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TECHNICAL REPORT

*to summarize the scientific rationale for the Natural Health Products Directorate's new guidance on the regulation of soy isoflavone products*

Natural Health Products Directorate (NHPD)

Health Canada (HC)

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b) On what scientific basis does Health Canada approve the following health claim for soy protein and isoflavone products providing 75-125 AIE when taken for at least six months by postmenopausal women: “Helps to attenuate/reduce post-menopausal bone mineral density (BMD) loss when used in conjunction with adequate amounts of calcium and vitamin D”?

c) On what scientific basis does Health Canada reject all health claims related to cardiovascular health?

d) On what scientific basis does Health Canada require the following cautionary statement on the labels of all soy protein and isoflavone products providing doses ≥ 30 mg AIE per day: “Consult a health care practitioner (HCP) for use beyond one year”?

e) On what scientific basis does Health Canada require the following cautionary statement on the labels of all soy protein and isoflavone products providing doses ≥ 30 mg AIE per day: “Consult a HCP prior to use if you are taking hormone replacement therapy (HRT)”?

f) On what scientific basis does Health Canada require the following contraindication statement on the labels of all soy protein and isoflavone products providing doses ≥ 30 mg AIE per day: “Do not use if you currently have or previously had breast cancer or if you have a predisposition to breast cancer such as an abnormal mammogram and/or biopsy, or a family member with breast cancer”?

g) On what scientific basis does Health Canada require the following cautionary statement on the labels of all soy protein and isoflavone products providing doses ≥ 30 mg AIE per day: “Before use, ensure that you are up-to-date on mammograms and endometrial ultrasounds/biopsies”?

h) On what scientific basis does Health Canada require the following cautionary statement on the labels of all soy protein and isoflavone products providing doses ≥ 30 mg AIE per day: “Consult a HCP prior to use if you have a history of hormonal or gynaecological disease including ovarian cancer, endometriosis and/or uterine fibroids”?
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Introduction

The purpose of this technical report is to summarize the scientific rationale for the Natural Health Products Directorate’s (NHPD) new guidance on the regulation of soy isoflavone products. This guidance translates to labelling requirements for currently marketed products. Specifically, the logic behind each efficacy and risk recommendation is conveyed through summary and commentary on the relevant scientific literature. Soy isoflavones have gained a tremendous amount of scientific and public attention based on their potential to influence human health and there is a wealth of data from which to consider the evidence to rationalize specific recommendations. Note that since there is insufficient evidence to establish recommendations or risk statements for use of soy isoflavone products in men, the recommendations and risk statements are focused on women in order to target the majority of users.

With respect to the involved pharmacokinetics, Tomar et al. (2008) included a much needed summary of dose-response information on soy isoflavones in humans. However, conducting a human health risk assessment study based on this information alone continues to be unreliable since dose-response information remains overall lacking for specific organs such as the thyroid gland, mammary gland, uterus and ovary. As such, it is currently exceptionally difficult to conduct a reliable human risk assessment study of soy isoflavones in these and other organs. Additionally, classical pharmacokinetics, which generally is designed to study the effects from drugs with one active ingredient, may not be the best approach for studying herbal products such as soy supplements. Herbal products are usually complex mixtures of bioactive components each with their own effects; additionally, the processing towards an extract or isolate from the original herbal species can drastically change its physiological consequences. Thus, for a better understanding of the effects from herbal products, complimenting classical pharmacokinetic work with a more physiologically based pharmacokinetic (PBPK) model is very enviable. Indeed, the current literature does make note of such a model (Zager et al. 2007; Schlosser et al. 2006). This approach should be considered when examining the potential risks and the pharmacokinetics of soy isoflavones in humans, and the model can be applied broadly to other natural health products (NHPs) with complex mixtures as well. More prevalent use of such a model would help to improve the understanding of soy isoflavone pharmacological and toxicological activities in both animals and humans (Law 2007).

For the efficacy recommendations, the scientific rationale is based on the totality of the available evidence and as such draws heavily on meta-analyses and systematic reviews. Recommendations are included for menopausal symptoms, bone health and cardiovascular health, three areas consistent with interest in soy isoflavones as an alternative to hormone replacement therapy (HRT). Overall, the efficacy recommendations provide guidance with respect to how soy isoflavone supplementation influences these areas of health and if there is justification for a health claim.

For the risk statements, the scientific rationale is based on the combined consideration of the uncertainty of evidence that exists in the literature, the severity of the risk in question and the logic of the precautionary principle. The logic behind the precautionary principle follows that if a particular potential risk can cause severe harm, then in the absence of scientific consensus that harm would not ensue, the responsibility is to protect the public and therefore issue a risk statement (EC 2001). In this regard, the need for a risk statement relates more to the nature of the effect and less to the strength of the evidence. The division between risk and no risk is challenging to articulate but frequently relates to high-risk populations. The amount of evidence available in these high-risk populations is minimal, particularly since those with the
condition in question are excluded from the majority of clinical studies. It is therefore noteworthy that a lot of the data available to consider risk statements are from case-reports or adverse events noted in select clinical studies. Yet, in accordance with the precautionary principle, these data, although not adequately assessed statistically, must be considered and may contribute toward a scientific rationale for a risk recommendation. In some cases, there are individual clinical studies that focus on the issue in question and there are available comprehensive review articles that speak to risk in various topic areas (Duffy et al. 2007; BFR 2007; Tomar et al. 2008). This overall approach to considering risk statement errs on the conservative side yet is appropriate given that these products are for individual use, are available over-the-counter and may not be used under the guidance of a health care practitioner.

In the context of both the efficacy and risk recommendations/statements, it must be stressed that food products and NHPs are regulated separately by Health Canada. NHPs are considered supplements and can therefore provide nutrients in excess of dietary recommendations which can lead to altered health effects. Indeed, there is a growing consensus that the health effects from soy isoflavone supplements differs from those from soy foods (Duffy et al. 2007; Helferich et al. 2008). Examples of soy and isoflavone NHP products include soy isoflavone extracts and soy protein extracts. The recommendation and risk statements for these soy isoflavone products refer to isoflavone dose amounts in terms of aglycone isoflavone equivalents (AIE). This is because the AIE best describes the bioactive form of isoflavones since cleavage of the glycosidic unit to produce an aglycone is likely necessary before isoflavones can be absorbed. It is central to note that since NHPs which contain soy or its constituents are not foods and since these NHPs have different pharmacological profiles than soy foods (Anupongsanugool et al. 2005; Vergne et al. 2008; Gardner et al. 2009), their labels can carry both health claims and risk statements. Nonetheless, risks in the literature from high daily dietary isoflavone over-consumption are considered in supporting risk statements for NHPs when they serve to underscore similar effects initially identified from the daily use of supplements. This is particularly important when the risk is potentially serious, such as interactions with blood thinners/anticoagulants.

References


TECHNICAL REPORT to summarize the scientific rationale for the Natural HealthProducts Directorate's new guidance on the regulation of soy isoflavone products
SUMMARY OF SCIENTIFIC RATIONALE:

a) On what scientific basis does Health Canada approve the following health claim for soy protein and isoflavone products providing 30-100 mg aglycone isoflavone equivalents (AIE), including at least 15 mg AIE from genistein, when taken for at least two weeks by menopausal and postmenopausal women: “May reduce severe and frequent menopausal symptoms (such as hot flushes/flashes and night sweats)”?

The biological plausibility to consider soy isoflavones for improvement of menopausal symptoms is established in their demonstrated weak estrogenic effects (Kuiper et al. 1998) and has created one of the most frequently studied area of soy and health as evidenced by the number of published reviews and meta-analyses (Messina and Hughes 2003; Williamson-Hughes et al. 2003; Krebs et al. 2004; Howes et al. 2006; Lethaby et al. 2007). The totality of evidence from these reviews has established the scientific rationale to support a health claim relating soy protein and isoflavone products to reduction of menopausal symptoms.

Messina and Hughes (2003) reviewed 13 human intervention studies (>1700 women) that investigated the effect of soy (34-100 mg isoflavones/day and in most cases ≥70 mg/day) on menopausal symptoms. Based on simple regression analysis, they found a significant relationship between treatment efficacy and initial hot flash frequency in that initial hot flash frequency explained about 46% of the treatment effects (P=0.01). Hot flash frequency decreased by about 5% (above control) for every additional initial hot flash per day experienced by women whose initial hot flash frequency was ≥5 per day. The authors summarized that although conclusions based on this analysis should be considered tentative, the available data justify the recommendation that patients with frequent hot flashes consider trying soy foods or isoflavone supplements for the alleviation of their symptoms.

Howes et al. (2003) performed a systematic review and meta-analysis of 17 randomized controlled trials (RCTs) to summarize the efficacy of isoflavone therapy (dose range 48-160 mg/d) in reducing menopausal flashes. Isoflavone supplementation was significantly associated with a reduction in hot flashes (effect size
of -0.28 (95% confidence interval (CI) -0.39 to -0.18, P<0.0001) and a weighted regression analysis revealed a predictive relationship between the number of baseline hot flashes (data were available for 0-16 baseline hot flashes per day) and the percent reduction in hot flashes. Overall, the results suggest that isoflavone supplementation may produce a slight to modest reduction in the number of daily flashes in menopausal women and that the benefit may be more apparent in women experiencing a greater number of hot flashes per day.

The idea of isoflavone profile affecting treatment outcomes was addressed by Williamson-Hughes et al. (2006) who focused their critical review on 11 studies were the first to investigate the effects of comparable isoflavone dose but varying isoflavone composition (with a focus on genistein) on hot flashes. Results showed a clear distinction in effect relative to genistein dose. Hot flashes were consistently significantly decreased in studies that provided ≥15 mg genistein daily (calculated as aglycone equivalents) (total of 5 studies, n=177, P values ranged from <0.01 to <0.05) but not in studies that provided <15 mg genistein daily (total of 6 studies, n=201). Thus, the reduction in hot flashes was related to genistein dose, not total isoflavone content of the treatments. These results raise the idea that studies concluding that isoflavone supplements do not significantly reduce hot flashes may be incorrect and that the lack of discrimination between individual isoflavones contained in heterogeneous isoflavone mixtures from differing sources may be the source of error. Importantly, these data form the basis that at least 15 mg AIE from genistein be included in the NHPD recommendation statement.

Overall, these reviews and meta-analyses have concluded beneficial effects of soy isoflavones on reduction of menopausal symptoms. The majority of evidence has related to hot flashes or night sweats, yet there is also some evidence to support benefit on other menopausal symptoms such as insomnia, nervousness, depression, vertigo, weakness, headaches (Han et al. 2002; Albert et al. 2002). For the NHPD recommendation statement, rationale for the dose of 30-100 mg AIE is based on the fact that few studies have examined doses outside this range. Further, inclusion of at least 15 mg AIE from genistein comes from the evidence of by Williamson-Hughes et al. (2006). The rationale for recommending a duration of consumption of at least 2 weeks comes from the shortest study demonstrating efficacy (Albertazzi et al. 1998), although durations of consumption of up to 1 year have been studied. Since the reviews summarize that significant effects are most apparent if the symptoms are severe and frequent, both terms are included in the NHPD recommendation. Finally the use of the word “may” is justified since there are some reviews have summarized that soy isoflavones do not significantly affect menopausal symptoms (Krebs et al. 2004; Lethaby et al. 2007). It should be noted that clarity of the literature is challenged by the frequent heterogeneity among studies that reduces the power of the systematic review and meta-analyses. Key methodological factors of consideration include the number of baseline hot flashes, isoflavone dose and isoflavone profile. Other factors that influence the likelihood of an effect include hot flash frequency and severity, and inter-individual differences in isoflavone metabolism and bioavailability. Occurrence of the placebo effect is common in these studies in that significant differences are found within but not between treatment and placebo groups. Nonetheless, a complete review of the literature to date provides a convincing number of studies, many of which have undergone systematic review and meta-analysis that demonstrate statistically and biologically significant improvements in menopausal symptoms.
SUMMARY OF SCIENTIFIC RATIONALE:

b) On what scientific basis does Health Canada approve the following health claim for soy protein and isoflavone products providing 75-125 AIE when taken for at least six months by postmenopausal women: “Helps to attenuate/reduce post-menopausal bone mineral density (BMD) loss when used in conjunction with adequate amounts of calcium and vitamin D”?

The effect of soy isoflavones on bone health is a highly studied area and is also highly relevant to the public health of postmenopausal Canadian women since approximately 1 in 4 women >50 years old has osteoporosis (Hanley and Josse 1996). Beyond actual fracture incidence, which is challenging to evaluate in a research setting, bone mineral density (BMD) is considered the best biomarker of osteoporosis. BMD is related to fracture risk (Khan et al. 2002) and reflects more of a long-term effect than do the more short-term biochemical measures of bone turnover.

Observational studies that have reported an association between isoflavone intake and improved BMD (Tsuchida et al. 1999; Mei et al. 2001; Kritz-Silverstein et al. 2002) have prompted the conduct of many human intervention studies. A 2003 review of the literature concluded that on balance, the available data suggests that diets rich in phytoestrogens (of which isoflavones are a major class) have bone-sparing effects.
in the long term, although the magnitude of effect is unclear (Setchell et al. 2003). Following more investigations, a meta-analysis of 10 RCTs (n=608 women) was conducted by Ma et al. (2008) and concluded that isoflavone consumption significantly attenuates bone loss in the spine of postmenopausal women. The results showed that isoflavone supplementation (range of 55.6-150 mg isoflavones/day) caused spine BMD to significantly increase by 20.6 mg/cm² (95% CI: 4.5-36.6 mg/cm², P=0.01). Further analysis showed greater effects with isoflavone intake >90 mg/day (28.5 mg/cm², 95% CI: 8.4-48.6 mg/cm²) and duration of treatment of at least 6 months (27 mg/cm², 95% CI: 8.3-45.8 mg/cm²). A recent review article by Atmaca et al. (2008) also summarized that epidemiological and clinical studies suggest that soy isoflavones have beneficial effects on BMD in postmenopausal women. Finally, although observational, it is worth noting the only prospective study to investigate fracture risk in relation to soy intake, in which Zhang et al. (2005) followed more than 24,000 postmenopausal Chinese women for 4.5 years, found that higher soy intake was significantly associated with a one third reduction in risk for all fractures (P<0.001).

Overall, the justified reliance on past (Setchell et al., 2003) and more recent (Ma et al. 2008; Atmaca et al. 2008) literature reviews as well as the single prospective study examining fracture risk (Zhang et al. 2005) provides justification for the health claim recommendation. It should be noted that the health claim specifies an attenuation of postmenopausal BMD (rather than an improvement) and this is because a favourable outcome would be a prevention of the expected decrease in BMD that occurs over time in a postmenopausal woman. Further, the evidence is only justified in the presence of adequate calcium and vitamin D which is therefore required in the claim wording. The dose range of 75-125 AIE is rationalized from the lowest dose of 76 AIE shown to produce a favourable effect on BMD and the upper dose of 125 AIE above which there is a lack of substantiated evidence. The duration of at least 6 months comes from the conclusions of the Ma et al. (2008) meta-analysis.

References


**SUMMARY OF SCIENTIFIC RATIONALE:**

c) On what scientific basis does Health Canada reject all health claims related to cardiovascular health?

Although the United States currently has a food health claim approved for soy protein (“25 g of soy protein a day, as part of a diet low in saturated fat and cholesterol, may reduce the risk of heart disease”) (FDA 1999), in 2008, Health Canada’s Food Directorate came to the conclusion that: “overall, existing data are inconsistent or inadequate in supporting most of the suggested health benefits of consuming soy protein or isoflavones” (Xiao et al. 2008).

Overall, there is currently insufficient evidence to support health claims for isoflavones in cardiovascular health. In 2005, the Tuft-New England Medical Center Evidence-based Practice Center prepared an evidence report that focused extensively on cardiovascular effects of soy protein and isoflavones and concluded that there were no significant effects (Balk et al. 2005). Soon thereafter, in 2006, the American Heart Association (AHA) conducted a literature review of studies that examined the effects of soy protein and soy isoflavones on circulating lipids in relation to cardiovascular health (Sacks et al. 2006). Among the 19 studies that examined isoflavones either within the soy protein matrix or in a pill format, only 3 studies demonstrated a significant reduction in LDL-cholesterol, and the weighted average effect among all 19 studies was 0%, as was the effect on HDL-cholesterol and triglycerides. Individual studies (Nahas et al. 2007; Ho et al. 2007; Aubertin-Leheudre et al. 2008) and a meta-analysis (Taku et al. 2008) published since the AHA review that have focused specifically on extracted soy isoflavone supplementation have also shown no significant effects on circulating lipids. In summary, the bulk of the evidence related to soy and cardiovascular health is in the area of soy food matrices. The role of isoflavone NHPs to improve cardiovascular health is an active area of research that includes expansion of CVD risk factors (such as C-reactive protein (Chan et al. 2008)) making it premature to accept any health claims for NHPs at this time.

**References**


SUMMARY OF SCIENTIFIC RATIONALE:

d) On what scientific basis does Health Canada require the following cautionary statement on the labels of all soy protein and isoflavone products providing doses ≥ 30 mg AIE per day: “Consult a health care practitioner (HCP) for use beyond one year”?

The primary scientific rationale behind this risk statement is that the majority of clinical studies that have investigated health and safety effects of soy protein and isoflavones have been <12 months in duration, therefore, generating minimal evidence to establish safety beyond 1 year. In addition, since yearly endometrial biopsy, cervical cytology, and mammogram clinical data are required by Health Canada for approval of a new HRT product (Health Canada 2000) and given the severity of an endometrial or breast cancer diagnosis along with the potential for progression of endometrial and mammary pathology, there is logic in applying the precautionary principle for this risk statement. It is further noted that individualized follow-up of HRT for women is recommended at intervals of at least one year following an initial follow-up examination within the first 3-6 months of use (Health Canada 2006). With respect to dose, since there are no substantiated risks or demonstrated reproductive-related effects for doses <30 mg AIE, precaution is only merited for doses ≥30 mg AIE.

References


SUMMARY OF SCIENTIFIC RATIONALE:

e) On what scientific basis does Health Canada require the following cautionary statement on the labels of all soy protein and isoflavone products providing doses $\geq 30 \text{ mg AIE per day}$: “Consult a HCP prior to use if you are taking hormone replacement therapy (HRT)”?

And:

f) On what scientific basis does Health Canada require the following contraindication statement on the labels of all soy protein and isoflavone products providing doses $\geq 30 \text{ mg AIE per day}$: “Do not use if you currently have or previously had breast cancer or if you have a predisposition to breast cancer such as an abnormal mammogram and/or biopsy, or a family member with breast cancer”?

And the part of risk recommendation g) that addresses mammograms:

g) On what scientific basis does Health Canada require the following cautionary statement on the labels of all soy protein and isoflavone products providing doses $\geq 30 \text{ mg AIE per day}$: “Before use, ensure that you are up-to-date on mammograms and endometrial ultrasounds/biopsies”?

Rationale for research into the health-related roles of soy isoflavones for postmenopausal women comes primarily from their potential to serve as a dietary alternative to HRT. Isoflavones are structurally similar to endogenous estrogen and are able to bind to the estrogen receptor with a preference for ER-β (Kuiper et al. 1998).

Consideration of the safety of isoflavones in postmenopausal women has focused in particular on exploring concern for an increased breast cancer risk. Cell culture evidence raises concern since at low ($<10 \mu\text{mol/L}$) physiologically-relevant concentrations, the isoflavone genistein stimulates growth of estrogen-dependent tumours and is only inhibitory at high ($>10 \mu\text{mol/L}$) physiologically-irrelevant concentrations (de Lemos, 2001). Animal data also raise concern following multiple studies reporting increased breast tumour growth in ovariectomized athymic nude mice that were implanted with estrogen-dependent (MCF-7) breast cancer cells and fed a variety of soy isoflavone products (Hsieh et al. 1998; Ju et al. 2001; Allred et al. 2001a; Allred et al. 2001b).

As for human evidence, epidemiological studies that have studied the link between soy and breast cancer risk have primarily shown either no significant relationship or a protective relationship (Duffy et al. 2007). In fact, 3 recent meta-analyses summarize a modest protective relationship between soy isoflavone exposure and breast cancer risk including that of Trock et al. (2006) who reported an OR of 0.86 (95% CI; 0.75-0.99) in their summary of 18 studies; Qin et al. (2006) who reported an RR of 0.81 (95% CI; 0.67-0.99) in their summary of 21 studies and most recently that of Wu et al. (2008) who focused on isoflavone dose in their summary of 8 studies and reported an OR of 0.86 (95% CI; 0.78-0.98) for isoflavone intakes around 10 mg/day and a more protective OR of 0.71 (95% CI: 0.60-0.85) for isoflavone intakes $\geq20 \text{ mg/day}$. With respect to this apparent protective relationship, it is noteworthy that evidence exists to suggest that it can only be realized if consumption occurs early in life. Indeed, there is evidence from animal (Lamartiniere et al. 2002) and numerous epidemiological (Shu et al. 2001; Wu et al. 2002; Korde et al. 2009; Lee et al. 2009)
studies to show that isoflavone exposure during early stages of life (including fetal, childhood and adolescence) reduces breast cancer risk. This notion is consistent with the idea that breast development is complex and occurs during many stages of life including fetal, puberty, pregnancy and lactation (Howard et al. 2000).

Nonetheless, in the face of these modest protective meta-analyses reports (Trock et al. 2006; Qin et al. 2006; Wu et al. 2008), a prospective United Kingdom study of 333 women (aged 45-75 years) by Grace et al. (2004) deserves mention as it reported that an increase in breast cancer risk was related to increased concentrations of isoflavones in the serum and urine, which are objective and accurate reflections of dietary isoflavone intake. Isoflavone intakes in the study were low, yet statistical analysis revealed significant log2 odds ratios (log2OR) (reflects a doubling of isoflavone exposure) for serum daidzein (log2OR=1.220; 95% CI: 1.005-1.481; P=0.044), serum equol (log2OR=1.455; 95% CI: 1.051-2.017; P=0.024) and urinary equol (log2OR=1.344; 95% CI: 1.063-1.699; P=0.013).

Overall, although the epidemiological evidence does not generally cause reason for concern, there remains the study by Grace et al. (2004) and the theory prompted from the cell culture and animal evidence that estrogenic isoflavones could stimulate growth of existing (known or unknown) estrogen-dependent breast tumours or cause an increase in breast cancer risk in women at an elevated risk of breast cancer.

In examination of evidence from human intervention studies, a highly cited (and also highly criticized) human study (Petrakis et al. 1996) flagged concern when it reported estrogenic effects of soy protein isolate containing 38 mg genistein on the healthy breast. Petrakis et al. (1996) monitored a group of 24 pre- and postmenopausal women over 1 year during which they consumed soy protein isolate from months 4-9. Nipple aspirate fluid (NAF) volume was increased in the premenopausal (but not the postmenopausal) women during soy consumption (months 4-9) compared to the control time period (months 1-3). Of most relevance to the current NHPD risk statement was the finding that among the 4 postmenopausal women who were using HRT, there was a distinct increase in NAF volume during the period in which they were consuming the supplement as compared to the control time period. Also of concern was the cytological detection of breast epithelial hyperplasia in 7 of the 24 women during the soy consumption months 4-9. Overall these findings are suggestive of an estrogenic stimulus of isoflavones on the breast, yet the study has methodological limitations, most notably the lack of a control group. Regardless, the precautionary principle requires note of this study as rationale for risk statements in relation to hormone exposure and breast cancer risk.

A subsequent RCT of improved design from Petrakis et al. (1996) was conducted in 48 premenopausal women with benign and malignant breast conditions who consumed 60 g/day of soy protein in a bread form (45 mg isoflavones). Compared with their normal diet, after just 14 days of the soy-supplemented bread, there was a significant increase in the number of breast epithelial cells in the S-phase and a trend toward an increase in proliferative antigen Ki67 in these cells, again reflecting an estrogenic response (McMichael-Phillips et al. 1998). In a continuation of this study, Hargreaves et al. (1999) expanded the sample to include 84 premenopausal women with the same benign and malignant breast conditions who underwent the same 14-day treatment. The results then revealed no significant increase in the number of epithelial breast cells in the S-phase; however, there was an increase in the expression of pS2 (an estrogen-regulated protein) in NAF which is indicative of an estrogenic effect on the breast tissue. There were no significant changes in breast epithelial cell proliferation, estrogen and progesterone receptor status, apoptosis, mitosis or Bc1-2
expression. The fact that this study did find an estrogenic effect (in the expression of pS2) contributes to the rationale for the current NHPD risk statements. Although this study was conducted in premenopausal women, the fact they had benign and malignant breast conditions makes the study relevant to any woman with a predisposition to breast cancer as well as to postmenopausal women exposed to estrogen through HRT.

In the face of these concerning results from human studies by Grace et al. (2004), Petrakis et al. (1996), McMichael-Phillips et al. (1998) and Hargreaves et al. (1999), more recent clinical studies have demonstrated no evidence of any increase in breast cell proliferation examined from breast biopsies taken after soy isoflavone supplementation in healthy postmenopausal women (Cheng et al. 2007) and women with breast cancer (Palomares et al. 2004; Sartippour et al. 2004). Other studies have examined mammographic density as an indicator of breast health which is relevant since research shows that HRT slows the age-related decline in mammographic density, suggestive of an increased breast cancer risk (van Duijnhooven et al. 2007). However, studies of isoflavone supplementation have consistently reported no significant effects on mammographic density (Maskarinec et al. 2004; Maskarinec et al. 2005; Maskarinec et al. 2009). Nonetheless, controversy remains with some data suggesting that supplemental genistein enhances the proliferation of estrogen-dependent human breast cancer tumour growth while genistein within the soy food matrix does not (Helferich et al. 2008).

It is also worth noting, although not of known statistical significance and most likely due to chance, select studies that have not found overall hormonally-related effects but have reported adverse events related to breast cancer. These findings include a woman who had a recurrence of breast cancer in a study that investigated the use of 114 mg soy isoflavones per day for 3 months in women with a history of breast cancer (Nikander et al. 2005) and a healthy woman who developed breast cancer in a study that examined 120 mg soy isoflavones per day for 6 months in healthy women without any history of benign breast disease, endocrine disease, gynaecological diseases, or neoplasia (Kaari et al. 2006).

There remains reason for caution and in fact, although the American Cancer Society has summarized that it is safe for breast cancer patients to consume up to 3 daily servings of soy foods, they have recommended against the use of isoflavone supplements (Doyle et al. 2006). It is also of value to consider summary statements included in relevant literature reviews including that of a German BfR governmental group safety review that documented ‘As women during and after menopause are at increased risk of breast cancer, the long-term intake of food supplements with a high level of isoflavones is not without risk for this consumer group’ (BfR 2007). A more focused comprehensive review of the implications of phytoestrogen intake for breast cancer summarized that ‘Research suggests that the relationship between phytoestrogens and breast cancer is not straightforward. There is evidence for both a protective role and a stimulatory role in breast cancer cell growth’ (Duffy et al. 2007). Finally, a comprehensive review by the American Environmental Protection Agency (Tomar et al. 2008) that summarized studies examining breast cancer risk and soy isoflavone use concluded that ‘isoflavones are weak estrogens and their effect depends upon the dose, time of exposure and species involved’ and that ‘it would not be safe to indisputably accept soy isoflavones to prevent breast cancer.’

In summary, isoflavones can interact with the estrogen receptor (Kuiper et al. 1998) and there is evidence from select studies raise concern regarding potential deleterious effects of isoflavones on the breast (Petrakis et al. 1996; McMichael-Phillips et al. 1998; Hargreaves et al. 1999; Grace et al. 2004). Although there is
substantial evidence to indicate no concern, the precautionary principle warrants the risk statement that women on HRT should consult their health care practitioner if they are on HRT and consuming soy protein and isoflavone products providing doses $\geq 30$ mg AIE per day. As well, given the above evidence and the summary statements from reviews such as that of BfR (2007), Duffy et al. (2007) and Tomar et al. (2008), the precautionary principle justifies a cautionary statement for women to ensure they are up-to-date on clinical tests such as mammograms. Finally, given the severity of illness that would result if the potential of isoflavones to contribute toward the growth of an estrogen-dependent breast tumour demonstrated in animals (Hsieh et al. 1998; Ju et al. 2001; Allred et al. 2001a; Allred et al. 2001b) was realized in humans, it is necessary to recommend a contraindication for women who have or previously have had breast cancer or have a predisposition to breast cancer (such as an abnormal mammogram and/or biopsy or a family member with breast cancer) on the labels of soy protein and isoflavone products providing $\geq 30$ mg AIE.

References


TECHNICAL REPORT

to summarize the scientific rationale for the Natural HealthProducts Directorate's new guidance on the regulation of soy isoflavone products


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Canada
SUMMARY OF SCIENTIFIC RATIONALE:

h) On what scientific basis does Health Canada require the following cautionary statement on the labels of all soy protein and isoflavone products providing doses ≥ 30 mg AIE per day: “Consult a HCP prior to use if you have a history of hormonal or gynaecological disease including ovarian cancer, endometriosis and/or uterine fibroids”

And the part of risk recommendation g) that addresses endometrial ultrasounds/biopsies:

  g) On what scientific basis does Health Canada require the following cautionary statement on the labels of all soy protein and isoflavone products providing doses ≥ 30 mg AIE per day: “Before use, ensure that you are up-to-date on clinical tests such as mammograms and endometrial ultrasounds/biopsies”?

The idea that isoflavones would influence hormonal-related tissues is not surprising given their structural similarity to estrogen. For example, the endometrium is a hormone-dependent tissue, and since estrogen clearly contributes to the etiology of endometrial cancer (Kaaks et al. 2002), particular concern is warranted. Furthermore, other hormonally-related gynaecological diseases including ovarian cancer or uterine-related problems warrant concern as well. As discussed below, the scientific basis behind the risk recommendations for these issues comes from evidence from the longest intervention study of relevance (Unfer et al. 2004), a related intervention study (Murray et al. 2003) and a group of case studies (Noel et al. 2006; Chandrareddy et al. 2008; Cecchi et al. 2009).

Unfer et al. (2004) conducted the longest intervention study of relevance to the endometrial effects of soy isoflavone supplementation. A randomized double-blind placebo-controlled design was utilized in which 376 healthy postmenopausal women consumed either 150 mg soy isoflavone tablets or a placebo for 5 years. From endometrial biopsies obtained at baseline, 30 months and 5 years, results showed that in the 298 women who completed the 5-year treatment, there were no cases of malignancy and 70% of the soy-treated women had atrophic (inactive) or non-assessable endometrium. However, of concern and relevance to the current NHPD risk statements, is that the occurrence of endometrial hyperplasia was significantly higher in the isoflavone group (3.37% of the subjects (n=4) compared to 0 in the placebo). This difference
was not noted at 30 months which is also relevant since 30-month duration is greater than that of previous studies which did not find any evidence of endometrial hyperplasia with soy isoflavone consumption. Unfer et al. (2004) concluded that the findings call into question the long-term safety of phytoestrogens with regard to the endometrium and that phytoestrogenic supplements should be reconsidered, particularly in women at high risk for endometrial cancer. Although the relevance of these results has been argued in an editorial (Arici and Bukuméz, 2004) and there is epidemiological data to suggest reduced endometrial cancer risk in relation to soy consumption (Goodman et al., 1997; Horn-Ross et al., 2003; Xu et al., 2004), the precautionary principle must prevail and thus this study contributes to the scientific basis for the NHPD risk recommendation statement in relation to soy protein and isoflavone product use in women with a history of gynaecological disease.

Another intervention study of relevance is that of Murray et al. (2003) who examined the interaction between isoflavones and estradiol (E2) on endometrial proliferation by studying 39 postmenopausal women who received various combinations of estrogen replacement therapy and isoflavones (0.5 mg E2 + placebo, 1.0 mg E2 + placebo, 0.5 mg E2 + 25 g soy protein isolate containing 120 mg isoflavones, or 1.0 mg E2 + 25 g soy protein isolate containing 120 mg isoflavones) for 6 months. This pilot study showed that endometrial thickness, hyperplasia and proliferation were similarly affected in all groups. However, there were equal incidences (4/8 in each group) of hyperplasia in soy protein isolate groups and the 1.0 mg E2 + placebo group, which was more than in the 0.5 mg E2 + placebo group (1/8). Although not sufficiently powered, Ki67 proliferative effects were statistically met in both the 1.0 mg E2 + placebo group (P<0.05) and the 0.5 mg E2 + soy protein group (P<0.04), while the 1.0 mg E2 + soy protein group (P<0.07) may have also shown significance if appropriately powered. This potentially means that the isoflavone treatments may affect the endometrium similarly to estrogen replacement therapy and that they did not protect the endometrium from E2-induced hyperplasia. This study highlights the potential for isoflavones to act as an alternative to HRT and therefore rationalizes that risk recommendations relevant to HRT also be relevant to isoflavones.

In addition to the studies by Unfer et al. (2004) and Murray et al. (2003), there have been select case studies documenting gynaecological abnormalities in women who have reported high soy consumption. Noel et al. (2006) reported on a 75-year-old woman who consumed 72 mg/day of ‘super-concentrated’ soy isoflavones (AIE not reported) for 5 years and developed a ureteral malignant mullerian carcinosarcoma in a context of florid endometriosis. The patient had a history of total hysterectomy with bilateral salpingo-oophorectomy 30 years earlier for extensive endometriosis. This is the first case of ureteral mullerian carcinosarcoma arising in endometriosis foci after extensive phytoestrogen supplementation and the data suggest that soy isoflavones (at least in concentrated form) may play a role not only in maintenance of endometriosis but also in its malignant transformation. More recently, Chandrareddy et al. (2008) documented 3 cases that linked intake of soy products (including soy beverage, soy protein concentrate, tofu and soy baloney) with endometrial pathologies including a case of postmenopausal bleeding with uterine polyp, proliferative endometrium and a growing leiomyoma; a case of severe dysmenorrhea, abnormal uterine bleeding, endometriosis and uterine leiomyoma not responding to treatment; and a case of severe dysmenorrhea, abnormal uterine bleeding, endometriosis, uterine leiomyomata and secondary infertility. All three women improved after withdrawal of soy from their diet and the authors concluded that additional information about the safety of phytoestrogen supplementation is required before they can be routinely used. Finally, most recently, Cecchi et al. (2009) reported that a 52-year old Caucasian postmenopausal woman who took soy isoflavones (dose not stated) for 4 months presented with high serum levels of CA 19-9 (66 U/mL, normal range 0-37 U/mL) and upon stopping supplementation, her CA 19-9 returned to normal within one
month. Prior to this, the woman had initially presented with a slight enlargement of the right ovary and uterine fibromyomatosis while on HRT. These findings are relevant as CA 19-9 is a carbohydrate marker of neoplastic disease, and it offers high sensitivity for the mucinous histotype of ovarian carcinoma.

In addition to the concerns raised from Unfer et al. (2004), Murray et al. (2003) and the case studies (Noel et al., 2006; Chandrareddy et al., 2008; Cecchi et al., 2009), it must also be noted that risks related to ovarian structure and function are not easily studied and often inadequately assessed resulting in a potential lack of complete information from the research. As well, women with a history of hormonal and/or gynaecological diseases are often excluded from isoflavone intervention studies resulting in less available safety information for this sub-group. Overall, there is sufficient scientific rationale to apply the precautionary principle for risks related to gynaecological diseases and to require risk statements on all soy protein and isoflavone products providing doses \( \geq 30 \) mg AIE per day stating that before use, women with a personal history of hormonal or gynaecological disease including ovarian cancer, endometriosis and/or uterine fibroids consult a health care practitioner and that women should ensure they are up-to-date on clinical tests such as endometrial ultrasounds/biopsies.

References


SUMMARY OF SCIENTIFIC RATIONALE:

i) On what scientific basis does Health require the following cautionary statement on the labels of all soy protein and isoflavone products providing doses $\geq 30$ mg AIE per day: “Discontinue use and consult a HCP if you experience breast pain, discomfort, soreness and/or tenderness or if you experience a recurrence of menstruation and/or uterine spotting”?

Given that symptoms such as vaginal bleeding and breast pain are side effects of HRT (Doven et al. 1996) and may be an early sign of a more serious abnormality including cancer, the potential for isoflavones to affect these symptoms deserves consideration.

Both breast pain and vaginal bleeding have been noted as an adverse event in clinical studies. For instance, Albert et al. (2002) reported that 2 of their 190 participants reported breast pain in their 4-month study examining 35 mg isoflavones (separated into 2 doses) per day on menopausal symptoms, however; the authors noted that it may not have been directly related to the soy treatment since one of the individuals was under gynaecologic vigilance because of breast microcalcification. Another study found that 4 of their 62 participants reported vaginal bleeding during 3 months consumption of 114 mg soy isoflavones per day, although overall no significant effects were detected in any of the variables measured in the endometrium (Nikander et al. 2005). With respect to bleeding, 8 of 395 participants in the study by Palacios et al. (2007) reported some kind of menstrual bleeding during consumption of 70 mg isoflavones per day for 12 months, yet there were no cases of endometrial hyperplasia or carcinoma. Overall, it must be noted that these observations are not statistically significant and most likely due to chance, yet they must be considered in accordance with the precautionary principle.

Case studies have also flagged concern regarding a possible link between soy isoflavones and vaginal bleeding. As mentioned in an earlier section, a series of 3 case reports by Chandrareddy et al. (2008) documented a case of postmenopausal bleeding with uterine polyp and 2 cases of severe dysmenorrhea with abnormal uterine bleeding that were linked to intake of soy products (including soy beverage, soy protein concentrate, tofu and soy baloney). In addition, a search of Health Canada’s Canada Vigilance Online Database for adverse reactions to “soy” for the period of January 1965 to May 2008 identified 4 relevant reports of adverse reactions to isoflavone-related products that involved either uterine bleeding (Adverse Event Report 134148 (Health Canada 2000)) or breast tenderness (Adverse Event Reports 154898 (Health Canada 2002) and 210296) (Health Canada 2006)).

In addition to these isolated reports, the previously presented evidence (in sections f, g and h) of soy isoflavone interventions causing increased NAF volume (Petrakis et al. 1996), occurrence of breast epithelial hyperplasia (Petrakis et al. 1996), increased proliferative antigen Ki67 in breast epithelial cells (McMichael-Phillips et al. 1998) and increased pS2 in NAF (Hargreaves et al. 1999) are relevant as they demonstrate estrogenic effects of soy isoflavone consumption and provide rationale for a potential link between breast and uterine symptoms with consumption of soy isoflavone products.

Overall, there is sufficient evidence to justify the requirement of a cautionary statement on the labels of soy protein and isoflavone products providing doses $\geq 30$ mg AIE per day for women who experience breast pain, discomfort, soreness and/or tenderness or a recurrence of menstruation and/or uterine spotting to
discontinue use and consult a health care practitioner. This approach is conservative but justified, particularly given the severity of the potential worst case outcome.

References


SUMMARY OF SCIENTIFIC RATIONALE:

j) On what scientific basis does Health Canada require the following cautionary statement on the labels of all soy protein and isoflavone products providing doses $\geq 30$ mg AIE per day: “Consult a HCP prior to use if you are taking blood thinners”?

The idea that any NHP that contains vitamin K can interfere with blood thinning medication is established in a review of the potential interactions between pharmacotherapies and herbal supplements (Brinker 2001; Boon and Smith 2004; Izzo et al. 2005). Since blood thinning/anticoagulant medication is a common cardiovascular pharmacotherapy (Izzo et al. 2005) and soy is a source of vitamin K, their potential interaction warrants consideration. It is also appropriate to examine any potential role of soy’s constituent isoflavones in relation to blood thinning, particularly since many soy supplements may not contain vitamin K.

To this regard, Rios et al. (2008) studied the effect of isoflavones on the coagulation and fibrinolytic system of postmenopausal women. In a double-blinded placebo-controlled design, 47 postmenopausal women consumed 40 mg of soy isoflavone (n=25) or a casein placebo (n=22) each day for 6 months. Results revealed isoflavone-induced significant changes in variables related to coagulation and fibrinolysis including reductions in plasma prothrombin fragments 1 plus 2, antithrombin, protein C and free protein S and an increase in D-dimers; however, these differences were seen within the isoflavone group and were not significantly different from placebo. Due to this, the authors concluded that the study could not support a biologically significant estrogenic effect of soy isoflavones on coagulation and fibrinolysis in postmenopausal women. Nonetheless, the precautionary principle warrants consideration of these results in rationalizing a cautionary statement related to blood thinning.

Also of relevance is a case-report from Cambria-Kiely (2002) who documented that a 70-year old Caucasian man on stable warfarin therapy developed subtherapeutic international normalized ratio (INR) values after consuming soy milk (480 mL/day providing 0.07 µcg vitamin K/day, 55 mg isoflavones/day) for 1 month. The INR values returned to therapeutic concentrations within 2 weeks of soy milk discontinuation and repeated coagulation test results during the next 2 months remained within the normal range.

A point of information more specific to vitamin K is based on the NHPD Multi Vitamin/Mineral Supplement monograph (Health Canada 2007) in which the caution “Consult a health care practitioner prior to use if you are taking blood thinners” is required for all products providing vitamin $K_1$ and $K_2$ at doses $\geq 6$ µg/day for peri- and postmenopausal women.

Overall, a risk statement regarding blood thinning medications is justified for soy products based on the presence of vitamin K in soy and the potential coagulative and/or anti-coagulative effects of isoflavones (40-55 mg/day). Furthermore, given the lack of data on the interaction of up to 39 mg/day isoflavones with
blood thinners and given the known physiological effects from 30 mg/day isoflavone products (Williamson-Hughes et al. 2006), this risk will be applied to all products containing ≥30 mg AIE following the precautionary principle.

References


SUMMARY OF SCIENTIFIC RATIONALE:

k) On what scientific basis does Health Canada require the following cautionary statement on products providing doses above 10 mg AIE per day “Consult a HCP prior to use if you have a liver disorder or develop liver-related symptoms (e.g. abdominal pain, jaundice, dark urine)”?

There has been no documentation to link soy consumption with either jaundice or liver cancer; however, there is minor evidence for a link with changes in liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST) which are common endpoints used to evaluate liver function (Winkel et al. 1975).

In a case-study report, Borghi-Scoazec et al. (2002) documented a 53 year old breast cancer survivor with no history of hepatic disease who had just finished treatment of 20 mg tamoxifen per day when she started soy isoflavone supplementation. She initially supplemented with 17.5 mg of isoflavones per day over 10 months with no negative effects and then increased to 35 mg per day. Within 10 days, she experienced abdominal pain, fatigue, hepatic profile anomalies, but also a normal abdominal ultrasound. As symptoms persisted for the next 2 months, further tests then showed increased serum ALT, AST, gamma GT and
alkaline phosphatase activity at levels from 3.5-20 times higher than normal. Bilirubin levels were also increased, indicating that jaundice could ensue. The symptoms disappeared once the soy isoflavone treatment was stopped and it took 2-4 weeks for the enzyme activity levels to return to normal. Since the woman had no history of hepatic disease, negative viral hepatic tests, an absence of auto-immunity indicators, did not consume alcohol, and took no other medications, there were no other obvious causes to which to attribute the abnormalities.

Beyond this case-report, an intervention study documented a significant increase from baseline in ALT (P<0.001) and AST (P<0.001) in women without hepatic disease who consumed a low-calorie diet in the form of a soy-based meal replacement (isoflavone dose not provided) for 8 weeks (n=104 women); however, the change was described as transient since the levels were back to normal 32 weeks later (n=47 women) (Gasteyger et al. 2008). The authors also noted that the changes were probably of multifactorial origin. In addition to these observations, a search of Health Canada’s Canada Vigilance Online Database for adverse reactions to “soy” for the period of January 1965 to May 2008 has documented reports of elevated liver enzymes (Adverse Event Reports 126290 (HC 1999) and 191425 (Health Canada 2005)), a hepatic malignant neoplasm (Adverse Event Report 219670 (Health Canada 2007a)) and a case of jaundice and abdominal pain (Adverse Event Report 220574 (Health Canada 2007b)) in connection with soy isoflavone supplementation (Health Canada 2009). It is noted, however, that only the case of jaundice and abdominal pain could be linked uniquely to a soy isoflavones product; all other case reports included concomitant administration of other medications and/or supplements.

Inclusion of a risk statement on the labels of soy-containing NHPs regarding a potential risk to health in people with a history of any liver dysfunction or disease is consistent with the precautionary principle and is consistent with concerns regarding liver issues cited within Health Canada’s previously published guidance for HRT products (Health Canada 2006). Given the lack of evidence and the severity of risk for liver-related effects, the cautionary statement will be effective starting from >10 mg AIE per day to practice the most conservative approach.

References


SUMMARY OF SCIENTIFIC RATIONALE:

1) On what scientific basis does Health Canada require the following cautionary statement on products providing doses above 10 mg AIE per day “Consult a HCP prior to use if you are taking thyroid hormone replacement therapy”?

The ability of soy isoflavones to inhibit thyroid peroxidase (Divi et al. 1997; Chang et al. 2000) and induce goiter (in presence of insufficient iodine) in animals (Sharpless et al. 1939; Wilgus et al. 1941; Halverson et al. 1949) has prompted concern for their potential for anti-thyroid effects in humans.

A 2006 review by Messina et al. (2006) concluded that there is little evidence to support an anti-thyroid effect in healthy adults. Of note is that this review included several studies of postmenopausal women which is relevant since postmenopausal women are considered more susceptible (BFR 2007) due to their relatively higher incidence of sub-clinical hypothyroidism (Schindler 2003; BFR 2007). Subsequent to this 2006 review, human intervention studies in healthy men (Dillingham et al. 2007) and postmenopausal women (Teas et al. 2007) have also reported no significant effects of soy protein on circulating thyroid hormones. An exception to this evidence is a 1991 Japanese study that did document anti-thyroid effects in healthy adults (Ishizuki et al. 1991). The study followed 3 groups of adults of heterogeneous age, gender and menopausal status who consumed soybeans pickled in rice-vinegar for 1 or 3 months. When compared to baseline, there were no changes in circulating triiodothyronine (T3) or thyroxine (T4), but there was a significant increase in thyroid stimulating hormone (TSH) and occurrence of goiter among 11 of the 37 subjects. It is relevant to note that this study is limited in design due to its lack of control group, lack of detail about the nutritional composition of the pickled soybeans and uncertainty regarding the iodine intake of the subjects.

Despite the apparent overall lack of effect of soy supplementation on thyroid function in healthy adults, there is evidence for potential concern for the use of soy among hypothyroid adults receiving thyroid replacement. To this issue, a case study documented that a female who was consuming a soy supplement required an elevated dose of thyroid replacement for her complete thyroidectomy (Bell et al. 2001).

Overall, although anti-thyroid effects have not been observed in healthy adults, there is potential concern for those who are hypothyroid (Bell et al. 2001; BfR 2007). The precautionary principle therefore warrants a cautionary statement for those who are taking thyroid replacement therapy to consult a health care practitioner if they consume soy products containing >10 mg AIE.
m) On what scientific basis does Health Canada require the following directions of use on the labels of products providing soy protein: “Take a few hours before or after taking other medications”?

The statement "take a few hours before or after other medications" is based on soy's mineral content. As per NHPD guidance, protein products providing calcium, zinc and iron must include this statement on their Product Licence Application and label [NHPD Multi Vitamin/Mineral Supplement monograph (Health Canada 2007a)]. As per the Canadian Nutrient File (Health Canada 2007b), soy protein products are known to contain each of these minerals to appreciable extents.
According to Health Canada data, soy protein can contain 10.78 mg (standard error ± 0.46 mg) of iron per 100 g of product (Health Canada 2007b). This is equivalent to 0.1078 mg (± 0.0046 mg) of iron per gram of soy protein. Similarly, soy protein can also contain 44.0 µg (± 8.2 µg) of zinc and 3.63 mg (± 0.03 mg) of calcium per gram of soy protein. As soy protein products routinely require ingestion of gram amounts in order to be effective, the statement "take a few hours before or after other medications" is required to mitigate any potential adverse interactive effects.

References


**SUMMARY OF SCIENTIFIC RATIONALE:**

n) On what scientific basis does Health Canada not require risk labelling on soy protein and isoflavone products providing doses ≤ 10 mg AIE per day?

The average Western diet contains between 0.1 to 3 mg AIE per day (Munro et al. 2003; Duffy et al. 2007), with vegetarians consuming an average of 15 mg AIE per day (Munro et al. 2003). Additivity between dietary and supplemental isoflavones sources is not considered a complete measure of the effects of isoflavone exposure due to known differences in their absorption and theoretical metabolic differences due to different soy-food matrix components. Nonetheless, the rationale for not requiring risk labelling on products providing daily doses ≤ 10 mg AIE takes into account the potential for additivity of supplemental and dietary isoflavones, evidence that daily isoflavone doses ≤ 15 mg AIE are biologically inactive, and dietary evidence suggesting that daily doses ≤ 10.2 mg AIE per day do not relate to increased breast cancer incidence over 7 years (Travis et al. 2008).

References


SUMMARY OF SCIENTIFIC RATIONALE:

o) On what scientific basis does Health Canada not require risk labeling targeted to those taking blood pressure medication?

There is insufficient information available to justify special consideration for those taking blood pressure medication. The large Shanghai Women's Health Study which included >45,000 women aged 40-70 years with no history of hypertension, diabetes, or cardiovascular disease found that soy protein intake was inversely associated with both systolic BP (P for trend=0.01) and diastolic BP (P for trend=0.009) (Yang et al. 2005). With respect to intervention studies, a 2003 review of studies investigating soy and blood pressure summarized that there is convincing evidence for a blood pressure lowering effect from clinical trials of soy foods and protein isolates but in contrast, phytoestrogen supplements (containing extracted isoflavones) do not reduce blood pressure (West et al. 2003), a finding most relevant to soy supplements. The 2003 review further summarized that few studies have examined effects of soy products on blood pressure in hypertensive individuals (West et al. 2003). Since this review, Welty et al. (2007) conducted a RCT of 60 normo-, pre- and hyper-tensive postmenopausal women and demonstrated that the observed reducing effect of consuming soy nuts (equivalent to 25 g soy protein and 101 mg AIE) for 8 weeks on systolic and diastolic blood pressure was greater in the pre- and hyper-tensive postmenopausal women. However, in another study of hypertensive adults (15 postmenopausal women, 26 men), 3 months of soy cereal consumption (40 g soy protein, 118 mg isoflavones) reduced daytime blood pressure but did not change average 24 hr ambulatory blood pressure parameters (Teede et al. 2006).

One case report does exist of a hypertensive crisis associated with a high dose soy isoflavone supplementation in a postmenopausal woman without history of hypertension or cardiovascular disease (Hutchins et al. 2005); however, the woman did receive an elevated amount of soy isoflavones [397.5 mg consisting of 250.4 mg genistein (63%), 111.3 mg daidzein (28%), and 35.8 mg glycitein (9%)]. No other reports of adverse blood pressure effects have been identified below this dose.

Overall, there is currently insufficient information to justify a risk recommendation for those taking blood pressure medications. Limited evidence exists for soy foods and soy protein isolates to reduce blood pressure, yet it is weak for extracted isoflavones (West et al. 2003). There is some evidence to demonstrate that soy consumption can reduce blood pressure in hypertensive adults (Rivas et al. 2002; Welty et al. 2007) but no evidence that it can interfere with blood pressure medication.

References


SUMMARY OF SCIENTIFIC RATIONALE:

p) On what scientific basis does Health Canada not require risk labelling targeted to women who did not consume soy regularly during childhood or adolescence?

There is evidence to support the idea that time of exposure will influence the efficacy of soy. In particular, animal (Lamartiniere et al. 2002) and epidemiological (Shu et al. 2001; Wu et al. 2002) studies suggest that soy consumption during childhood and/or adolescence is related to a reduced breast cancer risk. In fact, a review by Warri et al. (2008) suggests that a possible explanation for the discrepancy between the protective role of soy for breast cancer risk reported in meta-analyses (Trock et al. 2006; Qin et al. 2006; Wu et al. 2008), the inconsistent effects of soy on biomarkers of breast cancer risk in human intervention studies, and the results generated in animal studies during adult exposure to soy/genistein is that, to be protective, soy isoflavones may need to be consumed during early life.

Related to the influence of childhood exposure to soy to breast cancer risk, Maskarenic et al. (2006) conducted a longitudinal investigation of mammographic density over 20 years. Change in mammographic density (to reflect breast cancer risk) over time was related to soy intake at various exposure periods including the following: never, as a child only, as an adult only or as both a child and adult. The results showed only minor differences in mammographic density between childhood and adulthood soy exposure. These data contribute to the idea that there is no substantiated evidence to suggest that those who do not consume soy during childhood or adolescence are at risk. Thus, there is no evidence to justify a risk statement for women who did not consume soy regularly during childhood or adolescence.

References


**SUMMARY OF SCIENTIFIC RATIONALE:**

q) On what scientific basis does Health Canada not require risk labelling targeted to vegetarians and women who consume soy regularly?

Vegetarians often consume soy foods as a source of protein. To address the issue of whether there are increased health risks from soy consumption in these individuals, Travis et al. (2008) completed a prospective study of vegetarianism and isoflavone intake in relation to breast cancer. The study included 11,731 vegetarian women who reported a median isoflavone intake of 10.2 mg/day and 25,912 non-vegetarian women who reported a median isoflavone intake of 2.9 mg/day. Following a 7.4 year follow-up period, it was found that there was no significant association between breast cancer risk and vegetarianism (or isoflavone intake), including after adjustment of the data for several potential confounding variables (Travis et al. 2008).

It should be noted that the risk recommendations are referring to soy isoflavone supplementation and in the case of vegetarians, soy consumption is in the form of foods. Further, the risk statements are intended to address specific clinical situations whereas vegetarianism is a healthy situation and thus does not merit caution. Overall, the precautionary principle approach does not flag any evidence to warrant a risk statement for vegetarians in relation to use of soy isoflavone products.

**References**


**SUMMARY OF SCIENTIFIC RATIONALE:**

r) On what scientific basis does Health Canada not require risk labelling targeted to women with a kidney disorder?

As per Health Canada’s guidance on HRT products, conditions that can occur which are related to renal function and kidney health include cystitis, dysuria, sodium retention, fluid retention, and edema (Health Canada 2006). There is no evidence to suggest that isoflavones would alter any of these conditions related to renal function; in fact genistein has been reported to possibly help modulate inward potassium current to
help improve interstitial cystitis (Sun et al. 2007). Further, a search of Health Canada’s Canada Vigilance Online Database for adverse reactions to “soy” for the period of January 1965 to May 2008 has not identified any adverse case reports from soy supplementation that are related to kidney disease (Health Canada 2008).

In patients with end-stage renal disease on hemodialysis, there is some evidence to suggest a cautionary approach to isoflavone supplementation as there is clear evidence of elevated circulating isoflavone concentrations (although metabolite profiles are similar to healthy adults) (Fanti et al. 1999; Fanti et al. 2003). Even in this case, though, a study specifically addressing safety of soy protein (25 g protein, 4 times per week for 4 weeks) in 17 hemodialysis patients showed no evidence of adverse effects (Siefker et al. 2006). Overall, Health Canada has come to the conclusion that there is no justification for risk labelling for patients with renal disorders as it is clear that hemodialysis patients would be under close supervision of a health care team.

References


SUMMARY OF SCIENTIFIC RATIONALE:

s) On what scientific basis does Health Canada require testing for aflatoxins of soy products?

It is relevant to note that soy has been known to contain aflatoxin (Ok et al. 2007), and in this regard special consideration is warranted especially for those who are hepatitis B-positive (Ok et al. 2007). While every batch of product does not need to be tested for aflatoxin (i.e. no specific quality test will be required for each
batch), due to the known presence of aflatoxin in poorly controlled soy products, good collection and manufacturing practices must be followed and include periodic aflatoxin testing of raw materials.

References