OPTAVIA®

Soy Food and Health

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The Company ("We") recommends that you consult your healthcare provider prior to starting any weight loss program, and during the course of your weight loss program. Do NOT use any **OPTA**VIA Program, Plans, Products or Kits if you are pregnant or under the age of 13.

Before starting a weight loss program, talk with your healthcare provider about the **OPTA**VIA Program, Plans, Products, and Kits as appropriate, and about any dietary supplements or medications you are using, especially Coumadin (Warfarin), lithium, diuretics, or medications for weight loss, diabetes, high blood pressure or thyroid conditions. Do not utilize any **OPTA**VIA Program, Plans, Products or Kits until you are cleared by your healthcare provider if you have or have had a serious illness (e.g. cardiovascular disease including heart attack, diabetes, cancer, thyroid disease, liver, or kidney disease, eating disorders such as anorexia or bulimia), or any other condition requiring medical care or that may be affected by weight loss.

The **OPTA**VIA for Teens Plan is the only **OPTA**VIA Plan appropriate for teens (13 to 17 years of age). The Optimal Weight 5 & 1 Plan® is NOT appropriate for teens, sedentary older adults (65 years and older), nursing mothers, people with gout, individuals with Type 1 diabetes, and those who exercise more than 45 minutes per day or participate in high intensity activity - if you fall into one of these categories, please consult your healthcare provider, refer to **OPTA**VIA.com and talk with your independent **OPTA**VIA Coach about other **OPTA**VIA Plans that may be appropriate. For special medical or dietary needs, including food allergies or decreased appetite with weight loss medications, refer to our program information online, consult your healthcare provider and talk to your **OPTA**VIA Coach. Do not consume an **OPTA**VIA product if you are allergic to any of the product's ingredients, which are listed on the product packaging and on the **OPTA**VIA website.

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Before taking any dietary supplement or changing your dietary intake, or starting a weight loss or exercise program, we recommend consulting with your healthcare provider first, especially prior to starting any **OPTA**VIA ACTIVE® Plans and Products. Clients should seek professional support for specific exercise program prescriptions. The Optimal Weight 5 & 1 ACTIVE Plan™ is not appropriate for those who exercise more than 45 minutes per day or participate in high intensity activity. **OPTA**VIA ACTIVE products are not recommended for individuals under 18 years of age.

NOTE: Rapid weight loss may cause gallstones or gallbladder disease, temporary hair thinning, or muscle loss in some people. While adjusting to the intake of a lower calorie level and dietary changes, some people may experience dizziness, lightheadedness, headache, fatigue, or gastrointestinal disturbances (such as abdominal pain, bloating, gas, constipation, diarrhea, or nausea). Consult your healthcare provider for further guidance on these or any other health concerns. Seek immediate medical attention if you experience muscle cramps, tingling, numbness, confusion, or rapid/irregular heartbeat as these may be a sign of a more serious health condition.

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As individuals may have different responses to dietary products or changes in diet, consult with your healthcare provider regarding any medical concerns.

For further information regarding this Medical Disclaimer, contact the **OPTA**VIA Nutrition Support Team, available Monday through Friday 8:00 a.m - 5:00 p.m EST at 1.888.**OPTA**VIA (1.888.678.2842) or via text at 206.828.1605. You can also email at NutritionSupport@**OPTA**VIA.com.

Soy Food and Health

OPTAVIA, born from Medifast®, is a company dedicated to the achievement of optimal health: striving to provide innovative products, scientifically-based recommendations, and clinically proven plans to help people achieve a healthy weight and the development of healthy habits. With many different **OPTA**VIA Fuelings to choose from, our product line is designed to help meet a wide range of dietary needs and individual preferences.

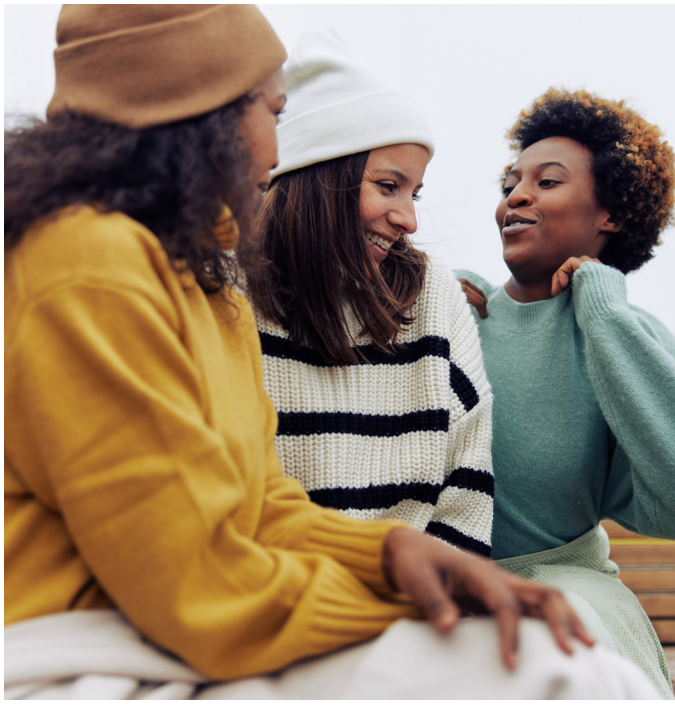
Many **OPTA**VIA Fuelings contain soy protein. Soy protein is a plant-based protein source recognized as equal in protein quality to animal protein.[1,2] Soy protein is a "complete" protein, as it provides all nine essential amino acids in amounts sufficient to help meet the body's physiology requirements.[2] However, unlike many sources of animal protein, soy is low in fat and saturated fat and naturally lactose and cholesterol-free. For more information about the **OPTA**VIA products that contain soy, visit the 'Product Claims Sheet' at www.ANSWERS.**OPTA**VIA.com.

In the last 20 years, there has been an impressive amount of research conducted on the health effects of soy. Research shows that soy is a great source of high-quality, low-fat plant protein that may help lower the risk of heart disease [3], osteoporosis [4,5], and certain forms of cancer.[6,7] Despite these supportive findings, confusion about the health effects of soy foods and soy isoflavones continues.

Since many of **OPTA**VIA's Fuelings contain soy, the purpose of this document is to help provide general information on soy, share established and emerging areas of research, and address some of the confusion about the health effects of soy. Then in collaboration with your healthcare provider, you can make informed decisions about what soy can mean for you, your meal planning, and your health. To use this resource, you can either quickly navigate to specific sections of interest by referring to the table of contents or read it in its entirety, from start to finish - whatever is most helpful for you. We recommend you discuss any concerns you have about soy and your health with your healthcare provider.

The Story of Soy

Foods made from soybeans have been consumed for many centuries, beginning first in China and then spreading to Japan and other Asian countries. Since then, soyfoods have become more familiar to consumers worldwide and have become a popular choice, especially among many health-conscious individuals, valued for their versatility, taste, nutritional content, environmental advantages, and health benefits.



A Truly "Green" Bean

Today, European and American governmental agencies recommend that individuals focus on eating more plant-based foods as a way to help decrease the risk of chronic diseases and control weight.[8] Soy fits well within these recommendations: it provides the same high-quality protein as meat, milk, and eggs, often with less saturated fat and cholesterol and a smaller carbon impact. When chosen in place of animal-based proteins, soy offers other health advantages as well.[8,9,10,11]

Soy Protein Quality

The protein quality of soy protein is equivalent to the quality of animal protein.[2] In general, the protein quality of plant protein is lower than that of animal protein, but this is not the case for soy protein. Soy protein receives the highest possible score according to the current method used by the United States Department of Agriculture for evaluating protein quality.[2] With a Protein Digestibility-Corrected Amino Acid Score ("PDCAAS") of 1.0, soy's protein quality is comparable to dairy, eggs and meat. Protein quality refers to the ability of a protein to meet our body's requirement for amino acids, the building blocks of protein.

Fermented & Unfermented Soy, Soy Processing and Soy Products

Fermented & Unfermented Soy

Fermented soyfoods include miso, natto and tempeh whereas unfermented soyfoods include tofu, soymilk, and edamame (green soybeans). Most soy consumed throughout the world is in unfermented form.[12] The soy found in **OPTA**VIA Fuelings is also unfermented.

Online sources often tout the alleged benefits of fermented soy over unfermented soy, typically claiming that the fermenting process eliminates "anti-nutrients." Anti-nutrients are compounds that can inhibit the absorption and/or utilization of other nutrients. Phytate and oxalate are examples of commonly cited anti-nutrients found in soy as they can inhibit the absorption of certain minerals such as calcium. However, despite containing phytate and oxalate, the absorption of calcium from soy is similar to the absorption of calcium from cow's milk.[13]

These "anti-nutrients", like phytate and oxalate, occur naturally in many wholesome foods such as whole grains and legumes/beans. The consumption of these foods has been associated with the reduced risk of certain cancers [14-16] and cardiovascular disease.[14]

Protease inhibitors are another commonly cited anti-nutrient found in soy that inhibits the digestion of protein. However, because protease inhibitors are inactivated by heat, the digestion of soy protein is excellent (~98%).[2] If it was not, soy protein would not be rated as the high-quality protein it is.[2] In summary, fermented soyfoods are nutritious additions to a healthy diet, but they are neither superior nor inferior to the unfermented form of soyfoods.

Soy Protein Processing & Hexane

Soy is a versatile food and has many forms. Whole soybeans, both immature, green "edamame" and fully ripened forms are high in protein, but also contain carbohydrates and fat. In order to create foods made with soy protein, such as soy-based meal replacements and soy-based meat alternatives, the protein portion must first be isolated. This is done by de-hulling and extracting the fat, in the form of oil, from the whole soybean.[17] Typically, this process includes hexane, a common solvent used to extract and separate vegetable oil from almost all oil-seeds, including soybean, sunflower seeds, and canola seeds.[17-20] Processing that utilizes hexane is tightly controlled, and the processing techniques ensure that all or virtually all residual hexane is removed from the separated oils and seed components and then retained and recycled. Hexane has been safely used in the process of separating oils from seed components for more than 70 years. The U.S. Food and Drug Administration ("FDA") has long recognized the use of hexane for processing soybeans and considers soybean oil and protein produced using hexane in the manufacturing process to be safe.[21,22]

Soy Protein Products

Soy can be processed into a variety of highly concentrated protein products, including, but not limited to, soy flour, soy protein concentrate, and soy protein isolate. The protein contribution for these various grades of soy range from about 50-90%. Soy protein products are widely used by the food industry for their functional properties, to boost protein content, and as a base for making meat substitutes and non-dairy beverages. In addition, because they are so easily incorporated into the diet, soy protein products are typically used in research rather than other types of traditional soyfoods. Hence, quite a bit is known about their nutritional properties.

Soy Protein & **OPTA**VIA

Many of the **OPTA**VIA Fuelings contain soy protein (concentrate and/or isolate). Our soy protein is prepared through a process using water extraction and minimum heat on soy flakes. Unlike whole soybeans (such as edamame which are green/immature beans or fully ripened whole soybeans), soy protein isolate is nearly carbohydrate free, low in fat and saturated fat, and is free from cholesterol and lactose, while isolating and retaining the high-quality protein. With a Protein Digestibility Corrected Amino Acid Score ("PDCAAS") of 1.0, it offers protein quality that's of parity to dairy, eggs and meat.

The OPTAVIA **Connection:**

Many of **OPTA**VIA's Fuelings contain soy protein. The soy found in **OPTA**VIA Fuelings is from unfermented soy.

In summary

- Soyfoods are high in protein, versatile, and often contain less saturated fat and cholesterol than protein from animal sources.
- Both fermented (e.g., natto, miso, tempeh) and non-fermented (e.g., soymilk, edamame, tofu) soyfoods are nutritious choices and considered to be a type of high-quality protein.
- Soyfoods come in a wide variety of forms and are used for many functional purposes.
- Many of **OPTA**VIA Fuelings contain soy protein. The soy found in **OPTA**VIA Fuelings is from unfermented soy and is a high-quality protein source.
- For more information about the **OPTA**VIA products that contain soy, visit the Product Claims Sheet at www.ANSWERS.**OPTA**VIA.com.

Research on Soy and Soy Foods

Evaluating Evidence

Before reading further about the potential health benefits of soy and soy foods, it will be helpful to understand some of the different types of research studies and what conclusions can be drawn from them. When reaching conclusions about the health effects of a specific diet or food, it is necessary to look at the totality of the evidence. That is, one can't just consider only a few studies or only those studies that support a specific perspective. One must also consider the type and quality of the study. Human studies are considered most credible and carry the most weight among scientists, whereas in vitro studies (studies involving cells or test tubes) and animal studies are primarily used as a basis for determining whether research in humans is justified.

There are two general types of human studies, observational (epidemiologic) and clinical studies. In the field of nutrition, a prospective observational study might assess the dietary intake of a group of individuals then follow them for a period of time (usually many years) to determine whether a specific food or dietary pattern is associated with a higher or lower risk of developing a particular health outcome. A case-control observational study might compare the dietary intake of a group of individuals with a specific disease or condition (cases) with a similar group of individuals (controls), but without that disease or condition.

Observational studies, though useful, have limitations such as the difficulty of accurately assessing dietary intake or the ability to control for confounding variables. For example, suppose people who regularly consume broccoli are less likely to develop breast cancer. But what if broccoli consumers also exercise more? Is it the broccoli, exercise, or a combination of both that is responsible for the observed effect? Consequently, because it is impossible to control for all confounding variables, observational studies don't allow cause and effect relationships to be established- these studies allow one to conclude that two factors are related to one another, but not that one causes the other.

The other type of human research is a clinical (intervention) trial. A clinical trial randomly assigns study participants to one or more health-related interventions to evaluate the effects on health outcomes. For example, one group of participants could be assigned to consume "Diet X" and the other group "Diet Y". After a period of time, the investigators compare health outcomes (such as weight, cholesterol levels, etc.) between the two groups. Clinical studies are considered most informative because they allow causal relationships to be established. (For example, if the group consuming "Diet X" lowered their blood pressure but those consuming "Diet Y" did not, it is possible to conclude that "Diet X" caused the reduction in blood pressure.) However, clinical studies are very expensive to conduct, so they are typically relatively short in duration, and involve fewer participants than is ideal. Participants may also not fully comply with the instructions they have been given. (For example, what if the people in the "Diet Y" group did not actually eat the foods recommended for "Diet Y"?)

The OPTAVIA Connection:

- **OPTA**VIA recognizes the importance of being able to identify and appropriately interpret well-designed research and translate these findings into evidenced-based plans and scientifically designed products. Our goal in including this section is to help further your understanding of how to evaluate the soy research presented within this document. As a Company, we will also continue to critically evaluate research to further our mission.
- The scientific heritage of Medifast is rich and has only continued to grow over time. In the last 10 years alone, more than a dozen scholarly articles of studies that used the Medifast/**OPTA**VIA products and/or plans were published in peer-reviewed scientific journals.[44-45][44-45] Soy protein has always been an ingredient used in the Medifast/**OPTA**VIA Fuelings; therefore, soy-containing and non-soy-containing products were used by participants enrolled in these clinical trials.
- For more information on Medifast's scientific heritage and clinical trials go to (Clinical Studies Overview).

In summary

- All study types have their own strengths and limitations.
- Human research carries more weight than non-human studies.
- When reaching conclusions about soy (or any other food) it is necessary to look at all the evidence and to consider both the type and quality of the studies involved.

Soy Isoflavones

Soybeans are unique because they are the only commonly eaten food that is a rich source of a group of naturally occurring plant compounds called isoflavones (ahy-soh-FLEY-vohnz or ahy-soh-FLĀ-vōnz).[34,35] Isoflavones are found in many foods but with the exception of soybeans, mostly only in very small amounts.

Misconceptions about Isoflavones

Isoflavones are commonly referred to as phytoestrogens or plant estrogens. As a result, some confusion has arisen over their reported health effects. Although isoflavones are classified as plant estrogens, they are different from the hormone estrogen. In some cases, isoflavones may not have any effect at all on tissues that are affected by estrogen and in others, isoflavones have the potential to act in ways opposite to those of the hormone estrogen. The ability of isoflavones to act so selectively is thought to be because they differ from estrogen in the way in which they interact with and bind to estrogen receptors in cells.[36] Therefore, no conclusions about isoflavone's health effects can be made based on the effects of estrogen. Instead, conclusions about isoflavones should be made based on clinical trials, that is, studies in which humans consume these soybean constituents.

Furthermore, remember that soybeans are more than just isoflavones. They provide protein, healthy fat and an assortment of other nutrients and biologically active components. Hence, conclusions about the effects of soybeans, soyfoods, and soy protein, should not be based on studies involving isolated isoflavones.

In summary

- Evidence suggests that many of the proposed benefits of soyfoods are due to their isoflavone content.
- Isoflavones are a part of a larger group of compounds called phytoestrogens, or plant estrogens, but **isoflavones are not the same as the hormone estrogen.**
- Conclusions about the health effects of soy isoflavones should not be made based on the hormone estrogen.
- Soy is more than just isoflavones and conclusions about soybeans, soyfoods, and soy protein should be based on human studies that involve more than just isolated isoflavones.

Heart Health: Cardiovascular Disease

Cardiovascular disease ("CVD"), which includes heart disease, hypertension, stroke, and heart attack, is believed to be the cause in one out of every three American deaths.[37] Approximately every 40 seconds an American will have a heart attack.

Despite these sobering statistics, there is some good news. Over the past 50 years or so there has been a sharp decline in mortality rates from heart disease and stroke throughout the industrialized world, with age-adjusted mortality rates having declined to about one-third of their rates in the 1960's.[38,39] There are undoubtedly many reasons for this decline, some of which include the rapid progress in both prevention and treatment of heart disease.[38,40]

Recommendations from the American Heart Association

The American Heart Association ("AHA") gauges the cardiovascular health of the nation by tracking 7 key risk factors and behaviors that reduce the risk of developing heart disease and stroke. These are called "Life's Simple 7" and are defined by the AHA as "the 7 risk factors that people can improve through lifestyle changes to help achieve ideal cardiovascular health". The 7 key risk factors are:

1. Manage blood pressure
2. Control cholesterol
3. Reduce blood sugar
4. Get active
5. Eat better
6. Lose weight
7. Stop smoking

Soy for Heart Health

Soy is good for heart health because it is a high-quality protein and, unlike many sources of animal protein, soy is low in fat and saturated fat and naturally lactose and cholesterol-free. Soy protein also directly lowers blood cholesterol levels. The cholesterol-lowering effect of soy protein was first demonstrated more than 50 years ago.[41] In 1999, the US Food and Drug Administration ("FDA") formally recognized the ability of soy protein to lower cholesterol when it approved a health claim for soyfoods and coronary heart disease.[42] According to the FDA, 25 grams of soy protein are needed daily to lower cholesterol. While not all studies show a reduction, a recently published statistical analysis that included nearly 50 clinical studies, found soy protein significantly reduced LDL-cholesterol (often called "bad cholesterol" because it is the type of cholesterol that raises the risk of heart disease) by about 3-4%.[43]

Although the effect of soy protein to lower LDL-cholesterol (by 3-4%) may seem modest, it is still clinically relevant. Each 1% reduction in LDL-cholesterol lowers the risk of heart disease by 2-3%.[44,45] Furthermore, when soyfoods replace traditional sources of protein, which tend to be high in saturated fat, there is a double benefit: the direct effect of soy protein plus the reduction in cholesterol that occurs when soy replaces saturated fat in the diet. Estimates are that as a result of this dual benefit, LDL-cholesterol can be lowered as much as 8% when soyfoods replace protein sources high in saturated fat.[46]

In addition to lowering cholesterol, soyfoods may work in other ways to reduce risk of heart attack and stroke:

- Several statistical analyses of clinical studies published over the past decade have concluded that soyfoods, soy protein or the isoflavones in soybeans lower blood pressure.[47-50]
- Soy protein has been shown to lower blood triglyceride levels,[51] a type of fat in the blood that raises risk of heart disease.[52]
- Several studies have found soy protein or the isoflavones in soy help to regulate glucose and insulin levels, which can help to reduce risk of CVD.[53-55]
- Isoflavones have been shown to improve the health of cells that line the arteries.[56]
- Given the different ways that soy can potentially help to reduce cardiovascular risk, individuals concerned about heart health should consider making soy a part of their diet.

The OPTAVIA Connection:

- Depending on the **OPTA**VIA Fuelings you select as a part of your meal plan, it is possible to get 25 grams or more of soy protein per day. This amount has been previously shown to help lower LDL or "bad" cholesterol in clinical studies.

In summary

- Soyfoods are high in protein, versatile, and often contain less fat and saturated fat than protein from animal sources, in addition to being lactose and cholesterol free.
- Soy protein has been shown to lower LDL, or "bad," cholesterol by about 3-4%.
- Studies have also shown that soyfoods, soy protein or the isoflavones in soybeans may also help protect against heart attack and stroke in other ways, such as by helping to lower blood pressure and triglycerides, regulate glucose and insulin, and improve arterial cell health.

Bone Health

Approximately 10 million Americans have osteoporosis. Although osteoporosis and concerns over bone health have historically been thought of as a "woman's disease", approximately 1 in 3 men are at risk of developing osteoporosis.[57] and another 44 million have low bone density, placing them at increased risk of having a fracture.[58]

The likelihood of having a fracture increases with age, ranging from approximately 2.6% for those in their 40's to more than 11% for those 80 and older.[59] Women are much more likely to have a fracture than men. Among others, general recommendations to promote bone health include:

- Getting enough calcium and vitamin D
- Engaging in regular exercise
- Avoiding smoking

In addition to taking the steps listed above, there is evidence that eating soyfoods may also promote bone health.

Soy & Bone Health

Beginning in about the third decade of life, bone loss exceeds bone formation. In women, bone loss speeds up as they enter menopause because of the decrease in the production of estrogen.[60]

The impact of soy on bone health has been studied for decades. However, most of the more recent research has focused on the effect of isoflavones, either in the form of supplements or soy protein, on bone mineral density and bone breakdown and formation.

Recently published reviews and statistical analysis of the scientific literature have concluded that isoflavones do indeed promote bone health.[61-63] Very recently, a two-year clinical trial found soy (tofu) increased the bone mineral density of postmenopausal women[64-45] while another trial found that isoflavone-rich soy protein increased levels of a hormone associated with bone strength.[65]

Despite the encouraging evidence, it is a bit premature to conclude that isoflavones reduce the risk of developing fractures. Regardless, soy protein is a high-quality protein that might promote bone health and the calcium from soyfoods is very well absorbed.[44-45,44-45]

The OPTAVIA Connection:

- All **OPTA**VIA Fuelings contain high-quality, complete protein sources and are fortified with calcium and vitamin D.

In summary

- Bone health is a concern for both men and women.
- Some studies suggest that isoflavones may play a beneficial role in bone health.
- All **OPTA**VIA Fuelings contain high-quality, complete protein sources and are fortified with calcium and vitamin D.

Cancer

Cancer is the second leading cause of mortality in the United States, accounting for 1 in 4 deaths.

Diet is thought to affect the chances of developing many different types of cancers although estimates of the degree to which this is true vary considerably and differ according to the type of cancer.[68,69] For example, a recent analysis found that among Americans, almost 40% of the colorectal (colon and rectal) cancer deaths were due to poor diet compared to only about 1% of pancreatic cancer.[69] Importantly, obesity has been recognized as a significant risk factor for 13 cancers[70] and may account for 16% of all cancer deaths.[69]

Being overweight or obese increases the risk of certain cancers such as cancer of the breast, colon/rectum, endometrium, esophagus, liver, and prostate, among others.[68,70]

Unfortunately, markers predictive of cancer risk are not as readily available as they are for other chronic diseases, making it more difficult to study. Consequently, much of our understanding about the diet-cancer connection comes from epidemiologic or observational studies, rather than clinical (intervention) studies.

In summary

- Diet is thought to affect the chances of developing many different types of cancers.
- Being overweight or obese can increase the risk of certain cancers.
- Being overweight or obese is associated with an increased risk of cancer recurrence and a lower survival rate.[68,70]

Breast Cancer

Approximately 1 in 8 American women (13%) will be diagnosed with invasive breast cancer in their lifetime and 1 in 39 women (3%) will die from this disease.[71]

The role of soyfoods in reducing the risk of developing breast cancer has been rigorously investigated for 30 years thanks in part to the National Cancer Institute ("NCI") who became interested in this area of research[72] because of the historically low incidence rates of breast cancer in soyfood-consuming countries, such as Japan[73] and the recognition that when Japanese migrate to higher-risk countries such as the United States, their risk of breast cancer increases; the quicker the adoption of a Western-style diet, the faster the increase.[72-74]

The results of observational studies show that women in Asian countries, such as Japan and China, who regularly consume soy are about one-third less likely to develop breast cancer than are women in those countries who tend not to eat soyfoods.[75] Since soy is a traditional part of the diet in Asia, regular soy-consumers aren't very different from their non-soy-eating counterparts. Consequently, the protective effects of soy observed in these studies are likely to be due to soy per se, rather than because of some other lifestyle characteristic common to soy consumers.

In contrast to the studies involving Asian women, studies involving non-Asian women have failed to show that soy is protective against breast cancer.[75] This finding isn't too surprising as soy intake among the general population of non-Asian countries is too low to produce biological effects.[76]

There may be an intriguing twist to the soy-breast cancer relationship. In 1995, it was proposed that soy consumption very early in life is protective against breast cancer.[77,78] That is, the consumption of soy during childhood and/or adolescence, but not necessarily consumption during adulthood, reduces risk of breast cancer later in life. This line of reasoning is consistent with evidence showing that early life events can impact the development of many cancers.[79-81] Since 1995, this "early intake" hypothesis has gained considerable support. The isoflavones in soybeans appear to affect cells in the developing breast in a way that makes them permanently less likely to be transformed into cancer cells.[82,83] The observational studies, which consistently show childhood and/or teenage soy intake is protective against breast cancer, indicate as little as one serving per day (~3-4 oz of tofu or 25 mg of soy isoflavones) reduces risk.[84-87]

Breast Cancer Patients & Survivors

Somewhat ironically, despite the low breast cancer rates in soy-consuming countries, in the late 1990s, concern arose that soy could worsen the prognosis of breast cancer patients. This concern was based almost exclusively on studies in mice.[88] In one type of mouse model, isoflavones act like estrogen, rather than as anti-estrogens, and as such, stimulate the growth of existing mammary (breast) tumors.[88] However, if this mouse model is tweaked ever so slightly, in a way that more closely matches the human condition, the effect of isoflavones is lost.[88]

More importantly, results from human research contradicts those from animal studies. Although it wasn't until about a decade later that they began to be published, human observational studies are completely supportive of the safety of soy consumption.[90,91] In fact, these studies (3 conducted in China and 2 in the U.S.), which total over 11,000 breast cancer patients, show consuming soy after a diagnosis of breast cancer was associated with reduced mortality and reduced risk of breast cancer recurrence.[90,92-94]

Based on results of clinical and observational studies showing soy does not adversely affect breast tissue and isoflavones have no effect on the proliferation of cells,[90,92-94] leading health agencies and organizations have concluded that soyfoods can be safely consumed by women with breast cancer and breast cancer survivors. These include the American Cancer Society,[95] the American Institute for Cancer Research,[96] the World Cancer Research Fund International[97] and the Canadian Cancer Society.[98] The positions of the European Food Safety Authority[99] and the Permanent Senate Commission on Food Safety of the German Research Foundation[100] are also supportive of the safety of soyfoods in women with breast cancer and breast cancer survivors.

Although these leading health agencies support the safety of soyfoods in women with breast cancer and breast cancer survivors, for those with concerns, **OPTA**VIA recommends for you to speak with your healthcare provider.

In summary

- Historically low rates of certain cancer types in countries where soyfoods are commonly consumed led investigators to study soy's potential cancer benefits.
- Soy appears to be especially protective against breast cancer when eaten in early life (as a child and/or teenager).
- Research has shown eating soy after a diagnosis of breast cancer was associated with reduced mortality and reduced risk of breast cancer recurrence.
- Leading health organizations around the world have concluded that soyfoods can be safely consumed by women with breast cancer and breast cancer survivors. However, for those with concerns, **OPTA**VIA recommends for you to speak with your own healthcare provider.

Prostate Cancer

Prostate cancer is the most common cancer among American men and the second most common cause of cancer death.[67]

Like breast cancer, interest in the role of soy in preventing and treating prostate cancer dates back to the early 1990s. And like breast cancer, prostate cancer incidence and mortality rates in soyfood-consuming countries are very low relative to Western countries.[101]

There is evidence that soy intake is associated with a reduced risk of developing prostate cancer. Researchers at the University of Illinois published a recent analysis of 16 observational studies[102] showing higher soy intake was associated with a 30% reduction in risk of developing prostate cancer. The results were highly statistically significant, which indicates the findings were quite robust.

Clinical studies examining the impact of soy and isoflavones on Prostate-Specific Antigen ("PSA") levels (a marker of prostate cancer risk and progression) in prostate cancer patients and men at high risk of developing this disease have produced mixed results.[103] Some have found that, in comparison to the placebo group, soy slows the rise in PSA levels over time, whereas others haven't shown any benefits. Soy and isoflavones, however, were not shown to increase PSA levels.[103, 104]

In summary

- Observational studies have shown a 30% reduced risk of developing prostate cancer in men with the highest soy intake.
- Clinical trials have shown mixed results on the impact of soy and isoflavones on PSA levels (a marker of prostate cancer risk and progression), with some finding benefit and others no benefit. Soy and isoflavones, however, were not shown to increase PSA levels.

Endometrial Cancer

The endometrium is the innermost lining layer of the uterus. Endometrial cancer is the most common gynecological malignancy in the industrialized world. The incidence and mortality rates vary markedly among geographical regions and countries, but are highest in the United States and Europe and the lowest in Asia and Africa.[73,101] Evidence from studies of migrants moving from low-risk countries to high-risk countries, indicates the international variation in endometrial cancer rates is due to environmental (lifestyle), not genetic factors.[105]

A statistical analysis of 10 observational studies found higher soy intake was associated with a lower risk of developing endometrial cancer.[106] Clinical studies are also supportive of the safety of soy and isoflavones. A statistical analysis of 23 clinical studies involving 2,167 women found no effect of isoflavones on endometrial thickness. Endometrial thickness is used as a screen for endometrial cancer, greater thickness is reflective of an increased risk.

Furthermore, when that analysis of 23 studies focused only on the 7 studies from North America (which involved 726 women) soy was associated with a decrease in endometrial thickness.[107] Thus, both the observational and clinical data suggest soy may reduce the risk of developing endometrial cancer. After reviewing the evidence, the European Food Safety Authority also concluded that neither soy protein nor soy isoflavones adversely affect the uterus.[99]

In summary

- Both observational and clinical studies suggest that a diet rich in soy may reduce the risk of developing endometrial cancer.

Other Cancers

Although to a more limited extent, soyfoods have been studied in relation to many other types of cancer. The available evidence is limited, but encouraging: statistical analyses of observational studies have found that higher soy intake is associated with a lower risk of ovarian,[108] stomach,[109] colorectal,[110] and lung cancer.[111] While this evidence appears promising, additional research is needed before more definitive conclusions can be made.

Menopausal Symptoms: Soy for Hot Flashes

Hot flashes are the most common reason given by women seeking treatment for menopausal symptoms. For 10-15% of the women who experience hot flashes, they are severe and frequent.[113] While the etiology of hot flashes is not fully understood, the natural decline in circulating estrogen levels that occurs during the years around menopause is thought to be a factor.

The low incidence of hot flashes among native Japanese women, combined with the recognition that isoflavones are classified as phytoestrogens, gave rise to the hypothesis that soyfoods prevent the onset of and/or are useful in the treatment of hot flashes.[114]

More than 20 trials have examined the effect of soy or isoflavone supplements on hot flash alleviation. In these trials, supplements of isoflavones are typically used rather than soyfoods because of the need to "blind" study participants so they are unaware of whether they are in the placebo or the active (isoflavone) group. It is much easier to blind participants if pills, rather than foods, are used. In these trials it is important to blind participants because hot flashes are subjectively determined (each person records the frequency and severity of the hot flashes they experience) and the placebo effect tends to be high. Typically, there is a 25% reduction in hot flash frequency even among women taking a placebo.

It should be noted that some reviews of the scientific literature have had inconsistent findings, ranging from no to appreciable benefits on hot flash alleviation. This confusion comes because these reviews have failed to recognize that two different types of isoflavone supplements have been used in the clinical trials, one of which works and one of which does not.

Supplements derived from the whole soybean, and which have the same isoflavone content or isoflavone profile as soybeans and soyfoods, consistently reduce hot flash frequency and severity. In contrast, supplements derived from soy germ or only a small (10%) portion of the whole soybean, have a different isoflavone profile and are ineffective. Traditional soyfoods and soy protein products have an isoflavone profile that matches the supplements that reduce hot flashes.

A systematic review and meta-analysis of isoflavone supplements from soy found that isoflavones significantly and consistently reduced the frequency (number per day) and severity of hot flashes by about 50%.[115] More recently published studies also confirm the efficacy of isoflavones for hot flashes.[116,117] The amount of isoflavones providing symptom relief is found in approximately 2 servings of traditional soyfoods - approximately 50 milligrams.[118]

The OPTAVIA Connection:

Traditional soyfoods and soy protein products, such as **OPTA**VIA Fuelings, have an isoflavone profile that matches the supplements that reduce hot flashes.

In summary

- In studies where isoflavone supplements closely matched the natural isoflavone profile found in soybeans, the frequency and severity of hot flashes were consistently reduced.

Building Muscle

There has been much discussion about whether some proteins promote greater gains in muscle mass and strength in response to resistance exercise compared to other protein types. Milk protein is comprised of 20% whey and 80% casein. Both whey and casein are high in leucine, an amino acid that stimulates muscle protein synthesis. Within the weightlifting community, these milk proteins, particularly whey protein, are often regarded as the optimal proteins for building muscle.

However, according to a recent review of the scientific literature conducted by a team of internationally-recognized experts, it is the amount of protein that matters, not so much the type, although high-quality protein is recommended.[119] Although the amount of protein each person needs varies depending on an individual's age, activity, and weight, this conclusion is supported by the results of a statistical analysis of 9 studies, ranging in duration from 6 to 16 weeks, that compared the effects of soy protein on muscle mass and strength with other proteins.[120] Five studies compared soy protein to whey protein and 4 compared soy protein to milk proteins or beef. The results showed soy protein supplementation produced similar gains in lean body (muscle) mass and strength in response to resistance exercise training as animal protein, including whey protein.

In summary

- Soy protein supplementation produced similar gains in muscle mass and strength in response to resistance exercise as animal protein, including whey protein.

Skin Health

There are two types of skin aging: intrinsic (occurs normally with the passage of time) and extrinsic (skin damage from solar exposure, etc.). Skin aging is influenced by genetic, environmental and hormonal factors.

Interestingly, several clinical trials in which participants consumed either isoflavone-containing soy protein or isoflavone supplements, have shown a reduction in wrinkles in the soy versus placebo group.[121-124] In fact, one study found a 10% reduction in wrinkles over a 14-week period! Although exciting, the data on soy and skin health is still quite limited and no conclusions can be made at this time.[123] A large, well-designed study examining the ability of isoflavones to reduce wrinkles is currently underway.

In summary

- Limited evidence suggests soy isoflavones may have a beneficial effect on skin health, including reducing wrinkles.

Cognitive Function

As the U.S. population ages, more Americans are concerned with making sure their later years are healthy ones. Health involves numerous components, including one that has received more attention in recent years, cognitive function.

Recently published analyses of clinical studies have concluded that soy may improve cognitive function. In the most recent analysis, which included 16 clinical trials and over 1,300 participants with an average age of 60, soy isoflavones were found to improve overall cognitive function and memory.[125] Despite these encouraging findings, more research is needed before claims about the benefits of soy on cognition can be drawn.

In summary

- Limited evidence suggests soy may be beneficial on cognitive function, but more research is needed in this arena.

Kidney Stones

Kidney stones are a common disorder of the urinary tract.[126] Kidney stones typically occur when stone-forming salts crystallize in the urine. In most industrialized countries, approximately 80% of the kidney stones are composed of calcium salts, usually occurring as calcium oxalate stones.[126] These stones are made up of calcium and oxalate, compounds naturally found in foods and in our own bodies.[91,92]

Oxalate is found primarily, but not exclusively in plants. It can bind calcium and reduce its absorption. In general, limiting oxalate intake appears to be beneficial for reducing stone formation, especially in hyper-absorbers of oxalate. Certain foods, such as spinach and some soy foods, are high in oxalates.[93] However, the soy protein used by **OPTA**VIA contains only a very small amount of oxalate. In fact, a typical **OPTA**VIA Fueling with 10 grams of soy protein has approximately 5 times less oxalate than a single almond.[93]

The OPTAVIA Connection:
The high quality soy protein in **OPTA**VIA's products contain only a small amount of oxalate. In fact, a typical **OPTA**VIA Fueling with 10 grams of soy protein has approximately 5 times less oxalate than a single almond.

In summary

- Kidney stones typically occur when stone-forming salts crystallize in the urine.
- Kidney stones are made up of calcium and oxalate, compounds naturally found in foods and in our own bodies.
- The high quality soy protein in **OPTA**VIA's products contain only a small amount of oxalate – a typical **OPTA**VIA Fueling with 10 grams of soy protein has approximately 5 times less oxalate than a single almond.

Fertility

It is ironic that concerns about both male and female fertility in relation to soy intake have arisen given the large populations of soyfood-consuming countries, such as China and Japan, who have been consuming soy for centuries. As discussed below, these concerns are without scientific foundation.

Male Fertility/Femininization

Sensationalized news stories based on a few rodent studies and 2 reported cases of individual men who developed dramatic changes in reproductive hormone levels after consuming excessive amounts of soy (~360 mg/day of isoflavones; almost 10 times the amount of soy typically consumed by Japanese men)[12] have led some to believe soy foods have a negative impact on male fertility or reproductive function.[128,129] However, these isolated cases simply illustrate that consuming excessive amounts of any food can lead to health problems. When anything approaching normal amounts of soy are consumed, these types of problems are not observed.[12]

A 2010 statistical analysis of more than 30 clinical studies showed that neither soyfoods nor isoflavones affect blood testosterone levels in men.[130] Furthermore, a comprehensive review of the scientific literature found soy did not exert feminizing effects of any kind, including on estrogen levels.[131]

Since 2010, quite a few clinical studies have evaluated the effects of soy on hormone levels in men. A comprehensive review published in 2020 further reinforces the findings that soy does not lower testosterone or raise estrogen levels in men.[132,133]

Three clinical studies have also examined the effect of soy on sperm concentration and found no adverse effects.[134-136] In one of these studies, men consumed an amount of isoflavones many times greater than Japanese intake without any noted effects on sperm.[136]

Indirect evidence about soy and sperm also comes from a recently published Danish study. Men adhering to a vegetarian-like dietary pattern, which included soyfoods, had a significantly greater sperm count than men adhering to a Western-style dietary pattern.[137] In addition, a study involving 184 men from couples undergoing infertility treatment with in vitro fertilization, found that male partner's intake of soyfoods and soy isoflavones was unrelated to fertilization rates.[138]

Female Fertility

Soy does not affect estrogen levels in women, the main female reproductive hormone.[139] Research published in the mid-1990s found soy consumption extended the length of the menstrual cycle; however, short, but not long, menstrual cycles have been linked to a longer time until pregnancy occurs.[140-144] Furthermore, an analysis published in 2009 found soy only increased the length of the menstrual cycle by about 1 day.[139] The evidence indicates soy does not adversely affect fertility.

Instead, there is some evidence that soy may enhance fertility. A Japanese study of 36 women with amenorrhea or anovulation for >6 months found there was a significant improvement in anovulation following the ingestion of soybeans.[145] Soy may also be useful in the case of assisted reproductive technology ("ART"). In one study, 315 women collectively underwent 520 ART cycles from 2007 to 2013.[146] The women who consumed the most isoflavones were nearly 90% more likely to give birth than women who did not consume isoflavones.

In summary

- There is no meaningful clinical evidence that soy protein or soy isoflavones lowers testosterone levels or exerts feminizing effects of any kind in men.
- Some evidence suggests that soy may slightly lengthen the menstrual cycle (by approximately 1 day).
- Soy does not affect estrogen levels or adversely affect fertility in women.

Soy Allergy

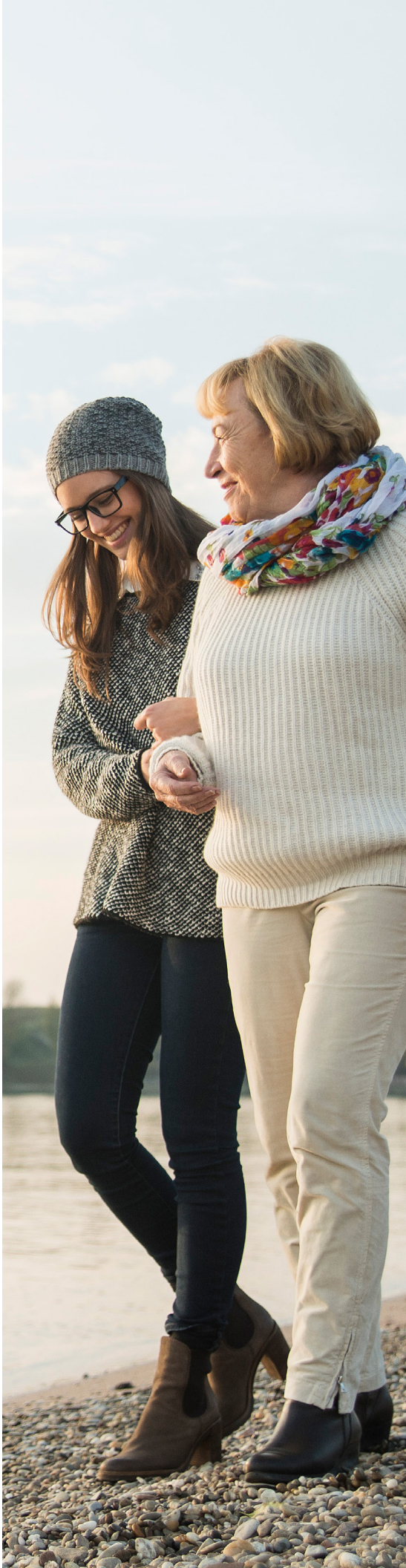
More than 200 foods have been shown to be allergenic.[147] In the U.S., approximately 90% of all food allergies are thought to be made up by the "Big 8" major allergens: eggs, peanuts, tree nuts, soy, fish, shellfish, wheat, and milk. The number of people affected and the level of response for each of these individual allergens varies quite dramatically. Surveys consistently show the prevalence of soy allergy is very low. In fact, soy allergy is lower than the prevalence of each of the other 7 major allergens.[148]

Results from surveys are self-reported and can vary, but on average, they indicate that approximately 3 out of every 1,000 adults are allergic to soy protein, a rate between about 3 and 41 times lower than milk/dairy allergy.[148,149-152]

Soy, Soy Lecithin, and **OPTA**VIA

While a majority of **OPTA**VIA Fuelings contain soy protein, some utilize other sources of high-quality protein, such as milk or egg. Further, select ingredients in certain Fuelings may still contain soy lecithin to help improve the products functionality and performance.

Soy lecithin is a common ingredient in many foods on the market, used primarily to prevent ingredients from separating, provide stability and texture consistency, and help with the flavoring of foods. Soy lecithin is generally derived from refined soybean oil by a process that removes most, if not all, of the soy protein that a person with a soy allergy would want to avoid. Despite the very low allergen concern, government regulations do require food labels to clearly state when any ingredient is derived from soy. While limited in breadth, studies



suggest that consuming products that contain soy lecithin is not usually an issue for those with a soy allergy.[148,149,152] However, **OPTA**VIA recommends that anyone concerned about an allergy to soy contact their healthcare provider to determine the best course of action based upon their medical history.

The OPTAVIA Connection:

- Many of the **OPTA**VIA Fuelings contain soy protein in addition to other sources of high quality, complete protein. Visit the Product Claims Sheet at www.ANSWERS.**OPTA**VIA.com for more information about **OPTA**VIA Fuelings that contain soy protein.
- Although research suggests soy lecithin may be safe for those with a soy allergy, **OPTA**VIA recommends those concerned about an allergy to soy contact their healthcare provider to determine the best course of action.

In summary

- The prevalence of soy allergy is very low. The lowest, in fact, of the "Big 8" major allergens in the U.S.
- Many of **OPTA**VIA's Fuelings contain soy protein in addition to other sources of high quality, complete protein.
- Although research suggests soy lecithin may be safe for those with a soy allergy, **OPTA**VIA recommends those concerned about an allergy to soy contact their healthcare provider to determine the best course of action.

Thyroid Function

The effect of soyfoods on thyroid function has long been an area of research. Concerns around soy and thyroid function arose based on in vitro ("test tube") and rodent studies, some published over 8 decades ago.[153,154,155] Fortunately, the extensive amount of human research conducted over past 10 to 15 years has cleared away the confusion that once surrounded this research area.[155-157]

The thyroid controls our body's metabolic rate, primarily by producing two hormones, thyroxine ("T4") and triiodothyronine ("T3").[158] A comprehensive narrative review[156] and a statistical analysis of the scientific literature,[157] as well as several authoritative health organizations, have concluded that in people with a normal functioning thyroid, neither soy protein nor isoflavones adversely affect levels of T4 and T3. Health organizations who have weighed in on this issue include the European Food Safety Authority[99], the Permanent Senate Commission on Food Safety of the German Research Foundation[100] and the U.S. Food and Drug Administration.[159] Thus, there is a strong scientific consensus.

Research has also dispelled concerns related to the effect of soy on thyroid function in people with low iodine intake. While it was once believed soy could impair thyroid function in this population[160] research published in 2012 indicates that even with inadequate iodine intake, soy is not problematic.[161] Iodine is an essential mineral needed for thyroid hormone synthesis. Due to the widespread use of iodized salt, iodine status in the United States is typically quite good, though this may not be true for other areas of the world.[81]

The concern that soy could worsen thyroid function in those whose thyroid function is compromised, such as patients with subclinical hypothyroidism has also been countered. Recently published research showed soy does not exacerbate thyroid function in persons with subclinical hypothyroidism.[160,162] However, it should be noted that although persons with subclinical hypothyroidism do not require thyroid medication, they are at an increased risk of developing low thyroid function (hypothyroidism), which would require the use of medication.[163]

Finally, for those taking thyroid medication, such as levothyroxine, for the treatment of hypothyroidism, it is important to recognize that food in general, which includes soy protein, may inhibit the absorption of thyroid medication, as do many herbs, supplements, and even items like coffee, fiber, calcium, and iron.[164-167] **OPTA**VIA Fuelings are fortified with vitamins and minerals, and many contain soy protein.

The OPTAVIA Connection:

- **OPTA**VIA Fuelings are fortified with vitamins and minerals, with many, but not all, containing soy protein.
- For this reason, **OPTA**VIA recommends the following for individuals taking thyroid medication:

  NOTE: *This information does not in any way constitute medical advice, an attempt to diagnose a medical condition, or substitute for medical treatment.* **OPTA**VIA recommends that you contact your healthcare provider before starting and throughout your weight loss journey.

  - Be sure to talk with your healthcare provider about the program and any medications or dietary supplements you are using, especially medications (e.g., Synthroid or levothyroxine) for thyroid conditions.
  - Certain foods and supplements, such as soy, coffee, fiber, calcium, and iron, may cause your body to absorb less of your thyroid medication. **OPTA**VIA Fuelings contain fiber, are fortified with vitamins and minerals, and many contain soy protein. [165-167]
  - We suggest waiting at least 60 minutes after taking your medication before eating an **OPTA**VIA Fueling.
  - It is important for you to talk with your healthcare provider about the **OPTA**VIA Fuelings and the changes you are making to your diet to ensure you are receiving the correct dose of medication. Your healthcare provider may provide special instructions and want to monitor your thyroid hormone levels and adjust your medication during your weight loss journey.
  - Many people with a thyroid condition are concerned about slower weight loss. Responses to medications and conditions vary from person to person, but having a thyroid condition does not mean you cannot successfully achieve or maintain a healthy weight. While having a thyroid condition may be something that is outside of your control, making healthy lifestyle changes is not. You can still develop healthy habits, such as eating portion-controlled meals, being physically active, drinking water, and getting adequate sleep.
  - Consult with your healthcare provider about the program, your goals, and your thyroid condition to see if **OPTA**VIA is right for you. If you have specific concerns about the side effects of your medication, talk to your healthcare provider for guidance.

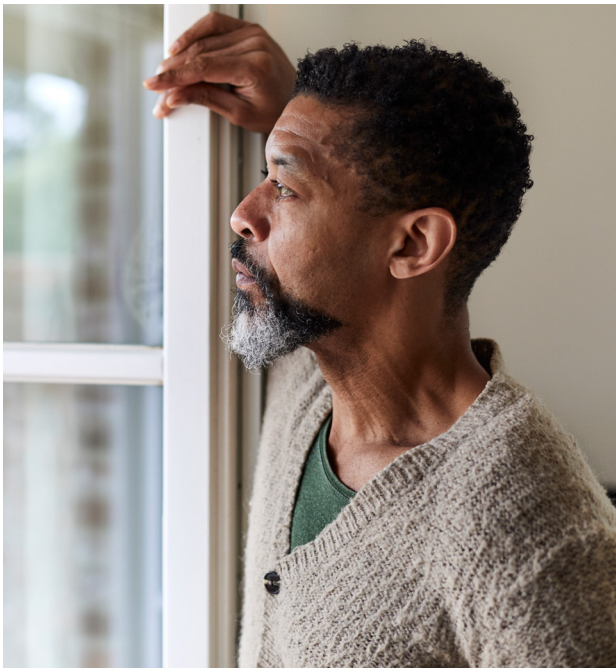
In summary

- In individuals with a healthy, normal functioning thyroid there is a strong scientific consensus that soy and isoflavones do not affect thyroid function.
- Recent research has dispelled concerns related to soy and thyroid function for those with suboptimal iodine intake and subclinical hypothyroidism.
- Certain foods and supplements, such as soy, coffee, fiber, calcium and iron, may cause your body to absorb less of your thyroid medication. **OPTA**VIA Fuelings contain fiber, are fortified with vitamins and minerals, and many contain soy protein. We suggest waiting at least 60 minutes after taking your medication before eating an **OPTA**VIA Fueling.
- It is important for you to talk with your healthcare provider about the **OPTA**VIA Fuelings and the changes you are making to your diet to ensure you are receiving the correct dose of medication. Your healthcare provider may provide special instructions, want to monitor your thyroid hormone levels, and adjust your medication during your weight loss journey.

Fibroids

Uterine fibroids ("UF"), also called leiomyomata, are benign, hormonally-dependent tumors that grow in the walls of the uterus. Fibroids are detected in 70-80% of women by age 50.[168] UF can cause symptoms such as heavy and irregular menstrual periods, frequent urination, and other problems depending on the size and location of the fibroid.[169] UF are listed as the leading risk factor for hysterectomy.[170]

A statistical analysis of 7 population-based studies found no relationship between soy intake and the risk of developing uterine fibroids.[171] The results of a Japanese study also suggest that soy intake may decrease the risk of having a hysterectomy.[172]



In summary

- Results of population-based studies did not find a relationship between soy intake and risk of developing uterine fibroids.

Bioengineered/Genetically Modified Organisms and Glyphosate

Bioengineered ("BE") and Genetically Modified Organisms ("GMO")

The safety of genetically modified ("GM") foods and glyphosate, one of the primary herbicides used on GM foods often generates a lot of heated discussion. Given that >90% of the soybeans grown in the United States are bioengineered ("BE") these discussions, not surprisingly, usually include soybeans.[173] However, the preponderance of evidence supports both the safety of GM soybeans and glyphosate.

Genetic modification is an umbrella term that broadly describes the process of altering the genetic makeup of an organism. Genetic modification is not new; selective or cross-breeding of plants has been done for thousands of years. In contrast to these traditional methods, modern biotechnology allows for genetic engineering of plants that is faster, easier, and able to more precisely target a specific gene in order to get a desired trait. The preferred terms for foods that undergo this more specific gene alteration are genetically engineered ("GE") or bioengineered ("BE"), rather than GM.

Specific to the U.S., the National Bioengineered Food Disclosure Law was passed into law to establish a national mandatory standard for disclosing foods that are or may be bioengineered. The standard defines bioengineered foods as "those that contain detectable genetic material that has been modified through certain laboratory techniques and cannot be created through conventional breeding or found in nature." In the U.S., all BE foods or foods containing BE food ingredients manufactured on or after January 1st 2022 must comply with this rule.[174]

A BE food disclosure is a marketing label, and does not convey any information about the health, safety, or environmental attributes of BE food as compared to non-BE counterparts.

However, BE food has been extensively examined by the scientific community. More than 3000 scientific studies have assessed the safety of BE foods and nearly 300 technical and scientific institutions recognize the safety of BE crops and their potential benefits, as do regulatory agencies from around the world.[175-180] A notable example of a rigorous examination of BE crops was done by the U.S. National Academy of Sciences, who comprehensively reviewed detailed data comparing currently commercialized BE and non-BE foods in compositional analysis, acute and chronic animal toxicity tests, long-term data on health of livestock fed BE foods, and epidemiological data and concluded there were no differences found that implicate a higher risk to human health safety from BE foods than from their non-BE counterparts.[181] Overall, there is a clear scientific consensus: GE crops are of no greater risk than those that have been developed by conventional breeding techniques. With respect to nutrient composition, it is well established there are no differences between BE soybeans and non-BE soybeans.[182-185]

In summary

- Bioengineered ("BE") foods have been rigorously and thoroughly examined.
- There is a clear scientific consensus that BE foods are as safe as non-BE foods.
- There is no difference in the nutritional composition of BE versus non-BE foods.

Glyphosate

As the scientific community has continued to generate data in support of the safety of BE soybeans, concern has shifted more toward the use of glyphosate. Glyphosate is a broad-spectrum systemic herbicide used to kill weeds that compete with crops by inhibiting the activity of an enzyme involved in the synthesis of certain (aromatic) amino acids.[186] Some crops (such as many of the soybeans grown in the U.S.) have been bioengineered to be resistant to the effects of glyphosate because they express an alternative form of the enzyme needed to make the aromatic amino acids. Thus, they can function normally even in the presence of glyphosate, allowing farmers to better control weeds without harming their crop.

Glyphosate has been the most widely used herbicide in the U.S. since 2001. It is also one of the most studied herbicides and has undergone rigorous review by the U.S. Environmental Protection Agency ("EPA"), the European Food Safety Administration, and the United Nations as well as many other regulatory agencies worldwide which found glyphosate poses no risk to human health when consumed via foods sprayed with it or when used as directed.[187]

Although, most scientific authorities have concluded that glyphosate is not toxic or carcinogenic to humans when consumed via foods sprayed with this herbicide, the World Health Organization's cancer authorities - the International Agency for Research on Cancer ("IARC") is the exception. The IARC conducted a hazard assessment on glyphosate and classified it as "probably carcinogenic to humans", a direct contrast to the broader, global consensus that dietary exposure to glyphosate is safe.[187,188]

The IARC's classification of glyphosate has been met with considerable controversy. Whereas other regulatory agencies used a risk-based, weight of the evidence assessment, which considers the full range of hazards and risks (including studies of cancer risks), the IARC used a hazard assessment. This type of an approach is different because it considers only the potential to cause harm, it does not determine whether or not the harm will occur or the likelihood of the harm occurring in real-world situations.[189] The EPA has criticized the methodology and sources of research used by the IARC to reach its conclusion about glyphosate.[190] The EPA alone has reaffirmed the safety of glyphosate on multiple occasions, including as recently as 2020.[187,189,191-194] Many other world regulatory bodies have independently evaluated glyphosate (both before and after the IARC) and have also concluded dietary exposure to glyphosate is safe.[187] As an example, the German Risk Agency concluded: "The lack of a plausible mechanism, along with published epidemiology studies which fail to demonstrate clear, statistically significant, unbiased and non-confounded associations between glyphosate and cancer of any single etiology, and a compelling weight of evidence, support the conclusion that glyphosate does not present concern with respect to carcinogenic potential in humans."[141,144] Finally, concerns have been raised related to human exposure to glyphosate, especially in agricultural workers, and an increased risk of non-Hodgkin lymphoma ("NHL").[193,195] Consistent with regulators in other countries, after a robust review of the relevant data, the U.S. EPA concluded the link between glyphosate and NHL was without foundation.[196] Thus the EPA, among other world regulatory bodies, remains steadfast in their conclusion that "the strongest support based on the weight-of-evidence is for glyphosate being characterized as 'not likely to be carcinogenic to humans' and is safe when used as directed."[194]

In summary

- The U.S. Environmental Protection Agency, among many other world regulatory authorities, has concluded that consumption of food sprayed with glyphosate is safe to eat and poses no harm to human health.
- The scientific consensus remains that glyphosate is safe when used as directed.

Monoamine Oxidate Inhibitors and Tyramine

Monoamine oxidase inhibitors ("MAOIs") were first introduced in the 1950s to treat depression.[197,198] They are a separate class from other types of antidepressants, treating different forms of depression as well as other nervous system disorders.[199] Although MAOIs were the first class of antidepressants available, they are now generally only a treatment option when other medications have been unsuccessful. This is because relatively soon after their introduction, MAOIs were associated with a potentially fatal interaction with tyramine-containing foods as well as other side effects and safety risks. The interaction between tyramine and MAOIs is relevant to soyfoods because some, but not all soyfoods contain tyramine and need to be avoided by patients on MAOIs.

MAOIs inhibit the activity of monoamine oxidase, an enzyme responsible for degradation of brain neurotransmitters such as norepinephrine, serotonin, dopamine, and tyramine. Inhibiting degradation leads to higher brain levels of neurotransmitters, allowing them to continue to influence the cells that have been affected by depression.[200]

No data on the tyramine content of soy protein isolate or concentrate was identified. However, given that these soy protein ingredients are not fermented, and that soy protein has a long shelf-life, indicating it is relatively stable, it is reasonable to speculate that the tyramine content of these products is extremely low.

For individuals using MAOIs it is important to avoid tyramine-containing foods, such as fermented forms of soy (including "stinky" tofu, soy sauce, miso, and natto), among other contraindicated food items. Although it is believed that unfermented forms of soy likely contain at most only low levels of tyramine, **OPTA**VIA recommends for anyone concerned about tyramine to speak with their healthcare provider.

In summary

- MAOIs have a known food-drug interaction with tyramine-containing foods. These foods should be avoided by anyone using a MAOI.
- Fermented foods, such as fermented soyfoods ("stinky" tofu, soy sauce, miso, and natto, etc.) are high in tyramine.
- Evidence indicates that unfermented soyfoods contain at most low levels of tyramine.
- Data is not available for the tyramine content of soy protein isolate or concentrate, but these are also believed to be low in tyramine.
- Anyone concerned with tyramine should speak to their healthcare provider.

Additional Resources on Soy

- ANSWERS.**OPTA**VIA.com
- The Soy Nutrition Institute Global
- The Soy Connection
- The International Food Information Council

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