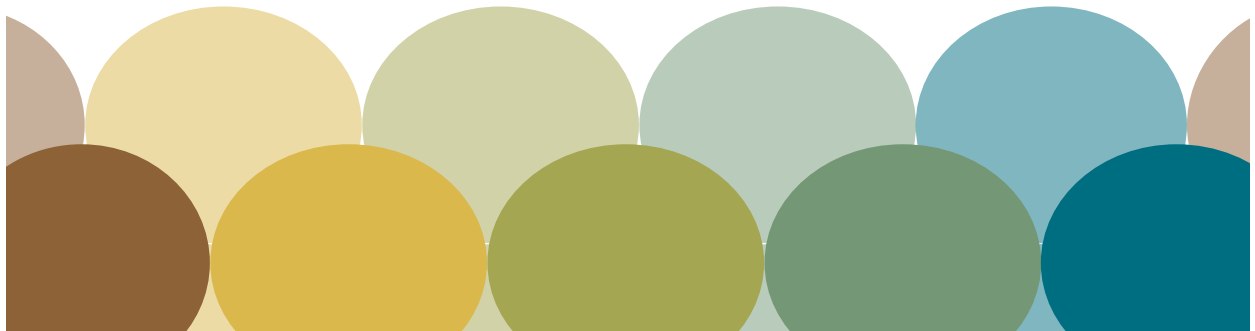


# *Soyfoods*

AND YOUR HEALTH





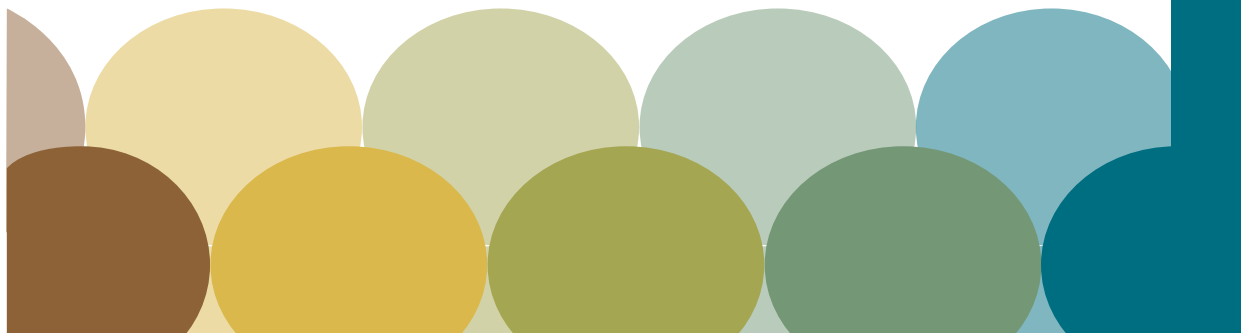
## Soyfoods Provide Isoflavones

As a rich source of isoflavones, soybeans are unique among commonly consumed foods (1). For more than 20 years these diphenolic compounds have been rigorously investigated for their potential health benefits (2). Because isoflavones have estrogen-like properties, they are referred to as phytoestrogens; however, they are different from the hormone estrogen (3, 4) and are more accurately classified as selective estrogen receptor modulators (SERMs) (5). Their SERM classification derives largely from the fact that they preferentially bind to and transactivate estrogen receptor (ER)- $\beta$  in comparison to ER $\alpha$ . In contrast, estrogen binds to and transactivates both receptors equally. The two ERs have different tissue distributions within the body and, when activated, often result in different and sometimes even opposite effects. For example, in the breast ER $\beta$  activation inhibits the proliferative effects of ER $\alpha$  activation (6, 7).

Examples of widely prescribed SERMs include the breast cancer drug tamoxifen (8) and the osteoporosis drug raloxifene (9). New SERMs are continually being developed by the pharmaceutical industry (10). Since there is no “class effect”, conclusions about the physiological effects of any individual SERM, such as isoflavones, can only be made on the basis of direct experimentation (5). The European Food Safety Authority recently suggested a somewhat different classification for compounds such as isoflavones—endocrine active substances (11).

Isoflavones also have non-hormonal properties that may contribute to their proposed physiological effects (12). In fact, it was the ability of the soybean isoflavone genistein to inhibit the activity of tyrosine protein kinase, an enzyme frequently overexpressed in cancer cells (13), which first led to widespread interest in the chemopreventive effects of isoflavones and the potential role of soyfoods in cancer prevention (2). Isoflavones occur in the soybean as glycosides (i.e., a sugar molecule is attached to the isoflavone backbone) (14), but upon ingestion, the sugar is hydrolyzed thereby allowing absorption to occur (15). In fermented soyfoods, such as miso, tempeh and natto, a large percentage of the isoflavones occur as aglycones due to bacterial hydrolysis. The three isoflavones in soybeans, genistein, daidzein, and glycitein and their respective glycosides, account for approximately 50, 40, and 10% of total isoflavone content, respectively (14).

Older adults in Japan and in Shanghai, China, typically consume about 30 to 50 mg isoflavones daily and approximately 10% of these populations consume at least 80 mg per day (16). Not surprisingly, per capita intake in Europe (17) and the United States (18) is quite low (<3 mg/d). Each gram of protein in traditional soyfoods is associated with approximately 3.5 mg isoflavones (expressed as aglycone equivalents). Therefore, one cup of soymilk made from the whole soybean, which typically contains about 7 grams of protein, will provide about 25 mg isoflavones. However, this mg to gram ratio does not hold for some modern soyfoods because, while they are typically good sources of protein, processing can cause a significant loss of isoflavone content. In China, isoflavone intake occurs mostly via nonfermented foods (19) whereas in Japan, roughly half comes from nonfermented soyfoods (20, 21).



## Soyfoods are Rich in Protein

Soybeans are a good source of fiber and a variety of vitamins and minerals such as B vitamins and potassium (22). But what soyfoods have long been prized for is their protein content. One serving typically contains between 7 and 15 grams. More importantly, unlike most plant proteins, the quality of soy protein is comparable to animal protein. It is highly digestible (23) and contains all indispensable amino acids in sufficient quantities (24) to meet biological requirements when consumed at the protein recommended dietary allowance (RDA) (25). Thus, soy protein is considered a complete protein. Isolated soy protein, which by definition is at least 90% protein, has a protein digestibility correct amino acid score of ~1.0 (26).

Mean US dietary protein intake exceeds the RDA but subsets of the population, such as teenage girls and older people, may not have sufficient intakes (27, 28). Furthermore, several research groups have recently suggested that the protein RDA is too low (29, 30) although there is disagreement on this point (31). In any event, soyfoods are especially good protein choices because they are low in saturated fat compared to more traditional sources of protein in Western diets (32) and evidence suggests soy protein does not stress the kidneys in the way that animal protein does (33).



## Soy and Heart Disease – Three Way Protection

The cholesterol-lowering effects of soy protein first received widespread attention in 1995 with the publication of a meta-analysis in the *New England Journal of Medicine* (34). Four years later, the US Food and Drug Administration (FDA) approved a health claim for soyfoods and coronary heart disease (CHD) based on the hypocholesterolemic effects of soy protein (35). Twenty-five grams per day was established by the FDA as the threshold intake for cholesterol reduction; however there is evidence that lower amounts may also be efficacious (36, 37). Since the claim was approved, the hypocholesterolemic effects of soy protein have come under challenge. In 2006, the American Heart Association (AHA), while acknowledging the important contribution soyfoods can make to heart-healthy diets because of their low saturated and high polyunsaturated fat content, concluded that the health claim was unwarranted since, according to their rough estimate, soy protein lowered LDL-cholesterol by about only 3 percent (38).

However, a recently conducted statistical analysis of the 22 studies upon which the AHA based their estimate, found they had considerably underestimated the extent to which soy protein lowers cholesterol (32). Further, when the analysis was limited to the 11 of 22 studies in which the soy and control diets were matched, soy protein was found to lower LDL-cholesterol 5.2 percent. Thus, the effects of soy protein are similar to that of soluble fiber, which also has an FDA-approved health claim for coronary heart disease (39). Soy protein also modestly lower blood triglyceride levels (~5%) and raises HDL-cholesterol (1-3%) (36, 40).

Soy oil is approximately 84% unsaturated fat with about two-thirds of that in the form of the essential omega-6 fatty acid, linoleic acid (41). About 7 to 8 percent of the total fatty acid content of soy oil is  $\alpha$ -linolenic acid, the essential omega-3 fatty acid (41). Evidence suggests  $\alpha$ -linolenic acid may exert independent coronary benefits (42, 43). A recent analysis estimated that when soyfoods are substituted for commonly consumed protein sources in the US diet, there will be reductions in LDL-cholesterol, depending on the amount of soy protein consumed, ranging from 3 to 6%, because of favorable changes in the fatty acid content of the diet.

When considering both the direct effect of the protein and the fatty acid displacement effects, soyfoods can be expected to lower LDL-cholesterol by approximately 8%, which over time may lower CHD risk as much as 15 percent (44, 45). Furthermore, the results of a newly published review show that CHD risk is reduced only when saturated fat is replaced by a mixture of omega-6 and omega-3 polyunsaturated fatty acids (46). Thus, soyfoods can be considered ideal substitutes for higher-saturated-fat foods.

Finally, there is evidence that soyfoods lower CHD risk independent of their ability to lower elevated LDL-cholesterol, which is just one CHD risk factor (47). Several Asian epidemiologic studies have found soyfood intake to be associated with reductions in the risk of stroke and heart disease far greater than can be attributed to cholesterol reduction alone (19, 48). Clinical studies have demonstrated that soyfoods increase LDL-cholesterol particle size (49) and decrease blood pressure (50), effects which lower CHD risk. However, data are sufficiently consistent and extensive enough to draw a definitive conclusion for only one cholesterol-independent risk factor. Isoflavones improve endothelial function in postmenopausal women although primarily in those with impaired endothelial function at baseline (51, 52). Thus, the evidence suggests soyfoods can reduce CHD risk even in those with normal blood cholesterol levels.

## Soyfoods and Menopausal Symptoms

The low reported incidence of hot flashes among Japanese women first prompted speculation that soy isoflavones might mitigate the drop in estrogen levels that occurs with menopause, thereby preventing the onset of hot flashes and possibly, other menopausal symptoms (53). More than 50 clinical trials have examined the impact of a variety of isoflavone-containing products on the frequency and severity of hot flashes in postmenopausal women. However, these studies have produced mixed results, although most reviews of the existing literature have concluded that more studies than not show benefits even if definitive conclusions are not possible (54-56). Explanations for the inconsistent data have been proposed; these include interindividual differences in isoflavone metabolism (57), differences in baseline hot flash frequency, (i.e., isoflavones are more effective in women with more frequent hot flashes) (58) and differences in the isoflavone content of the intervention products, i.e., products containing higher amounts of genistein are deemed to be most effective (59).

In the most comprehensive analysis of the literature conducted thus far, isoflavones were found to consistently alleviate hot flashes in peri- and postmenopausal women. This analysis included 17 studies, all of which involved supplements of isoflavones derived from soybeans or that were high in genistein. There was a net reduction (beyond the placebo effect) of ~20% (n=12 studies) and ~30% (n=8) for hot flash frequency and severity, respectively. When including the placebo effect, the overall reduction for both frequency and severity was approximately 50 percent. Additional analyses indicated that study duration was positively related to efficacy and that the reduction in frequency was approximately three times greater in studies that provided genistein above (>20.4 mg) in comparison to below the mean dose.

One recent study found that isoflavone-rich soy protein alleviated hot flashes to the same extent as hormone therapy but, in contrast to estrogen, did not increase the vaginal maturation index (a measure of estrogenic effects). Thus, this study indicates not only that isoflavones alleviate hot flashes but that they differ from estrogen. Two servings of traditional soyfoods provide approximately 50 mg total isoflavones and 25 mg genistein, amounts proven to be efficacious in the supplement studies, although the results from trials using soyfoods, which are much more limited in number, are not as impressive as the results from the supplement trials (60).

## Soy and Cancer Risk

The anticancer effects of soyfoods have been rigorously investigated since 1990 when the U.S. National Cancer Institute first expressed interest in this area of research (2). The initial focus on breast cancer can be attributed to the low breast cancer rates in soyfood-consuming countries (61) and animal research demonstrating the ability of isoflavones to inhibit the effects of estrogen (62, 63). Asian epidemiologic studies generally show that soy consumption is associated with a reduction in breast cancer risk (64). However, several lines of evidence indicate that to derive protection against breast cancer, soy must be consumed during childhood and/or adolescence (for reviews see references) (65, 66). Epidemiologic studies indicate that consumption of as little as one serving of soy per day during the early period in life is associated with reductions in risk ranging from 28 to 60 percent. The benefit of early soy intake is attributed to the effects of isoflavones on the developing breast tissue. These effects may be similar to those that occur in response to early pregnancy, which is also very protective against breast cancer (67, 68).

There has also been considerable investigation of the role of soy in preventing prostate cancer, which is not surprising given the low prostate cancer rates in soyfood-consuming countries (61). Isoflavone-rich soy protein and isolated isoflavones inhibit the development of prostate tumors in rodents (69) and, among Asian men, soy consumption is associated with marked reductions in prostate cancer risk (70, 71). There are also animal (72) and human (73) data indicating that isoflavones (genistein) inhibit prostate tumor metastasis. In addition, several studies reported that isoflavone exposure slowed the rise in prostate specific antigen levels (a marker of prostate cancer and tumor volume) in prostate cancer patients (74, 75), although the data are inconsistent (76). Finally, preliminary data indicate that isoflavones lessen the side effects of radiation treatment for prostate cancer (77). Since men are typically diagnosed with prostate cancer at a relatively late age and prostate tumors are usually slow growing, even a modest delay in tumor onset or slowing of growth in response to soy, could significantly reduce mortality.



## Soy and Bone Health

Soyfoods such as calcium-set tofu (78) and calcium-fortified soymilk (79, 80) are high in calcium and the absorption of calcium from these foods is comparable to the absorption of calcium from cow's milk. But soyfoods may contribute to bone health in other ways as well. For example, they are good sources of protein, which is essential for developing and maintaining strong bones (81). Furthermore, there has been rigorous investigation of the possible skeletal benefits of isoflavones, which is not surprising given that estrogen therapy reduces bone loss and fracture risk (82).

Epidemiologic studies generally show that among Asian women higher soy intake is associated with higher bone mineral density (BMD) (83). More relevant however are the results from the two prospective epidemiologic studies that evaluated the relationship between soy intake and fracture risk. When comparing women in the highest soy intake quintile or quartile with those in the lowest, both studies found fracture risk was reduced by approximately one-third (84, 85). In one, there were 1770 fractures of all types among the more than 24,000 Shanghai women who were followed for 4.5 years (84) and in the other, there were 692 hip fractures among the more than 34,000 Singaporean women who were followed for 7 years (85). Despite these impressive results, conclusions about the effects of isoflavones on bone health can only be based on clinical trials.

The more than 25 clinical trials evaluating the effects of isoflavones on BMD have produced mixed results as is evident from the conclusions of the numerous meta-analyses of this literature (86-92). However, many of these trials were not conducted for the two to three-year period that is considered optimal for studying skeletal changes (93). Importantly, the two 3-year trials that have been conducted have produced mixed results. In one, postmenopausal Italian osteopenic women were given either a placebo or 54 mg/day genistein (94) and in the other study, US women were given either a placebo or 80 or 120 mg/day total isoflavones (95). In the former study, there were dramatic improvements in both spinal and femoral neck BMD in the active group (94) whereas in the US study, there were no benefits in response to 80 mg/day isoflavones although after adjustment for several factors, the 120 mg/day dose was protective for femoral neck BMD in compliant women (95).

At this point, despite the impressive epidemiologic data, no conclusions about the direct skeletal effects of isoflavones can be made because of the conflicting clinical trial data. Nevertheless, because of their protein and calcium content, many soyfoods are good choices for bone-healthy diets.



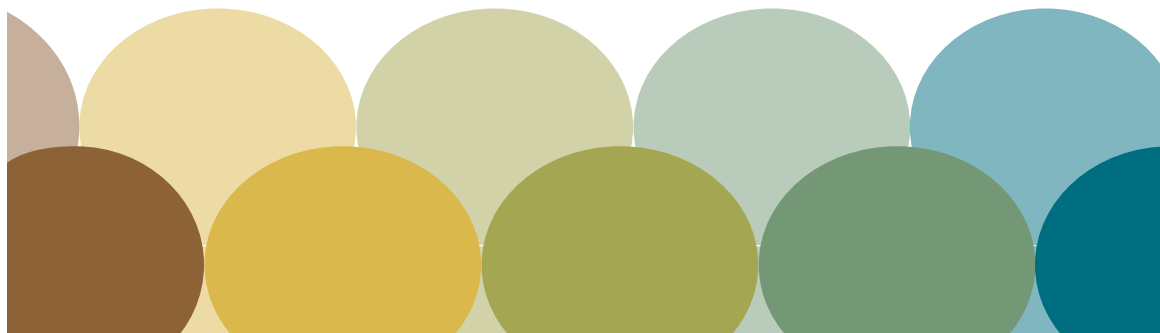
## Are Soyfoods for Everyone?

Despite their long history of consumption, and obvious nutrition and health attributes, the role of soyfoods in healthy diets is not without some controversy. For example, questions have been raised about possible feminizing effects of soyfoods on men, adverse effects on thyroid function, and impairment of mineral status. Almost without exception, safety concerns are based on animal data whereas the human evidence shows that, with the exception of those relatively rare individuals who are allergic to soy protein, soyfoods are a good fit for the diets of all healthy individuals (96). For example, clinical studies shown that neither soyfoods nor isoflavones significantly affect circulating levels of testosterone (97) or estrogen levels in men (98) and do not affect sperm or semen (98).

The clinical research also shows that in euthyroid individuals, neither soy nor isoflavones affect thyroid function (99); this research includes data from a 3-year trial that assessed very sensitive indicators of thyroid function (100). The effect of soy on thyroid function in subclinical hypothyroid patients remains to be determined. In relation to mineral status, as already discussed, calcium absorption from calcium-fortified foods is excellent, despite the fact that soyfoods contain rather large amounts of phytate (101, 102) and oxalate (102), two components that inhibit mineral absorption. Further, recent data suggest that iron absorption from soy has been markedly underestimated (103-105).

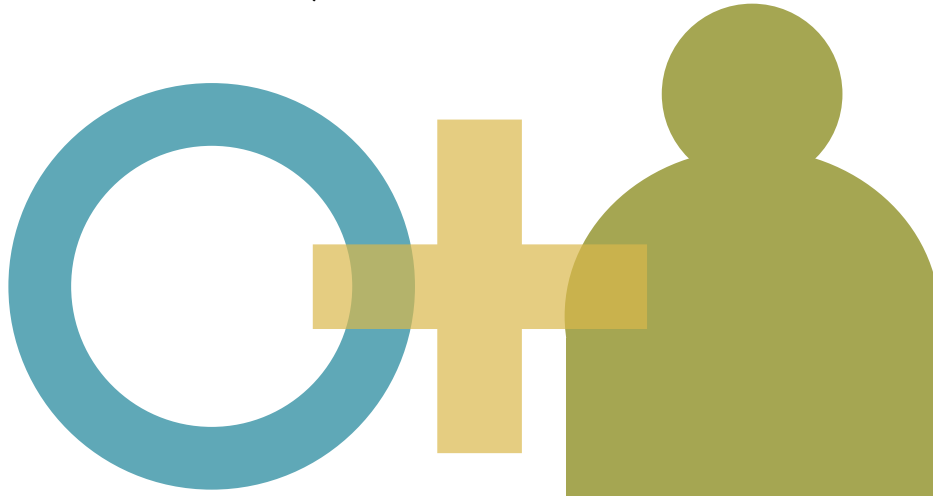
Undoubtedly, the most controversial issue is whether soyfoods are contraindicated for ER+ breast cancer patients. In one type of mouse model, isoflavone-containing diets do indeed stimulate tumor growth (106). However, in this same model, no such stimulation occurs in response to unprocessed soy (107). Furthermore, there is evidence that the results of this rodent model are unlikely to apply to humans, and recent human data are supportive of safety as well as potential benefit (108). Importantly in this regard, two recently published epidemiologic studies found that soy intake improves the prognosis of breast cancer patients (109, 110). What is not known is whether the results from these studies involving Chinese women who almost certainly consumed soy early in life can be applied to non-Chinese women who have not.

A recent commentary on the breast cancer controversy concluded that the current default position of most oncologists, which is to advise their breast cancer patients against the use of soy is no longer justified, but neither is recommending soy specifically for the purpose of improving prognosis (111). Rather, it was concluded that oncologists should allow breast cancer patients for whom soy has been a part of their diet to continue to consume it and to allow patients who want to begin consuming soy to do so. Nevertheless, it is important for breast cancer patients to consult with their health care provider before making any dietary decisions involving soy.



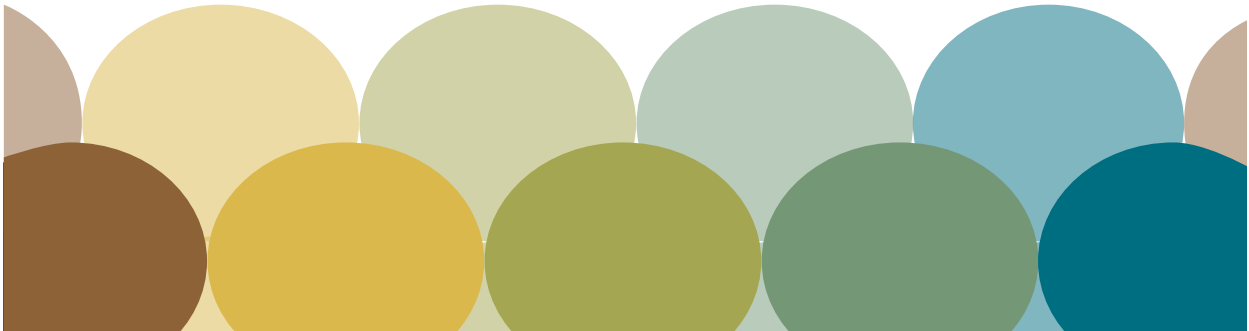
## Soy and Diabesity

The relationship between obesity and diabetes is of such interdependence that the term 'diabesity' has been coined. As healthy sources of protein, soyfoods are a good fit for those using higher-protein diets as an approach to weight loss (112). Whether soyfoods directly improve insulin resistance in individuals with the metabolic syndrome, which may include as many as 50 million Americans (113), is uncertain although some evidence suggests that this may be the case (114). However, the more impressive evidence suggests that soyfoods can help to address the primary complications of diabetes, such as renal disease and coronary heart disease.



## Recommended Soy Intake

No soy intake recommendations have been made by professional health organizations. However, it is possible to determine a reasonable and potentially beneficial intake level by looking at Asian intake as well as the amounts of soy found to be effective in clinical trials. Mean daily Japanese soyfood intake is approximately 1.5 servings (~10 g soy protein) but epidemiologic studies have found intakes exceeding two servings per day to be associated with improved health outcomes in a number of areas. In the clinical studies, generally between 50 and 100 mg/d isoflavones have been found to be efficacious (for example, reduction in hot flashes and improvement in endothelial function). These amounts are provided by two to four servings of traditional soyfoods. Thus, evidence suggests ideal intake is two to four servings per day. Three to four servings will likely provide the 25 g/day soy protein needed for cholesterol reduction. As part of a standard western diet, two to three servings of soyfoods would represent approximately 20 to 25% of total protein intake. There is no evidence that consuming more than four servings per day is disadvantageous, but in keeping with the important dietetic principles of moderation and diet diversity, it is not recommended.



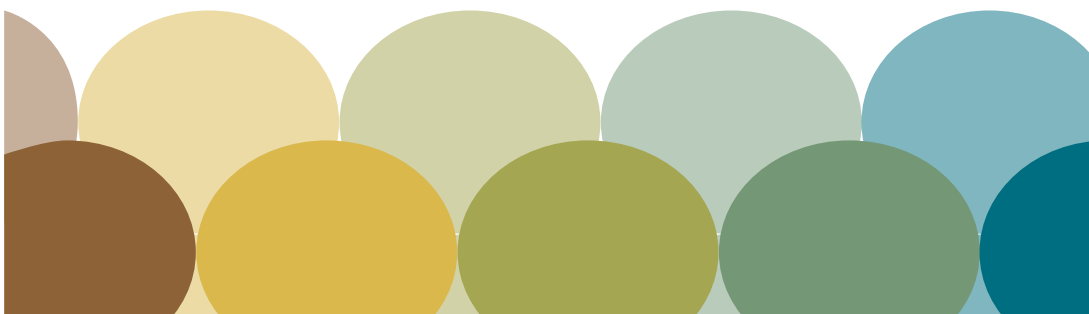
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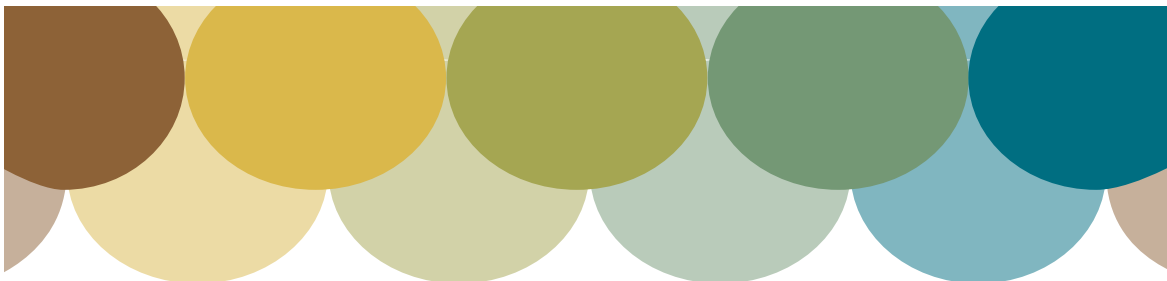
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