed comes from unfermented foods, with four foods – tofu, miso, natto and fried tofu – accounting for about 90 percent of all soy consumed.[11,17,18] In contrast, in Shanghai, and throughout much of China, nearly all of the soy consumed is unfermented as soymilk, tofu. Processed soy products other than tofu account for about 80 percent of total soy consumption.[19] In Korea, about 70 percent of the soy consumed is in unfermented form.[20]

Endocrine Effects

The classification of isoflavones as phytoestrogens has led to considerable investigation on the effect of soyfoods on hormone levels in both men and women, especially the reproductive hormones. In regards to men, two case reports each describing a single individual that experienced a decrease in testosterone and/or an increase in estrogen levels, are typically cited as evidence of effects on hormone levels.[21,22] However, both men reportedly ingested in the context of a nutrient deficient diet, about 360 mg/d isoflavones, an intake that is about nine-fold higher than is typical for Japanese men consuming a traditional diet.

In contrast to these case reports, a meta-analysis that included 32 clinical studies and 36 treatment groups found there were no significant effects of soy protein or isoflavone intake on levels of total testosterone, sex hormone binding globulin, free testosterone or the free androgen index.[23] Studies published subsequent to this analysis are supportive of this conclusion.[24-28] In addition, a narrative review that included nine clinical studies found no effect of soy on estrogen levels.[29] Research published subsequent to this review is supportive of this conclusion.[28,30] Importantly, even when isoflavone exposure exceeded typical Japanese levels, clinical studies show hormone levels were unaffected.

As is the case for men, the clinical data indicate soy does not affect estrogen levels in women. Hooper et al.[31] meta-analyzed the data from 47 clinical trials and found no effect of soy or isoflavone intervention on estradiol and other reproductive hormones in pre- and postmenopausal women.

Fertility

It is somewhat ironic that concerns about soy intake and fertility have been raised in traditionally high-soy-consuming Asian countries, given their large populations. In women, soyfoods appear to increase the length of the menstrual cycle by about one day.[31] However, ovulation is not prevented but is simply delayed. Furthermore, there is some evidence that isoflavones aid female fertility. For example, a prospective study found that among 315 women who collectively underwent 520 assisted reproductive technology cycles, soy isoflavone intake was positively related to live birth rates.[32]

In addition, soy consumption appears to negate the adverse reproductive effects of the endocrine disruptor bisphenol A (BPA) on fertility. In a study involving 239 women undergoing in vitro fertilization, among those who did not consume soyfoods, urinary BPA levels were inversely related to live birth rates per initiated cycle – whereas no such relationship existed among soy-consumers.[33] Although the low isoflavone intake among the soy consumers (mean intake, 3.4 mg/d) would normally raise doubt about the plausibility of these findings, they do agree with animal data.[34,35]

In men, a small pilot cross-sectional study found that very modest soy consumption was associated with lower sperm concentration – sperm count was not decreased – but there were many weaknesses to this study.[36] In fact, much of the decreased sperm concentration occurred because there was an increase in ejaculate volume in men consuming higher amounts of soy, a finding which seems biologically implausible. Furthermore, this same research group subsequently conducted a cross-sectional study involving 184 men from couples undergoing infertility treatment with in vitro fertilization. They found that the male partner's intake of soyfoods and soy isoflavones was unrelated to fertilization rates, proportions of poor quality embryos, accelerated or slow embryo cleavage rate, implantation, clinical pregnancy, and live birth among couples attending an infertility clinic.[37]

Finally, all three of the clinical studies conducted show that isoflavones have no effect on sperm concentration or quality.[38-40] In one, healthy volunteers took a daily supplement containing 40 mg isoflavones for two months.[38] In another, 32 healthy young men consumed diets in random order for 57 days that were supplemented with milk protein isolate or isolated soy protein containing a high or low amount of isoflavones.[40] In the third study, 20 volunteers were randomized to three different groups in which they were provided 60, 320 or 480 mg/d isoflavones for three months.[39] Interestingly, a case report indicated that daily isoflavone 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]
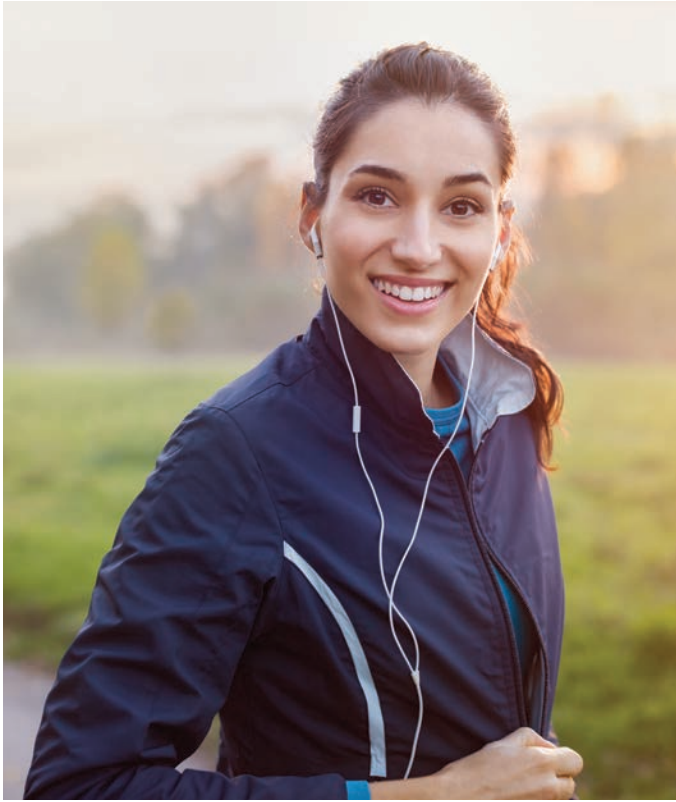
Soy, Isoflavones and Thyroid Function

Concerns about soy's effects on the thyroid are based primarily on in vitro research[42,43] and studies in rodents administered isolated isoflavones.[44,45] However, a comprehensive review published in 2006 that included 14 clinical trials found that the totality of the evidence showed that neither soyfoods nor isoflavones adversely affect thyroid function in healthy men or women.[46] Studies published subsequent to this review support this conclusion.[47-51] As previously noted, in 2015, the European Food Safety Authority concluded that isoflavone exposure doesn't affect thyroid function.[7] Studies published subsequent to this report support this conclusion.[52,53]

There is also concern that soy may worsen thyroid function in those whose thyroid function is compromised, such as subclinical hypothyroid patients and those whose iodine intake is marginal. The latter concern is based on the potential for isoflavones rather than the amino acid tyrosine to be iodinated, thereby inhibiting the synthesis of thyroid hormone.[54] However, clinical research published in 2012 showed that the iodination of isoflavones is negligible and clinically irrelevant.[55] One small British study did find that modest isoflavone exposure (16 mg/d) increased the likelihood of progressing from subclinical to overt hypothyroidism.[56] However, it would be premature to base clinical decisions on the findings from this one study. Furthermore, this study also found that in all participants, isoflavone exposure caused marked and statistically significant reductions in systolic and diastolic blood pressure, insulin resistance and inflammation (as assessed by C-reactive protein).[56]

Isoflavone Content of Soyfoods

SOYFOOD	SERVING SIZE	TOTAL (MG) ISOFALVONE/SERVING
Miso	1 tbsp	7
Soybeans, Green, Cooked	½ cup	50
Soybeans, Black, Cooked	½ cup	40
Soybeans, Yellow, Cooked	½ cup	78
Soybeans, Roasted, Plain	¼ cup	78
Soymilk, Plain, Unfortified	1 cup	10
Soymilk, Plain, Fortified	1 cup	43
Soy Flour, Defatted	¼ cup	42
Soy Flour, Full-Fat	¼ cup	33
Soy Flour, Low-Fat	¼ cup	50
Soy Crumbles	½ cup	9
Soy Protein Isolate Powder, Plain	⅓ cup	53
Textured Soy Protein, Dry	¼ cup	33
Tempeh	½ cup	53
Tofu	½ cup	25

Source: United States Department of Agriculture Nutrient Database.

Although soy has no effect on thyroid function in euthyroid individuals, soyfoods may increase the amount of thyroid medication needed by hypothyroid patients. This is not because of an effect on the thyroid, but because soy protein may interfere to some extent with the absorption of the medication.[57–60] However, soy is not unique in this regard, as many herbs, drugs, fiber, and calcium supplements have similar effects.[61–69] 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. Typically, it is recommended to wait one to three hours after taking thyroid hormone before consuming anything that might interfere with its absorption.

An alternative approach to temporal separation between thyroid hormone ingestion and the consumption of soy is to maintain consistency in medication administration and dietary habits so that the dose of medication can be adjusted, if necessary. As long as the medication is taken in a consistent manner and the amount of soyfoods consumed is relatively constant, soy should not be an issue.[70]

Fast Facts About Isoflavones

1 Isoflavones are one of five chemical classes of anticarcinogens found in soy

2 Soyfoods are the only significant natural dietary source of isoflavones

3 Research shows isoflavones may prevent the onset of osteoporosis and may protect against various forms of cancer

Breast Cancer Patients

Despite the proposed breast cancer–preventive effects,[71] there has been concern that because soyfoods contain isoflavones, they worsen the prognosis of women with breast cancer and increase the risk of developing breast cancer in women who are at high risk for this disease.[72] It is worth noting that although estrogen does stimulate the growth of some breast tumors, the evidence that estrogen therapy increases breast cancer risk is very unclear. In fact, in the Women's Health Initiative trials, estrogen therapy led to a statistically significant decreased risk of dying from breast cancer, whereas estrogen plus progestin therapy led to a significant increase.[73]

No intervention study has examined the impact of soy consumption on breast cancer recurrence and/or mortality. However, the impact of soy on several established markers of breast cancer risk, including mammographic density[74,75] and breast cell proliferation,[76] has been studied extensively. The results of this research are extremely reassuring, and they show that even

when isoflavone exposure greatly exceeds typical Japanese intake (~40 mg/d), 10 breast tissue is not adversely affected.[77-84] Not surprisingly, this was the conclusion reached by the European Food Safety Authority in 2015 after a multi-year comprehensive evaluation of the literature.[85]

In 2012, based on the epidemiologic data, the American Institute for Cancer Research (AICR)[5] and the American Cancer Society[4] concluded that breast cancer patients can safely consume soyfoods.

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In 2018, a report from the AICR and the World Cancer Research Fund concluded that post-diagnosis soy intake may improve the survival of breast cancer patients.[9] The positions of these cancer organizations are not surprising, given the results of meta-analysis (N=11,206) by Chi et al.[86] that included three prospective studies from China[87-89] and two from the U.S.,[90,91] that involved more than 11,000 women with breast cancer.

In this analysis, when comparing extremes of post-diagnosis soyfood intake, higher intake was associated with reduced mortality (hazard ratio, 0.84; 95 percent confidence interval: 0.71, 0.99). When comparing extremes of post-diagnosis isoflavone intake, intake was associated with a decrease in recurrence (hazard ratio, 0.74; 95 percent confidence interval: 0.64, 0.85).[86] The benefits of post-diagnosis soy intake were evident in both estrogen receptor-negative and estrogen receptor-positive breast cancer patients and was equally beneficial in Chinese and U.S. women.[92] Interestingly, in contrast to studies in mice, the epidemiologic data suggest that soy consumption may actually enhance the efficacy of chemotherapeutic agents used to treat breast cancer.[87,92]

Mineral Status

Soyfoods are frequently used in place of animal foods. Many animal foods are good sources of iron and zinc and in the case of dairy foods', calcium. Relatively little red meat is needed to meet daily iron and zinc requirements. As a result, questions about the effects of soy on the status of these two minerals pertains mostly to those eating a predominately plant-based diet.[93]

Like other legumes and whole grains, soybeans are high in phytate,[94] which acute studies show reduces the absorption of zinc and iron.[95] In the U.S., the Food and Nutrition Board (FNB) recommends a zinc intake for vegetarians whose diet contains generous amounts of grains and legumes that is 50 percent higher than the recommended dietary allowance (RDA) for non-vegetarians; although, the FNB has not formally established a vegetarian RDA.[96]

Zinc absorption from soyfoods is only modestly lower than that from animal sources. However, because soybeans contain relatively little zinc, unfortified soyfoods are not particularly good sources of this mineral.[97-100] Zinc status is difficult to assess.[101,102] Consequently, those consuming a plant-based diet are advised to specifically identify good plant sources of zinc in their diet and/or to take a zinc supplement.[103-107]

In contrast to zinc, soyfoods are relatively high in iron.[108] Until recently, it was believed that the iron was poorly absorbed from all plant foods, including soyfoods. For this reason, the vegetarian iron RDA is 80 percent higher than that for non-vegetarians. This higher RDA derives from the assumption that the bioavailability of iron from a vegetarian diet is about 10 percent whereas that from a non-vegetarian diet is 18 percent.[109]

However, relatively new research utilizing improved methodology indicates that iron absorption from soy may be much 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, clinical studies in which participants were fed either soyfoods or soybean ferritin show it to be highly bioavailable.[51,110,111]

Finally, a study published in 2015 shows that in contrast to older understanding,[112] there appears to be adaptation to the inhibitory effects of phytate on iron absorption.[113] For this study, 32 nonanemic premenopausal women with suboptimal iron stores were randomly assigned to a high or low-phytate diet for eight weeks. The serum iron response over four hours after a test meal containing 350 mg of phytate was measured at baseline and post intervention.

The serum iron response to the test meal increased in the high-phytate group at post intervention, resulting in a 41 percent increase in the area under the curve. However, no effect was observed in the low-phytate group. It is reasonable to speculate that chronically consuming a high-phytate diet will lead to a mitigation of the inhibitory effects of phytate on the absorption of not just iron, but possibly other minerals as well.

In addition to phytate, soybeans are also high in oxalate, another compound that binds calcium and reduces its absorption.[114] Oxalate is one reason that even though spinach is high in calcium, it is not a good source of this mineral. Calcium absorption from soybeans is surprisingly good – despite the presence of both phytate and oxalate.[115] This is also true for calcium-set tofu[116] and calcium-fortified soymilk.[117-119] In fact, the absorption of calcium from these foods is comparable to the absorption of calcium from cow's milk.

Allergies

Soy protein can cause allergic reactions in sensitive individuals, as is the case for essentially all food proteins. Soy protein is one of the eight foods that compromise the Big 8 and are responsible for approximately 90 percent of all food-induced allergic reactions in the U.S.[120] However, these foods are not equally allergenic and allergy to soy protein is relatively uncommon.[121] Furthermore, it is important to recognize that the Big 8 could have easily been a list of a different size as there is no scientific basis for this group being comprised of eight foods. In Europe, it is the Big 14[122] and in Japan it is the Big 7.[123]

If the U.S. list included only seven foods, it is likely soy would not be on the list. In support of this statement are the results of the Food Safety Survey, which is conducted by the FDA approximately every five years. Data for the most recent survey (2010), which involved nearly 5,000 participants, show that approximately only one out of 1,000 adults (0.1 percent) self-report a doctor-diagnosed allergy to soy protein.[124] In comparison, the prevalence of allergy to the other seven foods in the Big 8 is much higher: milk/dairy (2%), shellfish (1.6%), wheat and/or gluten (0.9%), fish (0.8%), tree nuts (0.7%), peanuts (0.6%) and eggs (0.5%). Furthermore, this survey found the prevalence of allergy to pea protein and chocolate was each 0.1%, the same as soy protein even though neither of these foods is included in the Big 8.

In general, the prevalence of food allergy among children is greater than among adults. However, similar to adults, the prevalence of soy allergy among children is relatively low compared to many other foods.[125] For example, in a survey involving nearly 40,000 individuals below the age of 18, the prevalence of allergic reactions to peanuts and milk was five and four times more common, respectively, than the prevalence of allergic reactions to soy protein.[125]

Data from Europe helps to emphasize that soy protein allergy is quite uncommon. Although soy is one of the Big 14, a recently published study involving six European countries found that the prevalence of allergy to 19 foods was greater than the prevalence of allergy to soy protein.[126] In agreement, a survey of nearly 5,000 adults in Western Europe found that of 24 foods evaluated, allergic reactions to 18 of these foods were more common than reactions to soy protein.[127]

It is particularly informative to note that according to a report from Europrevall, "… data indicate that some allergens for which labelling is mandated and for which management measures are therefore instituted (e.g. soy, mustard), appear to have a lower public health impact than some, which are not required to be declared (e.g. some fruits)."[128] EuroPrevall is a multidisciplinary project, including 62 institutions from 22 European countries. The organization is charged with studying the prevalence and distribution of food allergies in infants, children, adolescents, and adults in Europe.[129]

Soy Infant Formula

Soy infant formula (SIF) has been in use for more than 50 years. During this time, an estimated 20 million Americans used SIF during infancy. Current data from a nationally representative sample of 1,864 infants, zero to 12 months old, from the National Health and Nutrition Examination Survey, 2003-2010, show that among the 81% of infants who were fed formula or regular milk, 12.9% consumed SIF.[130]

SIF produces normal growth and development; nevertheless, SIF use has become controversial because of its high isoflavone content. In 2009, the U.S. National Toxicology Program (NTP) concluded there was minimal concern about the safety of SIF.[131] In response to this conclusion, the American Academy of Pediatrics submitted a letter to the NTP, which is now part of the public record, stating that, there was negligible concern about the safety of SIF. The five levels of concern at the time this letter was submitted were negligible, minimal, some, concern, and serious concern. studies. It is notable that a small Israeli study found SIF use wasn't associated with puberty onset in boys or girls.[140]

Considerable insight to the health effects of SIF will be gained over the next few years as a result of research underway at the Arkansas Children's Nutrition Center, University of Arkansas for Medical Sciences. At this center, they are comparing the health status of infants fed breast milk, cow's milk formula and SIF. Thus far, findings indicate that all health parameters assessed in infants fed SIF are well within the normal range.[132-136]

The first systematic review and meta-analysis focused on the safety of SIF concluded that SIF intake in normal full-term infants – even during the most rapid phase of growth – is associated with normal anthropometric growth, adequate protein status, bone mineralization and normal immune development.[137] However, the results of a very recently published epidemiologic study suggest that SIF may exert modest estrogenic effects in infant girls (not boys). Although, whether these observed effects are transient and whether they have any long-term clinical implications wasn't able to be determined.[138]

It is noteworthy in this regard that a very recent study found there were no long-term effects resulting from marked differences in growth patterns up to four months of age due to differences in formula feeding, on anthropometry

at four years of age.[139] This study should give considerable pause about drawing conclusions about the long-term health implications of formula feeding based on differences observed in infants. Insights about infant feeding patterns may need to come from long-term prospective studies or carefully controlled retrospective studies. It is notable that a small Israeli study found SIF use wasn't associated with puberty onset in boys or girls.[140]

Soyfood Processing

Tofu and miso are commonly consumed soyfoods in Asia whereas in the U.S., many people choose more refined forms of soy such as meat analogs and energy bars – which use as a base concentrated forms of soy protein.[10] Numerous human studies demonstrate that these modern soy products provide very high-quality protein.[141,142]

Depending on processing methods, the isoflavone content of these foods can be markedly reduced.[143] 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. Hexane is often used in the defatting of soybeans but only very trace amounts of this alkane can be found in the meal or oil.[144,145]

Many traditional soyfoods such as miso, tempeh, and natto undergo fermentation. Fermentation reduces the content of several compounds traditionally classified as anti-nutrients including phytate[146] and protease inhibitor,[147] and may even reduce antigenicity.[148] However, any benefits of these fermentation-induced changes have yet to be demonstrated clinically. To the contrary, several epidemiologic studies show protective effects against different cancers associated with the intake of only unfermented soyfoods.[149,150] Unfermented soyfoods have been consumed in Japan[151] and China[152] for at least 500 and 1,000 years, respectively. Even in Japan, where fermented soyfoods such as miso and natto are very popular, about half of the total soy consumed comes from foods that are not fermented (primarily tofu).[17,18] Among ethnic Chinese – including people from China, Singapore and Hong Kong – nearly all of the soy consumed is unfermented.[19]

Summary and Conclusions

When evaluating the safety of soyfoods, it is imperative to consider the totality of the scientific research and place appropriate weight on studies according to their experimental design. The research overall indicates that soyfoods can be safely incorporated into the diets of essentially all healthy individuals with the exception of those allergic to soy protein, which is relatively uncommon. 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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