Safety of Soy Products

Prepared for: National Safety Associates, Inc.

By:

Clare M. Hasler, Ph.D., M.B.A

September 20, 2004

Safety of Soy Protein Isolates

"Cinderella's Dark Side" is a feature story on Dr. Joseph Mercola's anti-soy website (http://www.mercola.com/article/soy/avoid_soy.htm) which lists a myriad of reasons why we should not consume soy. On this site, soy protein isolate (SPI) is deemed to be "not so friendly" because it "is not something you can make in your own kitchen" (how this relates to the so-called "danger" of soy is completely unclear) and the fact that it contains numerous anti-nutrients such as trypsin inhibitors and goitrogens. This story also states that the high temperature processing of SPI to remove trypsin inhibitors has the unfortunate side effect of "so denaturing the other proteins in soy that they are rendered largely ineffective" suggesting that soy is a poor quality protein source. This synopsis will briefly review the safety and quality of soy with an emphasis on soy protein isolate.

Protein quality. Proteins are an essential component of the diet needed for the survival of animals and humans. Soybeans are a major source of high quality vegetable protein in many countries around the world. Protein constitutes approximately 40% of the total dry matter of soybeans, making this essential nutrient the component present in soybeans in the greatest amount. Soy protein provides calories, nitrogen, as well as essential amino acids–the building blocks of protein. Although there are hundreds of amino acids in nature, only approximately 20 appear in proteins and only nine of these are "essential" which means we need to get them from dietary sources because our bodies do not synthesize them. The essential amino acids include: threonine, cyst(e)ine + methionine, valine, isoleucine, leucine, tyrosine + phenylalanine, histidine, lysine, and tryptophan.

The nutritional quality of proteins is largely dependent on the pattern of amino acids in a particular protein source. More specifically, protein quality refers to how closely a food's essential amino acid (EAA) pattern matches the needs of the body. Plant proteins tend to be limiting in one or more of the EAAs. Like proteins of most other leguminous plants, soy protein is low in sulfur-containing amino acids, with methionine being the most limiting, followed by cyst(e)ine and threonine (Eggum and Beames, 1983). A variety of chemical methods, *in vivo* assays (using either animals or humans), and *in vitro* acids methods (employing various proteinases) have been developed to evaluate protein quality. Since 1919, the preferred method of evaluating protein quality in both the U.S. and Canada has been the Protein Efficiency Ratio (PER). However, this method is based on the growth of young rats and since rats have a higher relative requirement for sulfur-containing amino acids (to support fur growth), the PER method tends to *undervalue* the protein quality of soybeans for humans (Liu, 1999). Another factor important in the determination of protein quality is digestibility, which is an index of bioavailability, and is not included in certain methods of assessing protein quality (e.g., amino acid score). To overcome the limitations of older methods of protein quality evaluation, a new method of evaluating protein quality was adopted by the World Health Organization in 1990 (FAO/WHO, 1990) called Protein Digestibility Corrected Amino Acid Score (PDCAAS). This method is based on a food protein's (1) profile of EAA, (2)

digestibility, and (3) ability to supply EAA in amounts required by humans and is calculated as follows:

$$\text{PDCAAS} = \frac{\text{Amino acid pattern of a protein}}{\text{Amino acid requirements for an organism}} \times \text{digestibility of the protein}$$

The highest possible score using PDCAAS is 1.0. All proteins with a PDCAAS of 1.0 are considered equally high in quality and provide all of the EAAs. According to the FAO/WHO (1990), SPI has a PDCAAS of 1.00, which is equivalent to casein and egg white protein. Thus, based on the PDCAAS method, the protein value of well-processed SPI is essentially equivalent to that of animal proteins and thus can serve as the major, or even sole, source of protein intake (Young, 1991).

Soy anti-nutrients. A basic principle of toxicology is that all chemicals are "toxic chemicals." It is the dose that makes the poison. This tenet holds true for all foods and food components, including soy and soy phytochemicals. More specifically, all foods contain components that, when consumed in excessive amounts, produce unwanted side effects—including the fruits and vegetables that we consume everyday and that are currently promoted for reducing cancer risk! An excellent example was eloquently presented in a classic paper published in the *Proceedings of the National Academy of Sciences*, one of the most prestigious biomedical journals, by Professor Bruce N. Ames of the University of California at Berkley. The review compared synthetic chemicals such as dioxin to natural chemicals, such as those found in broccoli and cabbage and determined that in high-dose tests, a high proportion of both natural and synthetic chemicals are carcinogens, mutagens, teratogens, and clastogens (i.e., agents that cause DNA breakage). In fact, about one-half of the natural "pesticides" that exist in many fruits and vegetables--including cabbage, grapefruit and broccoli--are cancer-causing agents at roughly the same proportion as synthetic pesticides (Ames et al., 1990). Natural toxins have the same mechanisms of toxicity as synthetic toxins. Soybeans contain a broad spectrum of 136 physiologically active components (Fang et al., 2004). Some of these components have been termed "anti-nutrients," which are defined as compounds that hinder the utilization of one or more nutrients and/or adversely affect nutritional status and health. The protease inhibitors have been considered to be a soy-antinutrient.

Protease inhibitors. Two primary types of protease inhibitors are present in soybeans: (1) the Kunitz inhibitor and (2) the Bowman Birk Inhibitor (BBI). The former inhibits the activity of the enzyme trypsin and the latter inhibits both trypsin and chymotrypsin. Approximately 6% of soybean protein is comprised of protease inhibitors (Rackis and Anderson, 1964) and the nutritional significance of this bioactive component has been the subject of considerable debate for many years (Leiner, 1995). Although protease inhibitors have been shown to suppress growth in young animals (Birk, 1993) as well as lead to hypertrophy and hyperplasia of the pancreas and pancreatic cancer at high levels

(McGuiness et al., 1984). There is absolutely no evidence that these effects occur in humans. Further, protease inhibitors are heat labile and about 80% of the trypsin activity is destroyed during the commercial processing of soybeans into soyfoods (Rackis and Gumbmann, 1982). Moreover, considerable research has demonstrated that BBI may have anti-carcinogenic activity (Kennedy, 1994). Protease inhibitors have been shown to have cancer chemopreventive activities both *in vitro* and *in vivo* (Kennedy, 1993). In animal carcinogenesis studies, a concentrate of BBI, BBIC, has been shown to suppress carcinogenesis in a wide variety of in vivo models of various types of cancer, including colon, lung, liver, oral, and esophageal (Kennedy, 1995). Human cancer prevention trials with BBI are ongoing.

Data from human studies suggest that dietary soy or isoflavones are unlikely to have an adverse effect on thyroid function in normal individuals with adequate iodine intake. However, it is *conceivable* that the thyroid function of *hypothyroid* individuals consuming *high levels* of isoflavone supplements *may* be adversely affected. Further, isoflavones could potentially interact with thyroxine medication in individuals diagnosed with congenital hypothyroidism and could lower the amount of thyroxine available in the free (active) form.

The thyroid gland is responsible for the production of hormones involved in regulating metabolism, body weight and oxygen requirements as well as normal growth and development during childhood. There are two primary thyroid hormones: (1) T_3 (tri-iodothyronine) and T_4 (thyroxine), both of which are synthesized in the thyroid gland from iodine and the amino acid tyrosine. The amount of T_3 and T_4 produced by the thyroid gland is controlled by thyroid stimulating hormone (TSH), which is secreted from the pituitary gland and is regulated by the central nervous system.

Goitrogens. It was first reported in the 1930's that soybeans had "goitrogenic" activity in rats (McCarrison, 1933), that is, caused the development of a goiter (an enlargement of the thyroid gland). Since then, other studies have shown that dietary soy or isoflavones can affect the thyroid function of rodents (Balmir et al., 1996; Mitsuma et al., 1998; Ikeda et al., 2000; Son et al., 2001). This is because isoflavones have a similar structure to T_3 and T_4, and studies conducted in vitro demonstrate that the isoflavones inhibit thyroperoxidase (TPO), an enzyme involved in the synthesis of T_3 and T_4. However, although reductions in TPO have been seen in rats fed isoflavones, the remaining activity of this enzyme is sufficient to maintain normal thyroid homeostasis. Further, Chang and Doerge (2000) found no differences in T_3, T_4, TSH concentrations or thyroid gland weight or histopathology in rats continuously fed a soy diet containing 60 mg genistein/kg diet compared with control animals.

Several studies have examined the effect of consumption of soybeans or isoflavones on thyroid function in adults (Duncan et al., 1999a; Duncan et al., 1999b; Persky et al., 2002; Jayagopal et al., 2002). Overall, data from these studies suggest that dietary soy or isoflavones are unlikely to affect thyroid function in normal individuals with adequate iodine intake. However, isoflavones could potentially interact with thyroxine medication given to patients diagnosed with congenital hypothyroidism. If a fixed dose

of thyroxine is used in treatment, ingestion of large amounts of soy isoflavones could lower the amount of thyroxine available in the free (active) form.

Very few studies have investigated the possible associations between soy isoflavones and thyroid cancer. A recent retrospective case-control study involving 1166 subjects in San Francisco (Horn-Ross et al, 2002) which examined the relationship between isoflavone consumption and risk of thyroid cancer actually found that increased consumption of unfermented soy-based foods was associated with a decreased risk of developing thyroid cancer. Tthere is no evidence that soy has an adverse effect on the thyroid gland in normal individuals with adequate iodine intake. Further, populations that consume relatively high amounts of soy (e.g., Japan) do not have a significantly higher incidence of hypothyroidism.

In summary, research continues to demonstrate the healthfulness and safety of soyfoods at doses currently recommended by the Food and Drug Administration, the American Heart Association and other public health organizations. Healthy adults should strive to consume approximately 10 to 25 g/day of soy protein for optimal health. This is not only a practical level of intake, but is also based on the level of soy intake observed in Asian countries (where there is a reduced risk of age-related chronic diseases) as well as evidence from safety and efficacy studies.

References

Ames BN, Profet MN. Gold LS. 1990. Nature's chemicals and synthetic chemicals: comparative toxicology. *Proceedings of the National Academy of Sciences*. U.S.A. 87:7782-7786.

Balmir F, Stack R, Jeffrey E, et al. 1996. An extract of soy flour influences serum cholesterol and thyroid hormones in rats and hamsters. *Journal of Nutrition* 126:3046-3053.

Chang HC, Doerge DR. 2000. Dietary genistein inactivates rat thyroid peroxidase in vivo without an apparent hypothyroid effect. *Toxicology and Applied Pharmacology* 168: 224-252.

Birk Y. 1993. Protease inhibitors of plant origin and role of protease inhibitors in human nutrition. In: *Protease Inhibitors as Cancer Chemopreventive Agents*. Troll W, Kennedy AR (Eds.), pp. 97-106, Plenum, New York.

Duncan AM, Merz BE, Xy X, et al. 1999a. Soy isoflavones exert modest hormonal effect in premenopausal women. *Journal of Clinical Endocrinology and Metabolism* 84:192-197.

Duncan AM, Underhill KEW, Xu X, et al. 1999b. Modest hormonal effects of soy isoflavones in postmenopausal women. *Journal of Clinical Endocrinology and Metabolism*. 84:3479-3484

Eggum BO, Beames RM. 1983. The nutritive value of seed proteins. In: *Seed Proteins, Biochemistry, Genetics, Nutritive Value*. Gottschalk E, Muller HP (Eds.), pp. 499-531, Martinus Nijhof/Junk, Hague.

Fang N, Yu S, Badger T. 2004. Comprehensive phytochemical profile of soy protein isolate. *Journal of Agriculture and Food Chemistry*. 52:4012-4020.

FAO/WHO. 1990. Protein quality evaluation. FAO/WHO Nutrition Meetings, Report Series 51. Food and Agriculture Organization/World Health Organization, Rome.

Ikeda T, Nishikawa A, Son HY, et al. 2001. Synergistic effects of high-dose soybean intake with iodine deficiency, but not sulfadimethoxine or Phenobarbital, on rat thyroid proliferation. *Japanese Journal of Cancer Research* 92:390-395.

Jayagopal V, Albertazzi P, Kilpatrick ES, et al. 1997. Beneficial effects of soy phytoestrogen intake in postmenopausal women with type 2 diabetes. *Diabetes Care* 25:1709-1714.

Kennedy AR. 1993. Overview: anticarcinogenic activity of protease inhibitors. In: *Protease Inhibitors as Cancer Chemopreventive Agents*. Troll W, Kennedy AR (Eds.), pp. 9-64, Plenum Publishing, NY.

Kennedy AR. 1994. Prevention of carcinogenesis by protease inhibitors. *Cancer Research* 54:1999S-2005S.

Kennedy AR. 1995. The evidence for soybean products as cancer preventive agents. *Journal of Nutrition* 125:733S-743S.

Leiner IE. 1995. Possible adverse effects of soybean anticarcinogens. *Journal of Nutrition* 125:744S-750S.

Liu K. 1999. Chemistry and nutritional value of soybean components. In: *Soybeans, Chemistry, Technology and Utilization*, p. 68, Aspen Publishers, Inc., Gaithersburg, MD.

McCarrison R. 1933. The goitrogenic action of soybean and ground-nut. *Indian Journal of Medical Research* 21:179.

McGuiness EE, Morgan RGH, Wormsley KG. 1984. Effects of soybean flour on the pancreas or rats. *Environmental Health Perspectives* 56:205-212.

Mitsuma T, Ito Y, Hirooka Y, et al. 1998. The effects of soybean diet on thyroid hormone and thyrotrophin levels in ageing rats. *Endocrinology Regulation* 32:183-186.

Persky VW, Turyk ME, Wang L, et al. 2002. Effect of soy protein on endogenous hormones in postmenopausal women. *American Journal of Clinical Nutrition* 75:145-153.

Rackis JJ, Gumbmann MR. 1982. The protease inhibitors: physiological properties and nutritional significance. In: *Antinutrients and Natural Toxicants in Foods*. Ory RL (Ed.), p. 203, Food and Nutrition Press, Westport, CT.

Son HY, Nishikawa A, Ikeda T, et al. 2001. Lack of effect of soy isoflavone on thyroid hyperplasia in rats receiving an iodine deficient diet. *Japanese Journal of Cancer Research* 92:103-108.

Soy and Pregnancy

A high estrogenic environment *in utero* may increase subsequent breast cancer risk according to a 1999 study in Oncology Reports highlighted on Dr. Joseph Mercola's website (http://www.mercola.com/1999/archive/pregnant_should_not_eat_soy.htm). The results from this study indicate that in utero exposure to genistein, dose-dependently increased the incidence of breast tumors when compared with controls (Hilakivi-Clarke et al, 1999a). The take home message is, according to the website: "avoid soy, especially if you are a pregnant woman."

This recommendation is simply ludicrous and taken completely out of context as is most information on this website.

Although the study by Hilakivi-Clarke et al. *suggests* that in utero exposure to genistein may increase the incidence of mammary tumors in the offspring, several additional studies are in direct conflict with these findings and support exactly the opposite hypothesis: that in utero exposure to soy isoflavones and genistein in particular may actually reduce breast cancer incidence later in life (Lamartiniere et al., 2000). In addition, another study published the same year by Hilakivi-Clarke et al. (1999b) reported that prepubertal exposure of rats to dietary genistein (1 mg/kg body weight/day) *decreased* the number of tumors per animals as well as tumor growth. Fritz et al. (1998) also showed that perinatal exposure to genistein (from conception to post natal day 21) through the maternal diet (25 or 250 mg genistein/kg diet) resulted in a dose-related decrease in chemically induced mammary tumors in rats. Most importantly, there is no evidence from human epidemiological studies that soy consumption during pregnancy increases the risk of breast cancer.

Exposure to phytoestrogens during development or early life may play an important role in programming hormonal homeostasis and thus influence an individual's later life risk of developing cancer. Although the animal data on breast cancer and exposure to isoflavones is somewhat conflicting (as is the case in most areas of research), a number of studies have shown that genistein has a protective effect in animal models of chemically induced cancer.

In May of 2003, a comprehensive report of the Committee on Toxicology of Chemicals in Food, Consumer Products and the Environment was drafted to advise on the health implications of dietary phytoestrogens through a comprehensive review of published scientific research and the United Kingdom's Food Standards Agency's Phytoestrogen Research Programme. This 441 page report concluded***: "animal studies suggest that exposure to phytoestrogens in early life inhibits development of breast cancer later in life."*** Although this working group recommends that future research examine what effects maternal exposure to phytoestrogens may have on the fetus and on the subsequent health status of the child (because there are no human studies published on this topic), *nowhere in this report does it state that pregnant women should avoid soy during pregnancy*.

There is ample reason to think that research currently underway will show that soy consumption is not contraindicated for women in any situation. In the meantime, pregnant women should feel confident (and in fact should consider) consuming a moderate amount of soy (10-25 grams) and soy isoflavones (30-100 mg) every day (Messina and Messina, 2003) for optimal health.

References

Committee on Toxicity. Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment. Phytoestrogens and Health. Food Standards Agency, May 2003 (http://www.food.gov.uk/science/ouradvisors/toxicity/COTwg/wg.phyto/).

Fritz WA, Coward L, Wang J, Lamartiniere CA. 1998. Dietary genistein, perinatal mammary cancer prevention, bioavailability and toxicity testing in the rat. *Carcinogenesis* 19: 2151-2158.

Hilakivi-Clarke L, Cho E, Clarke R. 1999a. Maternal exposure to genistein during pregnancy increases carcinogen-induced mammary tumorigenesis in female rat offspring. *Oncology Reports* 6:1089-1095.

Hilakivi-Clarke L, Onajafe I, Raygada M. et al. 1999b. Prepubertal exposure to zearalenone or genistein reduces mammary tumorigenesis. *British Journal of Cancer* 80: 1682-1688.

Lamartiniere CA, Zhao XY, Fritz WA. 2000. Genistein: mammary cancer chemoprevention, in vitro mechanisms of action, potential for toxicity and bioavailability in rat. *Journal of Women's Cancer* 2: 11-19.

Messina M, Messina V. 2003. Provisional recommended soy protein and isoflavone intakes for healthy adults. *Nutrition Today* 38 (May/June):100-109.

Soy Infant Formula: A Safe Viable Feeding Option for Infants

"All soy formula is worse than worthless for human infants and is nearly guaranteed to cause problems down the road" according to Dr. Joseph Mercola (http://www.mercola.com/2003/nov/26/soy_formula.htm; accessed June 26, 2004). Not surprisingly, this is the same "expert" who states: "it is important to note that when breast feeding it is wise to avoid drinking milk…" No one would argue that "breast is best" when it comes to infant feeding. The American Academy of Pediatrics is committed to the use of maternal breast milk as the ideal source of nutrition for infant feeding. However, by 2 months of age, most infants in North American are formula-fed; soy-based infant formula now constitute 25% of infant formula sales. Consequently, the nutritional adequacy and safety of soy protein is of paramount importance to this vulnerable segment of the population. Soy protein-based nutrition has been used during infancy for centuries in the orient and experts agree it is a perfectly safe feeding option for infants. This synopsis will *correctly* present the facts on soy infant formula as regards the presence of phytoestrogens, impaired thyroid function, and manganese and aluminum concentrations.

Phytoestrogens. Soy formula is a significant source of two primary isoflavones, daidzein and genistein (Essex, 1996). The main source of isoflavones in the pediatric age group is from soy-based infant formulas and it has been calculated that the daily isoflavone intake of infants may increase from 24.8 mg during the first week of life to 41.0 mg at 4 months of age (Setchell et al., 1997). Thus, when adjusted for body weight, infants exclusively fed soy-based formulas are exposed to isoflavones levels which are 6 – 11 times higher than adults consuming soy foods and 4 to 13-fold higher than the 0.7 mg/kg intake shown to exert significant physiologic effects on the hormonal regulation of the female menstrual cycle (Cassidy et al., 1994). However, it is important to note that 65% of the total isoflavones in soy formulas are present in the conjugated form (Setchell et al., 1997) and it has generally been agreed that isoflavone glycosides cannot be absorbed from the small intestine. Cleavage of the glycosidic bond occurs when the compound reaches the established flora of the large intestine. These bacteria are absent in infants, at least during the first few months of life and thus, most likely greatly reduce their estrogenic effect (Zung et al., 2001). However, the fact that plasma total isoflavone concentrations in infants fed soy-based formulas are 13,000 to 22,000 times higher than the plasma concentrations of estradiol suggests that infants are able to efficiently digest and absorb isoflavones. It has been postulated that isoflavone glycosides are glucuronidated and actively transferred across the jejunum and ileum without the need for bacterial flora (Spencer et al., 1999). However, several in vivo studies have shown that the biologic effects of these high concentrations of isoflavones are mitigated by low bioactivity, which results from their low affinity to estrogen receptors. In a long-term retrospective cohort study, Strom et al. (2001) followed 811 subjects (85% of the initial study cohort) in their 20's or early 30's who, as infants, had been given soy formula (120 males and 128 females) or cow-milk formula (295 males and 268 females) in a clinical trial. This study found no evidence of hormonal or other adverse effects. No statistically significant differences were found in general health and development between the two formula groups in either females or males. In a comprehensive review by Chen and Rogan (2004)

which evaluated the evidence on possible effects of isoflavones in soy infant formula from both experimental and epidemiological studies, the authors concluded, "Limited data did not indicate major developmental or functional disorders related to soy infant formula use…Because the soy-fed infant appears to be exposed to enough compounds to be pharmacologically active and yet there is not indication of such action in the 50 years the formulas have been used, a unified interpretation of the current literature is not possible." **There is no conclusive evidence that indicates that dietary isoflavones may adversely affect human health development or reproduction** (Klein, 1998; Merritt and Jenks, 2004).

Manganese. Manganese is a trace element essential for life. Manganese toxicity is extremely rare, but has been reported in mine workers exposed to high concentrations of manganese dust, resulting in a disorder known as "manganese madness" (PDR for Nutritional Supplements, 2001). There are also a few reports of manganese intoxication occurring in those on long-term total parenteral nutrition (TPN). Dietary or supplemental forms of manganese are quite safe. According to the Food and Nutrition Board of the U.S. National Academy of Sciences, the estimated safe and adequate daily dietary intake (ESADDI) level of manganese for infants aged 0 to 6 months is 300 to 600 mg; up to 10 mg is considered safe (PDR for Nutritional Supplements, 2001). There have been no reports of manganese toxicity in *healthy* infants fed soy-based formulas. Manganese levels in soy-based infant formula are higher than that of human breast milk. Human breast milk contains 1 microgram of manganese per 100 ml while soy-based formulas contain 25 micrograms of manganese per 100 ml. Thus, manganese levels in soy formula are more that of breast milk. Although one group of researchers did report neurotoxicity in rats given 500 micrograms of supplemental manganese (not soy formula) per day (Tran et al., 2002), this level of manganese would be impossible to attain by an infant consuming soy-based formula. In addition, rats absorb manganese differently than human infants and are more prone to manganese toxicity. **There have been no published studies linking the manganese content in soy formula fed to healthy infants to any adverse effect.**

Aluminum. Aluminum, the third most common element after oxygen and silicon, is not considered an essential nutrient for humans. However, it is widespread in food and water supplies because of its presence in soil, water and air. Due to the fact that the soybean plant accumulates aluminum from the soil, soy-based infant formulas are known to contain high levels of aluminum. The aluminum content of human milk is 4 to 65 ng/mL, while that of soy protein-based formula is 600 to 1300 ng/mL (Fomon and Ziegler, 1979). Despite the higher aluminum concentrations in soy formula, serum aluminum levels in breast fed infants do not differ significantly from levels in infants fed soy formula (Litov et al., 1989). Although there was a case report published in the Lancet in 1985 documenting a high concentration of aluminum in the brain of two infants with congenital kidney disease associated with the consumption of soy formula (Freundlich et al., 1985), these same researchers later acknowledged that unrecognizable sources of aluminum (e.g., intravenous fluids) may have contributed to the excessive concentrations of aluminum in the brain (Freundlich et al., 1990). **No other case reports have found problems with aluminum in soy formula.** Aluminum from infant formula is not of

concern for infants with normal kidney function, since the kidney absorbs very little aluminum and that which is absorbed is excreted by the kidney and eliminated through the urine. Further, the aluminum intake of infants using soy formula is only about 25% that of the upper tolerable level established by the Food and Agriculture Organization. The aluminum content of soy formula is not viewed as a contraindication to its use.

Thyroid Function. There is no convincing evidence that soy protein has an adverse effect on thyroid function in healthy human infants consuming adequate iodine (Messina, 2001). There is evidence that animals exposed to large amounts of soy protein will develop goiter, particularly when fed an iodine deficient diet (Filisetti and Lajolo, 1981). This is due to the fact that the principal isoflavones in soy, genistein and daidzein, have been shown to inhibit thyroid peroxidase (Divi et al., 1997) and 5'-deiodinase (Cody et al., 1989), key enzymes involved in thyroid hormone biosynthesis. The inhibition of these enzymes results in decreased levels of circulating thyroid hormones (e.g., T4 and T3), which leads to increased secretion of thyroid stimulating hormone (TSH) by the anterior pituitary. The increased levels of TSH provide a growth stimulus to the thyroid, resulting in goiter. It must be emphasized, however, that this occurs only with very large amounts of soy isoflavones in the diet and/or when the diet is low in iodine. Researchers at the National Center for Toxicological Research in Jefferson, Arkansas have found that, even though substantial amounts of thyroid peroxidase activity are lost when soy isoflavones are consumed by normal rats, the remaining enzymatic activity is sufficient to maintain thryoid homeostasis in the absence of additional perturbations (Chang and Doerge, 2000). Further, dietary soy isoflavones are not the only dietary flavonoids that can inhibit thyroid peroxidase. A variety of other flavonoids have also been shown to be even more potent in inhibiting the activity of this enzyme, including kaempferol, naringenin, and quercetin (Divi and Doerge, 1996). Such flavonoids are widely distributed in plant-derived foods and would be consumed daily at relatively high levels (possibly up to 1 gram or more per day) by vegetarians or semi-vegetarians, yet these individuals do not have a significant increased incidence of goiter. In the late 1950s, 10-15 cases of goiter were identified in infants fed non-iodized soy flour-based infant formula. However, this type of formula has not been used since the 1960s. Today, soy formula is based on soy protein isolate and is fortified with iodine. **No cases of goiter in infants, due to the consumption of soy protein isolate-based iodized formula as is used today, have been reported in the scientific literature**.

Conclusions

Soy infant formula has been used safely by millions of infants over the course of the last several decades. According to a 1998 policy statement from the American Academy of Pediatrics: "In term infants whose nutritional needs are not being met from maternal breast milk of cow milk-based formulas, **isolated soy protein-based formulas are safe and effective alternatives to provide appropriate nutrition for normal growth and development"** (American Academy of Pediatrics, 1998).

References

American Academy of Pediatrics. 1998. Soy protein-based formulas: Recommendations for use in infant feeding. *Pediatrics* 101:148-153.

Cassidy A, Bingham S, Setchell KDR. 1994. Biological effects of a diet of soy protein rich in isoflavones on the menstrual cycle of premenopausal women. *American Journal of Clinical Nutrition* 60:333-340.

Chang, HC, Doerge, DR. 2000. Dietary genistein inactivates rat thyroid peroxidase in vivo without an apparent hypothyroid effect. *Toxicology and Applied Pharmacology* 168:244-252.

Chen A, Rogan WJ. 2004. Isoflavones in soy infant formula: A review of evidence for endocrine and other activity in infants. *Annual Review of Nutrition* 24:33-54.

Cody V, Koehrle J, Hesch RD. 1989. Structure-activity relationships of flavonoids as inhibitors of iodothyronine deiodinase. In: Environmental Goitrogenesis, Gaitan, E. (ed), pp. 57-69, CRC Press, Boca Raton, FL.

Divi RL, Chang HC, Doerge DR. Anti-thyroid isoflavones from soybean. *Biochemical and Pharmacology* 54:1087-1096, 1997.

Essex C. 1996. Phytoestrogens and soy based infant formulas. *British Medical Journal* 313:507-508.

Filisetti TM, Lajolo FM. Effect of the ingestion of soybean fractions, raw or autoclaved, on the rat thyroid. *Arch. Latinoam. Nutr*. 1981;31:287-302.

Fomon SJ, Ziegler EE. 1992. Isolated soy protein in infant feeding. In: New Protein Foods in Human Health: Nutrition, Prevention. Steinke FH, Waggle DH, Volgarev MN (eds), pp. 75-83, CRC Press, Boca Raton, FL,.

Freundlich M, Zilleruelo G, Abitbol C et al. 1985. Infant formula as a cause of aluminum toxicity in neonatal uraemia. *Lancet* 2:527-529.

Freundlich M, Zilleruelo G, Strauss J, et al. 1990. More on aluminum toxic effects in children with uremia. *Journal of Pediatrics*. 117: 1007-1009.

Klein KO. 1998. Isoflavones, soy-based infant formulas, and relevance to endocrine function. *Nutrition Reviews* 56:193-204.

Litov RE, Sickles VS, Chan GM, et al. 1989. Plasma aluminum measurements in term infants fed human milk or a soy-based infant formula. *Pediatrics* 84: 1105-1107.

Merritt RJ, Jenks BH. 2004. Safety of soy-based infant formulas containing isoflavones: the clinical evidence. *Journal of Nutrition* 134: 1220S-1224S.

Messina M. 2001. Soy and Thyroid Function: Studies Show Little Effect. *The Soy Connection* 9 (2), Spring issue.

PDR for Nutritional Supplements. 2001. Hendler SS, Rorvik D (eds.). Medical Economics Company, Montvale, NJ.

Setchell KD, Zimmer-Nechemias L, Cai J, et al. 1997. Exposure of infants to phyto-oestrogens from soy-based infant formula. *Lancet* 5:23-27.

Spencer JP, Chowrimootoo G, Choudhury R, et al. 1999. The small intestine can both absorb and glucuronidate luminal flavonoids. *FEBS Letters* 458:224-230.

Strom BL, Schinnar R, Ziegler EE, et al. 2001. Exposure to soy-based formula in infancy and endocrinological and reproductive outcomes in young adulthood. *Journal of the American Medical Association* 286:807-814.

Tran TT, Chowanadisai W, Crinella FM et al. 2002. Effect of high dietary manganese intake of neonatal rats on tissue mineral accumulation, striatal dopamine levels, and neurodevelopmental status. *Neurotoxicology* 23:635-643.

Zung A, Reifen R, Kerem Z, Zadik A. 2001. Phytoestrogens: the pediatric perspective. *Journal of Pediatric Gastroenterology and Nutrition*. 33:112-118.

Soy and Breast Cancer: What's the Real Story?

The low breast cancer mortality rates in soyfood consuming populations has prompted researchers to examine the role of soy and soy components in reducing the risk of various types of hormone-dependent cancers (Messina et al., 1994; Fournier et al., 1998), particularly breast cancer (Barnes et al., 1997). The relationship between soy intake and breast cancer risk is one of the most controversial areas of soy research today. This is primarily because soy contains isoflavones, which have estrogen-like activity and greater lifetime exposure to estrogen has been associated with increased breast cancer risk. Further, a small number of animal studies resulting from one research group have shown that when immune deficient mice who have had their ovaries removed (to stop estrogen production) were implanted with estrogen receptor positive breast cancer cells and then given the isoflavone genistein, tumor growth was stimulated in comparison to mice not given genistein (Hsieh et al., 1998; Allred et al., 2001). However, this model of breast cancer has been very highly criticized on methodological grounds and cannot be extrapolated to postmenopausal women who have some (albeit low) level of circulating estrogen. Further in a similarly designed experiment in which mice were not ovariectomized (and thus serum estrogen levels were high), genistein actually inhibited, rather than stimulated tumor growth (Shao et al., 1998). Nevertheless some so-called experts state that that soy consumption may actually increase the risk of breast cancer (http://www.mercola.com/2000/aug/20/soy_dangers.htm: accessed August 2, 2004). However, there is absolutely no convincing epidemiological or clinical evidence that soy consumption increases a woman's risk for breast cancer. In fact, some experts state that even breast cancer patients can safely consume moderate amounts of soy (Messina and Loprinzi, 2001). This review will briefly review the role of soy in breast cancer risk and present a balanced view of the evidence.

Interest in the potential role of soy in breast cancer prevention stemmed initially from the observation that women from Southeast Asia have very low rates of breast cancer mortality compared to Western women. For example, the breast cancer death rates (per 100,000) in Japan are 6.7 compared to 27.4 in the U.S. (Meng et al., 1997). In addition, when women from Southeast Asia immigrate to Western countries, their breast cancer rates increase within one to two generations, suggesting that differences in breast cancer rates between Southeast Asian and Western countries are not due to genetics but rather environmental factors (Shimizu et al., 1991), including dietary. Lending further credence to this hypothesis is the fact that soy intake in Southeast Asian populations is significantly higher than that of Western populations (Nagata, 2000). These observations prompted the National Cancer Institute to hold a workshop on the potential role of soy in reducing the risk of cancer, during which five known anti-carcinogenic compounds in soybeans were identified: saponins, phytates, protease inhibitors, phytosterols, and isoflavones (Messina and Barnes, 1991). Of these, it has been unquestionably the isoflavones that have garnered the most research attention. Over 600 research papers are published annually on this soy phytochemical (Lu et al., 2001).

Isoflavones are a type of flavonoid, a class of compounds widely distributed through nature. However, soybeans are the only significant dietary source of these bioactive components as demonstrated in the United States Department of Agriculture's online database: (http://www.nal.usda.gov/fnic/foodcomp/Data/isoflav/isoflav.html). From a biochemical and physiological standpoint, isoflavones are intriguing in that they have a molecular structure similar to that of the human estrogens and thus elicit estrogen-binding activity. However, isoflavones act as weak estrogens, binding to the estrogen receptors with only 10^{-5} and 10^{-2} of the activity of 17ß-estradiol. Additionally, more recent research has demonstrated that isoflavones bind to, and preferentially activate, the newly discovered estrogen receptor, estrogen receptor beta (ER-ß), which is differentially expressed in tissues. Isoflavones are increasingly being viewed as selective estrogen receptor modulators (SERMS), meaning that they exert estrogen-like effects on the bones, coronary vessels and the brain and anti-estrogenic effects on the breast and endometrial tissue (Setchell, 1998). In fact, some experts object to referring to isoflavones as phytoestrogens. SERMs such as tamoxifen (a breast cancer therapeutic agent) and raloxifene (an osteoporosis therapeutic agent) have estrogen-like effects in some tissues but either null or antiestrogenic effects in other tissues. Similarly, soy isoflavones are thought to exert the same beneficial effects of estrogen without the disadvantages, including increasing cancer risk.

With the exception of the studies utilizing athymic, immune-deficient mice discussed above, the bulk of in vivo studies show that soy at least modestly inhibits mammary tumorigenesis in adult animals. Although the addition of soy to a standard laboratory diet does not significantly inhibit tumor *incidence* (the percentage of animals in the group with tumors, in most cases, soy consumption does inhibit tumor *multiplicity* (number of tumors per animal) by 25 to 50% (Haddak et al., 2000). Perhaps the most intriguing animal data come from researchers at the University of Alabama (Lamartiniere, 2000). They have shown that in rats, neonatal exposure to genistein reduces later development of carcinogen-induced mammary cancer by approximately 50% (Lamartiniere et al., 1995a; Lamartiniere et al., 1995b; Murrill et al, 1996). These findings are thought to be due to the fact that exposure to genistein during critical periods of mammary gland development can render the mammary gland less susceptible to DNA damage by carcinogens later in life. These animal studies are supported by recent epidemiological findings. In a recently conducted large scale case-control study in Shanghai (Shu et al., 2001), women who consumed approximately 11 grams of soy protein per day during their teenage years (13-15) were almost 50% less likely to develop breast cancer as adults than adult women who consumed $\leq$2 grams of soy protein/day during this period. Thus, it may be important for adolescent and teenage girls to consume soy daily at a level resembling Asian soy consumption (15 grams of soy protein; 50 mg isoflavones) to reduce risk of breast cancer later in life (Messina and Messina, 2003).

Increases in mammographic density have been associated with a 4- to 6-fold increased risk of breast cancer (Atkinson et al., 1999) and soy intake has been associated with reduced mammographic density patterns. A randomized, placebo controlled study investigating the effect of an isoflavone supplement (40 mg/day) has suggested a significant reduction in density in women aged 56-65 compared to age matched controls

(Atkinson and Bingham, 2002). Similar results were noted in a cross-sectional study in Singapore-Chinese women who were asked to self-report dietary intake of soy and soy isoflavones (Jakes et al., 2002). Women with the highest reported dietary intake of soy and soy isoflavones were associated with low-risk mammographic parenchymal patterns.

Although two human studies have prompted concerns about women with estrogen receptor positive breast cancer consuming soy, both of these studies were methodologically flawed. The first study found that daily consumption of 38 g soy protein over 5 months in premenopausal women was associated with an increase in breast nipple aspirate fluid secretion and breast cell proliferation (Petrakis et al., 1996), which is typically viewed as a marker for increased breast cancer risk (Preston-Martin et al., 1993), but not always (Mommers et al., 1999). However, this study lacked a control group and fluid secretion also continued to increase in women even after soy feeding was discontinued. Further, Bouker and Hilakivi-Clarke (2000) noted that women were eligible for the study only if they were secretors of nipple aspirate fluid. The second study that has raised concern in breast cancer survivors examined the effects of feeding 60 g of textured vegetable protein (containing 45 mg isoflavones) for 2 wk on breast cell proliferation in premenopausal women with benign or malignant breast disease A preliminary analysis of this study based on biopsies from only half of the subjects indicated soy consumption markedly increased breast cell proliferation (McMichael-Phillips et al., 1998). However, in the final analysis, which included all 84 subjects, no such effect on breast cell proliferation was noted (Hargreaves et al., 1999).

In conclusion, on the whole, the evidence suggests that consuming moderate amounts of soy is much more likely to be of overall benefit to health rather than harmful, both in terms of breast cancer risk and other chronic diseases.

References

Allred CD, Allred KF, Ju YH. 2001. Soy diets containing varying amounts of genistein stimulate growth of estrogen-dependent (MCF-7) tumors in a dose-dependent manner. *Cancer Research* 61:5045-5050.

Atkinson C, Warren R, Bingham SA, Day NE. 1999. Mammographic patterns as a predictive biomarker of breast cancer risk: effect of tamoxifen. *Cancer Epidemiology Biomarkers & Prevention* 8:863-866.

Atkinson C, Bingham SA. 2002. Mammographic breast density as a biomarker of effects of isoflavones on the female breast. *Breast Cancer Research* 4:1-4.

Barnes S. 1997. The chemopreventive properties of soy isoflavonoids in animal models of breast cancer. *Breast Cancer Research and Treatment* 46:169-79.

Bouker KB, Hilakivi-Clarke L. 2000. Genistein: does it prevent or promote breast cancer? *Environmental Health Perspectives* 108:701-708.

Fournier DB, Erdman JW, Jr, Gordon GB. 1998. Soy, its components, and cancer prevention: a review of the in vitro, animal, and human data. *Cancer Epidemiology Biomarkers & Prevention* 7:1055-1065.

Hakkak R, Korourian S, Shelnutt SR, et al. 2000. Diets containing whey proteins or soy protein isolate protect against 7,12-dimethylbenz(a)anthracene-induced mammary tumors in female rats. *Cancer Epidemiology Biomarkers & Prevention* 9:113-117.

Hargreaves DR, Potten CS, Harding C, et al. 1999. Two-week dietary soy supplementation has an estrogenic effect on normal premenopausal breast. *Journal of Clinical Endocrinology and Metabolism* 84:4107-4024.

Hsieh CY, Santell RC, Haslam SZ, et al. 1998. Estrogenic effects of genistein on the growth of estrogen receptor-positive human breast cancer (MCF-7) cells in vitro and in vivo. *Cancer Research* 58:3833-3838.

Jakes RW, Duffy SW, Ng FC, et al. 2002. Mammographic parenchymal patterns and self-reported soy intake in Singapore Chinese women. *Cancer Epidemiology Biomarkers & Prevention* 11:608-613.

Lamartiniere CA, Moore J, Holland M, Barnes S. 1995a. Neonatal genistein chemoprevents mammary cancer. *Proceedings of the Society of Experimental Biology and Medicine* 208:120-123.

Lamartiniere CA, Moore JB, Brown NM, et al. 1995b. Genistein suppresses mammary cancer in rats. *Carcinogenesis* 16:2833-2840.

Lamartiniere CA. 2000. Protection against breast cancer with genistein: a component of soy. Am*erican Journal of Clinical Nutrition* 71:1705S-1707S.

Lu LJ, Tice JA, Bellino FL. 2001. Phytoestrogens and healthy aging: gaps in knowledge. A workshop report. *Menopause* 8:157-170.

McMichael-Phillips DF, Harding C, Morton M, 1998. Effects of soy-protein supplementation on epithelial proliferation in the histologically normal human breast. *American Journal of Clinical Nutrition* 68:1431S-1435S.

Meng L, Maskarinec G, Wilkens L. 1997. Ethnic differences and factors related to breast cancer survival in Hawaii. *International Journal of Epidemiology* 26:1151-1158.

Messina M, Barnes S. 1991. The role of soy products in reducing risk of cancer. *Journal of the National Cancer Institute* 83: 541-546.

Messina MJ, Persky V, Setchell KD, Barnes S. 1994 Soy intake and cancer risk: a review of the in vitro and in vivo data. *Nutrition and Cancer* 21:113-131

Messina M, Loprinzi C. 2001. Soy for breast cancer survivors: A critical review of the literature. *Journal of Nutrition* 3095S-3108S.

Messina M, Messina V. 2003. Provisional recommended soy protein and isoflavone intakes for healthy adults. *Nutrition Today* 38:100-109.

Mommers EC, van Diest PJ, Leonhart AM, et al. 1999. Balance of cell proliferation and apoptosis in breast carcinogenesis. *Breast Cancer Research and Treatment* 58:163-169.

Murrill WB, Brown NM Zhyang JX, et al. 1996. Prepubertal genistein exposure suppresses mammary cancer and enhances gland differentiation in rats. *Carcinogenesis* 17:1451-1457.

Nagata C. 2000. Ecological study of the association between soy product intake and mortality from cancer and heart disease in Japan. *International Journal of Epidemiology* 29:832-836.

Petrakis NL, Barnes S, King EB, et al. 1996. Stimulatory influence of soy protein isolate on breast secretion in pre-and postmenopausal women. *Cancer Epidemiology Biomarkers & Prevention* 5:785-794.

Prestin-Martin S, Pike MC, Ross RK, Henderson BE. 1993. Epidemiologic evidence for the increased cell proliferation model of carcinogenesis. *Environmental Health Perspectives* 101 (suppl. 5): 137-138.

Setchell KDR. 1998. Phytoestrogens: the biochemistry, physiology, and implication for human health of isoflavones. *American Journal of Clinical Nutrition* 68: 1333S-1346S.

Shao ZM, Wu J, Shen ZZ, Barsky SH. 1998. Genistein exerts multiple suppressive effects on human breast carcinoma cells. *Cancer Research* 38:4851-4857.

Shimizu H, Ross RK, Bernstein L. 1991. Cancers of the prostate and breast among Japanese and white immigrants in Los Angeles County. *British Journal of Cancer* 63:963-966.

Shu XO, Jin F, Dai Q, et al. 2001. Soyfood intake during adolescence and subsequent risk of breast cancer among Chinese women. *Cancer Epidemiology Biomarkers & Prevention* 10:483-488.

Soy and Menopause

Menopause is defined as the spontaneous, permanent ending of menstruation that is not caused by any medical intervention. In the Western world, most women experience natural menopause between the ages of 40 and 58 with the average age being 51 (North American Menopause Society, 2003). Perimenopause includes the 3-6 year interval before the last period and is characterized by wildly fluctuating hormones resulting in a plethora of symptoms, including hot flashes, night sweats, vaginal dryness, insomnia and mood swings (Love, 2003). The hot flash is the most common discomfort experienced by perimenopausal women.

The potential role for soy and/or soy isoflavones as an alternative for hormone replacement therapy (HRT) (Messina, 2003; Wuttke *et al*., 2003) and particularly in the alleviation of the vasomotor symptoms associated with menopause (Messina and Hughes, 2003) has been a subject of much discussion over the last several years, particularly in light of the results of two large clinical trials: (1) Heart and Estrogen/Progestin Replacement Study and (2) Women's Health Initiative (WHI)—both of which showed that the long-term possible harm of HRT outweighed any potential benefit.

The WHI was a National Institutes of Health (NIH) multi-center trial that began in 1993. One arm of the trial consisted of a randomized, blinded, placebo-controlled hormone study involving 16,608 women, aged 50 to 79 (average age 63.2) who received either placebo or continuous combined estrogen (0.625 mg/day conjugated equine estrogens)-progestogen (2.5 mg/day of medroxy-progesterone acetate) therapy (Prempro). Risk of coronary heart disease (CHD), stroke and breast cancer increased by 29%, 41% and 26%, respectively, while the risk of colon cancer and osteoporosis of the hip and spine decreased 37%, 34% and 34%, respectively (Rossouw et al., 2002). Because of these findings, the combined estrogen-progestogen arm of the trial was terminated after 5.6 years rather than the planned 8.5 years. Although the estrogen-only treatment group was allowed to continue, this arm was also terminated on February 2, 2004 when the NIH concluded that, after an average of nearly 7 years of follow-up, estrogen alone does not appear to affect (either increase or decrease) heart disease, a key question of the study. At the same time, estrogen alone appears to *increase* the risk of stroke similar to what was found in the WHI study of estrogen + progestin when that trial was stopped in July 2002. (http://www.nlm.nih.gov/databases/alerts/estrogen_alone.html, accessed August 7, 2004). No increase in breast cancer was noted. As HRT data have been further analyzed the cardiovascular and dementia risks have also been identified. In summary, according to WebMD Health (http://www.webmd.com/) accessed August 7, 2004):

- HRT-related breast cancers first become apparent after 4 years of HRT use. The number of HRT-related breast cancers increased with each additional year of HRT use. Women taking HRT generally had larger, more advanced tumors than women who developed breast cancer while taking placebo treatment (Rossouw et al., 2002)
- HRT slightly increases heart attack and stroke risk in all healthy postmenopausal women regardless of risk factors (Manson et al., 2003).

- HRT slightly increases the risk of blood clots in the lungs and legs in all healthy postmenopausal women regardless of risk factors (Wassertheir-Smoller, 2003)
- HRT increases the risk for Alzheimer's disease and other dementias in women aged 65 and older. The increased risk first becomes apparent in women taking HRT for more than 4 years. The WHI researchers have concluded that HRT does not provide protection from dementia or cognitive impairment, as was previously believed (Shumaker et al., 2003).
- Among HRT users, the number of abnormal mammograms increases by approximately 4% per year, first apparent after 1 year of HRT use. Daily estrogen plus progestin increased breast density compared to estrogen alone or placebo.

The Heart and Estrogen/progestin Replacement Study (HERS), was a randomized clinical trial of estrogen plus progestin, with or without statin drugs, vs. placebo, in 2763 postmenopausal women with heart disease. HRT resulted in a statistically significant increase in early risk for primary events in women who did not use statins (Relative Hazard =1.75, 95% CI 1.02 to 3.03, P=0.04) but not in statin users (RH=1.34, 95% CI 0.63 to 2.86, P=0.45).

Due to findings from the WHI and HERS studies, the percentage of women aged 50 to 74 taking HRT has declined from 42% in 2001 to 38% in July 2003. The decline in the use of Prempro, the specific type of HRT used in the WHI has been even more dramatic—decreasing by 70%. Women are seeking alternatives to HRT and one of the leading alternatives they are turning to is soy.

The role of soy in the amelioration of hot flashes and night sweats associated with menopause was first noted more than 10 years ago by Lock (1991) in a survey of over 2,600 Japanese and Canadian women. She noted that 30.9% of the Canadian women had experienced a hot flash in the preceding two weeks compared to only 9.7% of the Japanese women. In addition, only 3.6% of the Asian women experienced night sweats compared to 19.6% of the Canadian women. These findings are consistent with the fact that approximately two-thirds of North American women experience perimenopausal hot flashes (North American Menopause Society, 2003) while American women of Chinese and Japanese ancestry are about one-third less likely to report experiencing hot flashes (Gold et al., 2000).

It was first suggested by Adlercreutz et al. (1992) that the estrogen-like properties of isoflavones might explain the low incidence of hot flashes reported by women in Japan. Since that time, more than two-dozen clinical trials have been conducted to investigate the efficacy of either soy or red clover isoflavones in alleviating hot flashes. A recent review of 19 trials involving more than 1,700 women evaluated the efficacy of soyfoods and isoflavones supplements for the alleviation of hot flashes (Messina and Hughes, 2003). Overall, they found that there was a statistically significant relationship (p=0.01) between initial hot flash frequency and treatment efficacy with initial hot flash efficacy explaining about 46% of the treatment effects. The frequency of hot flashes decreased by approximately 5% (above placebo or control effects) for every additional hot flash per day in women who experienced five or more hot flashes per day. More specifically, of the 11 studies that examined the effects of soyfoods (see references 48-58 in the review

by Messina and Hughes), only one (Albertazzi et al., 1998) found a statistically significant decrease in hot flash frequency in the treatment versus the control group. Although an additional study by Washburn et al. (1999) found that soy protein isolate reduced hot flash severity but not incidence, this only occurred when the isolate was consumed twice per day.

In contrast to the relative lack of effect of soy foods on hot flashes, four out of five studies utilizing isoflavones supplements indicate a statistically significant decrease in hot flashes compared to the control treatment (Upmalis et al., 2000; Scambia et al., 2000; Han et al., 2002; Faure *et* al., 2002). The isoflavones concentrations in these studies ranged from 50 mg to 100 mg per day and resulted in an absolute percent change in hot flash frequency versus the treatment group ranging from 19.5% to 35.8%. The authors conclude: "Although conclusions based on this analysis should be considered tentative, the available data justify the recommendations that patients with frequent hot flushes consider trying soyfoods or isoflavones supplements for the alleviation of their symptoms" (Messina and Hughes, 2003). In a recent position statement, the North American Menopause Society recommends that, for relief for mild vasomotor symptoms, women should first consider lifestyle changes, either alone or combined with a nonprescription remedy, such as *dietary isoflavones*, black cohosh, or vitamin E.

References

Albertazzi P, Pansini F, Bonaccorsi G. *et al*. 1998. The effect of dietary soy supplementation on hot flushes. *Obstetrics and Gynecology* 91:6-11.

Adlercreutz H, Hamalainen E, Gorbach S, *et al.* 1992. Dietary phyto-oestrogens and the menopause in Japan. *The Lancet* 339:1233.

Faure ED, Chantre P, Mares P. 2002**.** Effects of a standardized soy extract on hot flushes: a multicenter, double-blind, randomized, placebo-controlled study. *Menopause* 9:329-334.

Gold EB, Sternfeld B, Kelsey JL *et al.* 2000. Relation of demographic and lifestyle factors to symptoms in a multi-racial/ethnic population of women 40-55 years of age. *American Journal of Epidemiology* 152:463-473.

Han KK, Soares JM, Jr, Haidar MA, *et al*. 2002. Benefits of soy isoflavone therapeutic regimen on menopausal symptoms. *Obstetrics and Gynecology* 99:389-394.

Herrington DM, Vittinghoff E, Lin F, et al. 2002. Statin therapy, cardiovascular events, and total mortality in the Heart and Estrogen/Progestin Replacement Study (HERS). Circulation 105:2962-2667.

Manson JE, et al. 2003. Estrogen plus progestin and the risk of coronary heart disease. *New England Journal of Medicine,* 349: 523–534.

Rossouw et al, 2002. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *Journal of the American Medical Association* 288:321-333.

Lock M. 1991. Contested meaning of the menopause. *The Lancet* 337:1270-1272.

Love SM. 2003. What does it feel like? In: Dr. Susan Love's Menopause & Hormone Book, pp.46-72, Three Rivers Press, New York.

Messina MJ. 2003. Potential public health implications of the hypocholesterolemic effects of soy protein. *Nutrition* 19:280-281.

Messina M, Hughes C. 2003. Efficacy of soyfoods and soybean isoflavone supplements for alleviating menopausal symptoms is positively related to initial hot flush frequency. *Journal of Medicinal Food* 6:1-11.

North American Menopause Society. 2003. Menopause guidebook. The North American Menopause Society, Cleveland, OH.

North American Menopause Society. 2004**.** Treatment of menopause-associated vasomotor symptoms: position statement of The North American Menopause Society. Menopause. 11:11-33.

Scambia G, Mango D, Signorile PG et al. 2000. Clinical effects of a standardized soy extract in postmenopausal women: a pilot study. *Menopause* 7:105-111.

Shumaker SA, et al. 2003. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women. The Women's Health Initiative memory study: A randomized controlled trial. *Journal of the American Medical Association* 289: 2651–2662.

Washburn S, Burke GL, Morgan T, Anthony M. 1999. Effect of soy protein supplementation on serum lipoproteins, blood pressure, and menopausal symptoms in perimenopausal women. *Menopause* 6:7-13.

Upmalis DH, Lobo R, Bradley L, et al. 2000. Vasomotor symptom relief by soy isoflavone extract tablets in postmenopausal women: a multicenter, double-blind, randomized, placebo-controlled study. *Menopause* 7:236-242.

Wassertheir-Smoller S. 2003. Effect of estrogen plus progestin on stroke in postmentopausal women. The Women's Health Initiative: A randomized trial. *Journal of the American Medical Association* 289: 2673–2684.

Wuttke W, Jarry H, Becker T. 2003. Phytoestrogens: endocrine disrupters or replacement for hormone replacement therapy. *Maturitas* 44 (suppl.):S9-S20.

Soy and Brain Function: Fact vs. Fiction

"Soy shrinks the brain" is the proclamation seen on many "anti-soy" websites. Such sites state that this sobering soybean revelation is "for real" and not "science fiction."

The reality is that concerns about soy consumption and brain dysfunction are based almost exclusively on a single study from the Honolulu-Asia Aging Study published by Dr. Lon White and his colleagues in 2000 (White *et al,* 2000). The study had many confounding factors and limitations as discussed below.

This prospective, epidemiologic (population-based) study involved 3,734 Japanese-American men living in Hawaii who were tested with the Cognitive Abilities Screening Instrument (CASI) during a 1991-1994 examination. During that time, the subjects were asked about tofu consumption at two different time points during midlife: 1965-1967 and 1971-1974. The investigators found that poorer cognitive test performance in later life was weakly associated with a more oriental midlife diet. More specifically, men who consumed tofu approximately 2-4 times per week had odds ratios (OR) in the range 1.6 to 2.85 when compared with those eating less than 2 servings/week during the 30 year follow-up period. For markers of cognitive impairment (i.e., poor cognitive test scores), the OR was 1.62 (CI 1.06-2.46); for low brain weight the OR was 2.08 (CI 0.97-11.45) and for ventricular enlargement the OR was 2.85 (CI 0.73-11.16).

It must be noted that epidemiologic studies such as this one cannot be used to establish *cause and affect relationships*; they can only identify *associations*. This study relies on the accuracy of tofu intake data and the results may have been influenced by inaccuracies resulting from the imprecise nature of the methodology employed as discussed in greater detail below. The realities of the study conducted by White and colleagues are these:

1. Tofu consumption may be an *indicator, not a cause,* of other risk factors associated with dementia. There are many environmental and genetic factors involved in the development of dementia. It is possible that other foods or lifestyle factors linked with high tofu consumption, not the consumption of tofu per se, were responsible for the relationship found.

2. East Asian countries have a lower incidence of dementia and tend to have a lower incidence of Alzheimer's disease than do European countries. Therefore, it would be inconsistent to conclude that high tofu consumption (which is indicative of an Asian lifestyle) increases the risk of dementia if rates of dementia increased as a Western lifestyle is adopted.

3. An article published by Dr. White in the Journal of the American Medical Association in 1996 (White et al., 1996) found that dementia was probably more prevalent among those men who did not return for cognitive exams compared to those who participated. The absence of data from these men could have greatly skewed the study results, particularly if they were low tofu consumers. Inclusion of data from these men in the study might have shown that dementia levels do not change with the amount

of tofu consumed. In fact, in a letter to the editors of the Journal of the American College of Nutrition (Guo et al., 2000), it was pointed out that handling of missing data for 596 individuals in the 2000 study by White could have led to an overestimation of the odds ratios. More specifically, there were 596 individuals who were nonrespondants to the 1971-1974 interview and hence provide no information for the second measurement of tofu consumption. White and his colleagues assigned missing values for all 596 individuals and treated them as reporting having one serving of tofu per week. This could have resulted in a biased overestimation of odds ratios.

4. Many foods in addition to tofu comprise a traditional Asian diet. Dr. White's study looked at only 26 of these foods. In addition, the form documenting dietary intake in 1965 may not have been the best tool to collect these data. The revision of the tool for the 1971 collection changed the way tofu intake was recorded. Tofu intake may not have been accurately measured when these two data sets were combined for Dr. White's analysis.

5. Finally, and most importantly, this is only a single study. No public health recommendations should even be hinted at, let alone declared, with such a paucity of data. More recent research supports the hypothesis that soy isoflavones may have a *beneficial*, not a harmful, effect on cognitive function. Animal studies have demonstrated that following dietary administration, soy isoflavones enter the brain in sufficient quantities to activate estrogen receptor ß, a newly discovered estrogen receptor to which isoflavones appear to preferentially bind (Enmark and Gustafsson, 1999). Moreover, administration of soy isoflavones has been shown to improve cognitive function in female rats (Pan et al., 2000; Lephart et al., 2002).

According to a recent comprehensive report on Phytoestrogens and Health prepared by Food Standards Authority Committee on Toxicity (2003), the report by White et al., 2000 did not provide sufficient evidence to confirm the association between high levels of consumption of soy-based foods and decreased cognitive function in a group of Japanese-American men and women as the report "lacked sufficient detail and the associations may have resulted from inaccuracies in the methods employed."

More importantly, three clinical intervention studies (one in young men and women and two in postmenopausal women have found that a high soy diet (100 mg isoflavones per day) or the use of isoflavone supplements (60 – 70 mg/day) favorably affected several aspects of memory and cognition.

In the first study by File et al. (2001), the effects of soy on cognitive function were assessed in a 10-week placebo-controlled intervention trial of student volunteers aged 22-30 years (15 males and 12 females) who were matched for age, IQ, measures of anxiety and depression and caffeine intake. Subjects consumed calorically equivalent diets containing 0.5 or 100 mg total isoflavones per day. Tests of cognitive function were assessed relative to a pre-study baseline and compared with the placebo group. The tests included measures of attention, short-and long-term memory and mood. Subjects in the high isoflavone group showed small but statistically significant improvements in tests of

short and long term memory ($p < 0.05$), mental flexibility ($p < 0.05$) and were treated as more restrained in a self-assessment of mood ($p < 0.05$).

A second study by Kris-Silverstein et al. (2001) involving 56 women (ages 55-74) randomly allocated to placebo or soy isoflavones (110 mg/day) for 6 months found that those receiving soy showed significantly greater improvement in category fluency, story recall, and task planning, suggesting that isoflavone supplementation has a favorable effect on cognitive function, particularly verbal memory, in postmenopausal women.

In a third study by Duffy et al., (2003), 33 postmenopausal women (50-65 years) not receiving convention hormone replacement therapy (HRT) were randomly allocated in a double-blind parallel study to receive a soy supplement (60 mg total isoflavone equivalents/day) or placebo for 12 weeks. They received a battery of cognitive tests and completed analogue rating scales of mood and sleepiness before the start of treatment and then after 12 weeks. Those receiving the isoflavone supplement showed significantly greater improvements in recall of pictures and in a sustained attention task. Isoflavone supplementation also significantly improved learning rule reversals and task planning.

In conclusion, does soy in fact "shrink the brain"? To the contrary, soy isoflavone consumption appears to favorably affect several aspects of memory and cognition, although the overall data are too limited to be used for the basis of intake recommendations at this time (Messina and Messina, 2003).

References:

Committee on toxicity. 2003. Committee on toxicity of chemicals in food, consumer products and the environment. Phytoestrogens and Health. The Food Standards Agency, London.

Enmark E, Gustafsson JA. 1999. Oestrogen receptors—an overview. *Journal of Internal Medicine* 246:133-138.

File SE, Duffy R, Wiseman H. 2001. Improved memory and frontal lobe function after 3 months' treatment with soy supplements. *European Journal of Psychopharmacology* 157: 430-436.

Duffy R, Wiseman H, File SE. 2003. Improved cognitive function in post-menopausal women after 12 weeks of consumption of a soya extract containing isoflavones. *Pharmacology Biochemistry and Behavior* 75:721-729.

Guo G, Wilkens LR, Maskarinec G, Murphy S. 2000. Examining associations of brain aging with midlife tofu consumption. *Journal of the American College of Nutrition* 19:467 (letter to the editor).

Kritz-Silverstain D, Von Mű̈hlen D, Barrett-Connor E, Bressel MAB. 2003. Isoflavones and cognitive function in older women: the Soy and Postmenopausal Health in Aging (SOPHIA) Study. *Menopause: The Journal of the North American Menopause Society* 10:196-202.

Lephart ED, West TW, Weber KS, et al. 2002. Neurobehavioral effects of dietary soy phytoestrogens. *Neurotoxicology and Teratology* 24: 5-16.

Messina M, Messina V. 2003. Provisional recommended soy protein and isoflavone intakes for healthy adults. *Nutrition Today* 38:100-109.

Pan Y, Anthony M, Watson S, Clarkson TB. 2000. Soy phytoestrogens improve radial arm maze performance in ovariectomized retired breeder rats and no not attenuate benefits of 17 ß-estradiol treatment. *Menopause: The Journal of the North American Menopause Society* 7: 230-235.

White LR, Petrovitch H, Ross W, et al. 2000. Brain aging and mid-life tofu consumption. *Journal of the American College of Nutrition* 19:242-255.

White L, Petrovitch H, Ross GW, et al. 1996. Prevalence of dementia in older Japanese-American men in Hawaii: the Honolulu-Asia Aging Study. *Journal of the American Medical Association* 276:955-960.

.