TRADICHEM
[ACTIVES & INGREDIENTS]

TRADICHEM
[INDUSTRIAL SERVICES]

September 2020

GRAS STATEMENT OF SOLGEN

We certify that our product **SOLGEN** is safe under the conditions of its intended use.

SOLGEN has the appropriate food grade specifications and is produced by current Good Manufacturing Practices, to be generally recognized as safe (GRAS)

TRADICHEM claims that the GRAS determination has been affirmed by an independent Panel of Experts qualified by scientific training and experience to evaluate the safety of food ingredients, and in particular SOLGEN.

Because of the existence of the Expert Panel Report, the stakeholder is not required by FDA to notify its GRAS determination before adding the substance to food.

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GRAS (Generally Recognized as Safe)
Application for Isoflavones prepared for SOLBAR PLANT EXTRACTS LTD.
January 2001
Prof. Kennetch D.R. Setchell, Ph.D

Summary

Concerns have been raised by the National Center for Toxicological Research (NCTR), several scientists, and a number of focus groups, and media regarding the safety, toxicity and health concerns of soy isoflavones.

As leading International experts and researchers in phytoestrogens, and specifically of soy isoflavones, we have carefully reviewed the literature related to these issues. We concur with the universal agreement that soy isoflavones are biologically active *in vivo* and *in vitro* in animal systems and cell lines[1-4]. However, we also find no valid clinical or scientific evidence to support claims of potential adverse effects of these compounds to the health of humans, especially where isoflavones are consumed at levels typical of normal dietary intakes from soy foods. Notwithstanding, this Expert Panel recognizes that there is a small proportion of the population who exhibit allergenicity to soy products[5], a well known phenomenon that relates to the presence of two major heat-stable proteins β-conglycin and glycinin[6] and not the constituent isoflavones. Clinical and nutritional confidence in soy foods should be obvious from the experience of countries where soy is consumed as a dietary staple. Such countries have the lowest incidence of hormone-dependent diseases that presently constitute the major causes of morbidity and mortality in Western countries where isoflavone-rich diets are not typically consumed[7, 8]. Soy foods and their constituent isoflavones have over time met and exceeded the rigors of drug testing, having been consumed by millions of people for thousands of years.

Concerns that have been raised regarding the safety of soy isoflavones are mostly based upon the findings from animal species and studies of cell-lines grown *in vitro*, and are subject to questionable interpretation where extrapolation to humans is applied. We have reviewed carefully these data as follows:

In our expert opinion, justifiable questions relate to two areas only. Firstly, the issue of early infant exposure to isoflavones from soy infant formulas[9-12], and secondly whether women at high risk for breast cancer, or those with pre-existing malignancy should be advised to avoid consuming soy foods or isoflavone supplements[13]. Presently though, these concerns remain hypothetical in the absence of any evidence to indicate risk. Soy isoflavones have also been linked to dementia and brain abnormalities[14] and many myths have surfaced propagating media hype and unnecessary alarm to consumers. It has been claimed that isoflavones cause endocrine disruption in humans, and that these compounds interfere with pubertal development of children. All of these concerns are highly speculative, hypothetical, and while academically interesting, are not supported by clinical evidence. It would be difficult to convince Asians and Vegetarians who are exposed to the highest levels of isoflavones that their diet, rich in soy isoflavones[15], poses a risk to their health. This is not supported by epidemiological data of such populations[16].

Soy isoflavones and thyroid function

Recent attention has been given to the possible goitrogenic effects of soy isoflavones because of their ability to interfere with the enzyme thyroid peroxidase (TPO) and to compete for iodine as a substrate[17, 18]. The IC_{50} for inhibition of TPO by the isoflavone, genistein, is considerably higher than the circulating concentration of free genistein in the plasma of infants fed soy formulas[9, 19], or adults consuming soy foods[3, 20, 21]. Many flavonoids, highly promoted for their antioxidant activity and found in fruits and vegetables inhibit this same enzyme with similar IC_{50} values[17].

The average dietary intake of flavonoids[22] is comparable to that of isoflavones if soy foods are consumed. If soy isoflavones are a concern for the development of sub-clinical thyroid disease then recommendations to avoid consuming fruits and vegetables is equally warranted. This is not consistent with current nutritional guidelines. Thyroid hormones are crucial to normal development in early life and many studies have shown that the growth and development of infants fed soy formula is no different from that of infants fed cow-milk formula or breast milk[23-26]. The susceptibility to thyroid disease is strongly linked to iodine deficiency[27] and for most of the Western world there is adequate iodine in the diet. Soy infant formulas have been fortified with iodine since 1960. Any increase in thyroid disease, and this is questionable, is more likely explained by reductions in salt intake, since iodized salt is one of our main sources of iodine. The most important evidence for lack of effect of soy isoflavones on thyroid hormone status comes from our failure to find more than 12 cases of thyroid disease precipitated by soy formulas[28-34], when in the last 40 years we estimate that 18 million infants have been raised on soy formulas in the USA alone. Presently, about 25% of all infants are fed soy infant formula in the USA. In a frequently cited report of a cohort of 59 children with autoimmune thyroid diseases it was suggested that the frequency of soy infant formula use was greater in the patient group compared with a group of healthy siblings and controls[35]. This would be expected as autoimmune thyroid disease is gender-biased, favoring mainly females[27], as seen by the 4:1 female:male ratio in the patient group in this study. The comparison groups of infants comprised mainly males. Interestingly, of the 59 children with autoimmune thyroid disease reported in this study, 35% were raised on cow-milk formula 34% on breast milk, and 31% were fed soy formula[35]. The clinical experience with soy infant formula far outweighs the usual experience required for the approval of new pharmaceutical agents. Indeed, side effects from common drugs prescribed every day far outnumber the known reported cases of adverse effects from soy infant formula, and if drug criteria for safety are applied to soy infant formula then it is without question safe.

Soy foods, isoflavones and breast cancer

This Expert Panel recognizes that one of the more important issues to address is the role of isoflavones in breast cancer and specifically the potential risks isoflavones may present to women who have either been diagnosed with breast cancer, or who fall into the category of being at high risk for the disease. Some 80% of all breast cancers are estrogen receptor-positive(ER-positive)[36] (note that there no routine clinical tests as yet to differentiate between ERα or ERβ, which might be of prognostic value), meaning they are stimulated to grow in the presence of estrogen. The standard therapeutic approach that has been employed for more than 30 years for this type of breast cancer is to administer the 'estrogen-like' drug, tamoxifen, which binds to these receptors and antagonizes the stimulatory actions of endogenous estrogens[37]. The close similarity in the chemical structure of isoflavones to estradiol has unfortunately led soy isoflavones to be viewed as 'estrogens' leading to the recent recommendations by some health professionals that women with breast cancer should avoid eating soy foods or taking isoflavone supplements. There is no clinical evidence to support such a view.

X-ray crystallographic studies show that genistein binds estrogen receptors differently from estradiol. It binds in an almost identical manner similar to that of the recently approved selective Estrogen Receptor Modulator (SERM), Raloxifene[37], and as such isoflavones should be classified as natural SERM's[38]. Data from the Multiple Outcomes Raloxifene Evaluation (MORE) study of 7705 postmenopausal women followed over a 4-year period showed a highly protective effect of Raloxifene compared to placebo against the occurrence of breast cancer[39]. By virtue of the

similarity in binding characteristics of soy isoflavones and Raloxifene to the ER[40] a strong case can be made for isoflavones conferring a similar protective effect on breast cancer rather than the opposite. Interest in the role of soy isoflavones and breast cancer was stimulated by the early proposals that the low incidence of breast cancer in Asia might be explained in part by the high dietary intakes of soy isoflavones[7]. This is supported by data from animal models of breast cancer where soy isoflavones in a dose-dependent manner inhibit the growth of tumors in two of the most widely used models of chemically-induced breast cancer[41]. The anticancer activity of isoflavones has been further confirmed from a wealth of data of in vitro studies of cultured human breast cancer cells[42-44]. Contradicting these findings are studies showing that genistein causes the growth of breast cancer cells transplanted in the athymic mouse[45]. This model is highly immune compromised and one used to assess chemotherapeutic agents rather than to study the effects of breast cancer promotion. The in vitro activity of an estrogenic substance can be influenced markedly by the conditions under which the cells are incubated. Isoflavones can be made to behave as antagonists or agonists depending upon how conditions are manipulated[46, 47].

This Expert Panel recognizes that prospective clinical studies are needed to definitively establish if soy and isoflavones can protect against breast cancer, and 'secondary prevention' trials in breast cancer patients may help to clarify the safety of consuming soy foods for such patients. One animal study has shown that the chemotherapeutic effects of tamoxifen in animals with chemically-induced mammary cancer is enhanced significantly when the fermented soy food miso was fed to the animals[48]. If this finding can be extrapolated to humans it suggests that patients with breast cancer treated with tamoxifen might benefit from isoflavone-rich diets. Based on the currently available evidence there is no reason to deter women with breast cancer from consuming soy foods.

Soy foods and dementia

A recent report suggested that isoflavones in tofu may cause of dementia and brain abnormalities in middle-aged Japanese-American's living on the island of Oahu[14]. A study of 8005 adults followed since 1991 showed a dose-dependent increased risk of up to 2.8-fold for the development of vascular dementia when 2-3 or more servings of tofu were consumed weekly. Cognitive Abilities Screening Instrument (CASI) scores and brain weights were lowest in those subjects consuming the most tofu. The authors first concluded[49] that this study "provides evidence that soy (tofu) phytoestrogens cause vascular dementia". This study, while interesting merely showed an association, and not a cause/effect relationship. The study had limited data on the diet, and other factors explain the increased risk amongst the tofu eaters. Interestingly, miso was one of 26 foods also examined but similar relationships were not found for this isoflavone-rich fermented soy food. The authors concluded[14] that age, education, and history of a prior stroke explained 27.8% of the variance in CASI scores while tofu intake accounted for only 0.8%. This Expert Panel concludes that there may be concerns for Japanese-Americans living on Oahu and consuming tofu, but there is no evidence to indicate that soy isoflavones are the agent responsible for brain aging and cognitive decline in this population. It is noted that the incidence of dementia in Japan is no higher than in the USA where tofu is not commonly consumed[50], while results from the Adventist Health Study showed that the risk for dementia was highest in meat eaters and not in vegetarians consuming soy foods[16]. It should be noted that estrogen use by postmenopausal women is associated with protection from Alzheimer's and improved cognitive function[51, 52].

Soy isoflavones and infant formula

The most controversial safety concerns have focused attention on infants and soy formulas. The isoflavone content of soy formula was first eluded to in 1987[53], and then a decade later[9] it was reported that commercially available soy formulas made from soy protein isolates expose infants to 22-45 mg each day of total isoflavones, mainly in the form of β-glycosides[9, 10]. This is in a similar range to the estimated isoflavone intake of Japanese adults eating traditional diets containing soy foods[54]. Soy infant formulas produced for Western countries have since 1960 been made from isolated soy protein and fortified with micronutrients. Formulas elsewhere have used "whole soybeans" and these deliver to infants isoflavone levels 5-fold higher (Setchell KDR et al unpublished data). Plasma isoflavones concentrations of infants fed soy formulas are high and exceed endogenous estradiol levels by 13,000- to 22,000-fold[9]. This finding raised hypothetical concerns over the safety of soy formulas. The difficulty in evaluating the safety of soy, or its constituent isoflavones, is that there is no satisfactory animal model to study infant development, and human studies are unlikely to yield definitive data unless they are statistically powered high and done prospectively. This seems unlikely given the prohibitive costs of such an approach, so we are left with the experience of more than 40 years of soy formula use in an estimated 18 million infants to draw conclusions.
To this end there are no clinical data pointing to adverse short or long-term effects from soy formula use in infancy. In accord with the American Academy of Pediatrics Position Statement on infant feeding[55] we strongly recommend that all infants be breast-fed, but there are infants that cannot be breast fed, and many women who choose not to breast-fed. Save, low birth weight preterm infants (<1.8 Kg) who require specialized formulas[55], there is little reason for concern over the use of soy infant formulas for healthy full-term infants, and there may even be some long-term benefits to be gained from early exposure to phytoestrogens if some of the findings from animal studies have relevance to human disease[56].

Soy isoflavones and endocrine disruption

Phytoestrogens have been found to cause reproductive abnormalities in several animal species[57-60]. These effects are explained by species differences in the metabolism of phytoestrogens, or by chronic ingestion of extremely high doses. It is noted that most commercial rodent diets used by animal husbandary suppliers contain high levels of isoflavones because they are formulated with added soy protein[61, 62]. Animals are exposed to doses of 48-80 mg/kg body weight/day (typical doses that humans consume range 0.5 –1.5 mg/kg body weight/day when soy foods are consumed) from these diets and yet reproduction in rodents is not affected by dietary isoflavones. It has been suggested that isoflavones cause delayed puberty in boys and early puberty in girls. Studies show that the timing of puberty in boys has not significantly changed in the last 40 years[63] and while the age of onset of menarche has decreased 3-4 months each decade due to improved nutrition, since the mid-1970's it has remained relatively stable for girls[64]. Studies of premenopausal women have shown that a diet rich in soy isoflavones leads to significant endocrine effects on the regulation of the menstrual cycle. These include a prolongation in cycle length, an effect consistent with reduced risk for breast cancer, and a suppression in pituitary gonadotrophins[65]. Other studies have shown diets rich in isoflavones lead to reduced levels of estrogens[66] and it is known that estrogen concentrations of Japanese women are 20-30% lower than Western women and related to soy intake[67, 68]. Plasma cholesterol, which is regulated by estrogen, is also lower in people consuming soy foods[54]. These endocrine effects are consistent with long-term health effects.

Conclusions

There is presently no convincing evidence to warrant concerns over the safety of soybean isoflavones when ingested at typical dietary intakes found in soy foods. The safety of isoflavones is supported by a long history of the consumption of soy foods in people living in countries where these are a dietary staple and in vegetarian groups. Both groups have high and sustained plasma isoflavone levels. In these groups, epidemiology speaks for the safety of soy foods and their constituent isoflavones. There is no clinical evidence supporting the many speculative safety and toxicity concerns that have been raised. Furthermore, the epidemiological data and human studies where potential beneficial effects have been demonstrated have mostly been performed with isoflavones in the presence of the soy protein matrix, be it tofu, soy flour, textured vegetable proteins, soy grits, or soymilks. Because of their wide-ranging biological activity of isoflavones we have concerns about the possibility of negative effects from mega-dosing with high dose isoflavone supplements. Overall, the weight of evidence indicates that diets rich in soy and its isoflavones are likely to confer long-term health benefits.

In summary, we, the Expert Panel, have critically evaluated the information summarized in this report. We conclude that isoflavones manufactured by Solbar Plant Extracts and produced from soy molasses with the natural proportions of genistein, daidzein and glycitein isomer forms found in soy beans, meeting the appropriate food grade specifications, and produced by current good manufacturing practice, to be generally recognized as safe (GRAS), using scientific procedures, for use as an ingredient in adult health replacements, beverages, and snack bars to a level of 50-60 mg per day.

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