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January 24, 2005

Docket # 2004Q-0151 Solae Company Health Claim on Cancer

Dear Ms. Anderson:

Please consider the attached document regarding the Qualified Health Claim: Soy Protein and Cancer. This represents our response to the Solae Company's letter of August 17, 2004 posted August 20, 2004 in Docket #2004Q-0151, in which Solae attempted to dismiss the many valid and carefully referenced concerns raised by the Weston A. Price Foundation.

We maintain that Solae has still not established the safety of soy protein; that it has chosen to dismiss well-designed studies that show adverse effects on the thyroid; reproductive and other systems of the body; that it has failed to prove that soy protein prevents cancer; and that it has ignored evidence showing that soy protein can contribute to or even cause cancer. Both our original submission dated June 14, 2004 and this rebuttal refute Solae's contention that their data establish that there is "consensus among experts qualified by scientific training and experience to evaluate such claims regarding the relationship between soy protein products and a reduced risk of certain cancers."

We especially wish to bring to the attention of the FDA a statement on page 22 of Solae's document in which Dr Yan and Dr. Potter write: **"**It is important to note that flavonoids are not constituents of soy." This statement is not true, and is an error so elementary that it casts doubt on the expertise of Solae's scientific advisers and the credibility of its document.

Solae concludes its document with the words "We urge FDA to expedite publication of their ruling so food manufacturers can convey this important dietary health information to consumers on food labels." Rather, we urge the FDA to protect the American consumer and to promptly reject Solae's soy protein/cancer health claim.

The following are excerpts from Solae's August 17, 2004 letter and our response to their comments.

1. GRAS STATUS OF SOY PROTEIN

In 1999 Archer Daniels Midland (ADM) Corporation submitted a petition requesting GRAS status for soy isoflavones. This petition was returned by CFSAN because of ADM's failure to properly report adverse effects. Solae is correct in stating that ADM had intended to obtain GRAS status for soy isoflavones and not soy protein. However isoflavones are a constituent found in virtually all soy protein products that reach the marketplace. In 1999 Daniel M. Sheehan, Ph.D., and Daniel R. Doerge, Ph.D., expert toxicologists from the FDA's National Laboratory for Toxicological Research urged the FDA to reject a health claim for soy protein and coronary heart disease, in part, because the known dangers of the soy isoflavones in soy protein.

We disagree with Solae's claim that soy protein is "safe and lawful." As we established in our original comments to the FDA dated June 14, 2004, soy protein was NOT widely used in the food supply prior to January 1, 1958 (although it was used prior to that date as an industrial product to bind and seal paper products). We maintain that there are valid reasons for the fact that soy protein was not officially granted GRAS status in 1979 and that the safety issues raised by the Select Committee on GRAS Substances (SCOGS) have yet to be resolved. The fact that soy protein is widely found in the food supply today does not prove its safety. Furthermore, we would like to remind the FDA of the language it used regarding GRAS status in the Proposed Rule, Food Labeling: Health Claims: Soy protein and Coronary Heart Disease (63 FR 62977). "FDA tentatively concludes that the petititioner has provided evidence that satisfies the requirement in §101.14 (b)(3)(ii) that use of soy protein at the levels necessary to justify the claim is safe and lawful. We believe that the word "tentatively" acknowledges that the FDA recognizes that the GRAS issue has not been resolved.

Solae predicts that soy protein consumption would likely double in the United States following approval of another health claim. This possibility makes it imperative

that the concerns voiced by the Select Committee on GRAS substances (SCOGS) in 1979 about lysinoalanine, nitrites and nitrosamines be addressed. Today, more than 30 years later, these safety studies have yet to be carried out. Today, Americans eat ten times more soy protein isolate (SPI) – and other highly processed forms of soy included in readymade foods – than they did in 1979. Vegetarians who rely on meat substitutes, analogues, energy bars, shakes and other products made with soy protein isolate and health conscious individuals who may dramatically increase their soy consumption because of claims that it prevents cancer could easily consume 100 times more than the 150 mg SCOGS determined as safe. Leading toxicologists, endocrinologists and other expert scientists have repeatedly questioned the safety of soy protein because of the known presence of antinutrients (trypsin inhibitors, phytates, lectins, saponins and oxalates) as well as the plant hormones known as phytoestrogens. A large body of research exists documenting these hazards, refuting Solae's claim that "there are no known safety hazards associated with ISP, SPC [soy protein concentrate], SF or other soy protein foods." Until soy protein is given a clean bill of health by qualified researchers without ties to the soy industry, soy protein must not be assumed safe.

2. PROCESSING OF SOY PROTEIN PRODUCTS DO NOT RESULT IN HARMFUL LEVELS OF CARCINOGENIC SUBSTANCES.

Solae claims that nitrosamines "are not present in soy foods." This statement is untrue. Nitrites, precursors to nitrosamines, have always been present in soy protein products. In 1979, the SCOGS committee reported to the FDA that the nitrites found in soy protein – either directly in soy food or indirectly from migration from the soy protein isolate used in packaging – was likely to be so small (50 parts per million) and that nitrosamines would not pose a health hazard to the public because the average person consumed no more than 150 mg per day of soy protein.[1] Today, people are consuming ten times more soy protein than they did in 1979. In addition to containing nitrites, soy protein isolates and other products that have undergone acid washes, flame drying or high temperature spray-drying processes that contribute preformed nitrosamines. In USDA studies undertaken in

the 1980s, researchers found that soy protein isolate contained about twice the nitrite content found in other soy protein products, including overly toasted soy flour. They also found levels of 1.5 parts per billion of a potent nitrosamine known as N-nitrosodimethylamine (NDMA) in soy protein.[2] More recently, this highly volatile nitrosamine has been found in significant quantities in SPI.[3]

The California Environmental Protection Agency Office of Environmental Health Hazard Assessment has established safe levels for nitrosamines ranging from 40 ng per day for NDMA to 80 ug per day for the relatively weak nitrosamine N-nitrosdiphenylamine. According to Mike Fitzpatrick, Ph.D., a person who eats 100 grams of soy protein would exceed safe levels if NDMA is present in excess of 0.20 parts per billion in steam-treated soy flour or 0.36 parts per billion in soy protein isolate. The safe level of N-nitrosdiphenylamine would be exceeded if present at levels in excess of 0.42 parts per million in steam-treated soy flour or 0.72 parts per million in soy protein isolate. Though very little information has been published on the levels of nitrosamines in soy products – and levels vary from batch to batch – this level of toxicity is not only possible but likely. Taking the USDA finding of 1.4 parts per billion, people eating 100 grams per day of soy protein – a goal promoted as healthful by Protein Technologies International (PTI) in their 1999 petition to the FDA and already consumed by some health-conscious Americans -- could be exposed daily to 35 times the safe limit of NDMA. Finally, Dr. Fitzpatrick notes that the safe levels are defined for a 70 kg adult male and that lower levels should be established for adult women, teenagers, children and infants.[4]

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Solae states that “modern processing procedures eliminate the potential for lysinoalanine production.” This statement is also untrue. Lysinoalanine is a cross-linked amino acid that is produced when the essential amino acid lysine is subjected to strong alkaline treatments. The modern food processing industry uses alkali to turn soybeans into soymilk, tofu, textured soy protein (TSP), SPI, soy protein concentrate (SPC) and other products quickly and profitably. Only old-fashioned, fermented soy products or precipitated tofu made at home or in small, cottage-type industries can bill themselves as "lysinolanine-free."[5,6]

Ghulam Sarvar, Ph.D., of the Nutrition Research Division of the Banting Research Centre in Ottawa, writes: "The data suggested that LAL (lysinoalanine), an unnatural amino acid derivative formed during processing of foods, may produce adverse effects on growth, protein digestibility, protein quality and mineral bioavailability and utilization. The antinutritional effects of LAL may be more pronounced in sole-source foods such as infant formulas and formulated liquid diets which have been reported to contain significant amounts (up to 2400 ppm of LAL in the protein) of LAL"[7]

The highest levels of lysinoalanines are found in soy protein isolates manufactured using high alkaline solutions for use as sizing and coating adhesives for paper and paperboard products. Rats fed soy proteins processed using similar high-alkali baths have suffered kidney damage, specifically increased organ weights, lesions and kidney stones. The soy industry assures us that soy proteins intended for human consumption are safer because they are extracted at a pH level below 9.[8-11] A look at new processes receiving patents today, however, reveals that the food processing industry has not made it a priority to keep alkaline levels low. For example, Kraft recently developed a process to "deflavor" soy milk, flour, concentrates and isolates by adjusting the pH to a level ranging from 9 to 12. This makes it possible to dissolve the soy proteins and release the "beany" flavors through a special ultrafiltrated membranous exhaust system.[12]

Other cross-linked amino acids, whose toxic effects are suspected but not yet thoroughly researched, may also occur as a result of high alkali baths. Arginine, an important amino acid for proper growth, may be converted to the amino acid ornithine and from there into the problematic ornithinoalanine. Threonine produces methyl-dehydroalanine, which can undergo further reactions to form methyl-lysinoalanine and methyl-lanthionine. Cysteine can produce dehydroalanine and methyl-dehydroalanine.[13-15]

Solae continues its claim of safety for soy protein by stating that the Bowman-Birk and Kunitz trypsin inhibitors in soybeans "are inactivated by heat applied during modern processing techniques." This statement is only partially true.

Heat deactivates most – but not all – the protease inhibitors in soy. The only way to deactivate all of them is through the fermentation techniques used to make tempeh, miso and natto.[16] Otherwise some trypsin inhibitors *always* remain. The heat,

pressure and chemical treatments used by modern food processors reduce all the different protease inhibitors by 80-90 percent. At best, this 80- 90 percent success rate is a promise, not a guarantee. The level of live protease inhibitors remaining in soy products varies from batch to batch, and investigators have found unexpectedly high protease inhibitors present in soy foods, and startlingly high levels in some soy formulas and soy protein concentrates.[17-22]

Levels of trypsin inhibitors are not only higher in genetically modified (GM) soybeans but also stubbornly resistant to deactivation by "toasting," a heat treatment typically used by food processors. Researchers performing safety tests for Monsanto found that the only way to eliminate sufficient numbers of the trypsin inhibitors was to toast the GM soybean repeatedly, causing destruction of the most of the value of the soy protein at the same time. This and other evidence suggest that genetically modified soybeans are not "substantially equivalent" to conventional soybeans and that safety issues have not been properly addressed.[23] Yet, soy foods made with both GM and regular soybeans would be eligible for the proposed health claim.

1. Life Sciences Research Office, Federation of American Societies for Experimental Biology for the Bureau of Foods, Food and Drug Adminsitration, 1979, Contract #FDA 223-75-2004. Evaluation of the health aspects of soy protein isolates as food ingredients.

2, Rackis JJ, Gumbmann MR, Liener IE. The USDA trypsin inhibitor study: 1. Background, objectives and procedural details. *Qual Plant Foods Hum Nutr*, 1985, 35, 225.

3. Fazio T, Havery DC. Volatile n'nitrosamines in direct flame dried processed foods. *IARC Sci Publ,* 1982, 41, 277-286.

4. Fitzpatrick, Mike. Response to a submission by Protein Technologies International petition for a soy/coronary health claim, n.d.

5. Life Sciences Research Office.

6. Friedman M. Lysinoalanine in food and in antimicrobial proteins. *Adv Exp Med Biol,* 1999, 459, 145-149.

7. Sarwar G, L'Abbe MR et al. Influence of feeding alkaline/heat processed proteins on growth and protein and mineral status of rats. *Adv Exp Med Biol,* 1999, 459, 161-177.

8. Life Sciences Research Office.

9. Liener IE, Implications of antinutritional components in soybean foods. *Crit Rev Food Sci Nutr,* 1994, 34, 1, 31-67.

10. Yannai, Shmuel. Toxic factors induced by processing. In Irvin E Liener, ed. *Toxic Constituents in Plant Foodstuffs* (NY Academic, 2nd ed, 1980) 408-409.

11. Sternberg M, Kim CY, Schwende FJ. Lysinoalanine: presence in foods and food ingredients. *Science,* 1975, 190, 992-994.

12. Kraft develops process to deflavor soy-based foods, ingredients. European Patents via NewsEdge Corporation. Posted 6/20/2002. www.soyatech.com

13. Yannai

14. Liener

15. Friedman

16. Anderson RI, Wolfe WJ. Compositional changes in trypsin inhibitors, phytic acid, saponins and isoflavones related to soybean processing. *J Nutr*, 1995, 125, 581S-588S.

17. Peace RW, Sarwar G et al. Trypsin inhibitor levels in soy-based infant formulas and commercial soy protein isolates and concentrates. *Food Res Int*, 1992, 25, 137-141.

18. Billings PC, Longnecker MP et al. Protease inhibitor content of human dietary samples. *Nutr Cancer,* 1980, 14, 2, 85-93.

19. Brandon DL, Bates AH, Friedman M. Monoclodal antibody-based enzyme immunoassay of the Bowman-Birk protease inhibitor of soybean. *J Agri Food Chem*, 1989, 37, 1192-1196.

20. Rouhana A, Adler-Nissen J et al. Heat inactivates kinetics of trypsin inhibitors during high temperature-short time processing of soymilk. *J Food Sci,* 1996, 61, 2, 265-269.

21. Roebuck. Trypsin inhibitors: potential concern for humans. *J Nutr,* 1987, 117, 398-400.

22. Doell BH, Ebden CJ, Smith CA. Trypsin inhibitor activity of conventional foods which are part of the British diet and some soya products. *Qual Foods Hum Nutr*, 1981, 31, 139-150.

23. Kawata, Masaharu. Monsanto's dangerous logic as seen in the application documents submitted to the Health Ministry of Japan. Third World Biosafety Information Service, July 28, 2003. www.organicconsumers.org.)

3. REVIEW OF SCIENTIFIC LITERATURE

The Totality of Scientific Evidence

Solae states that it established its soy protein/cancer health claim based on epidemiological studies. As documented in our June 14, 2004 protest of Solae's petition, we believe that the evidence in these epidemiological studies is mixed at best, with many other foods and lifestyle factors contributing to reduced risk of breast, prostate and GI tract cancers in Asia. Furthermore, if soy is to be credited for lowered rates of breast and prostate and gastrointestinal cancers in Asia, then the same logic requires us to blame soy for the higher rates of cancer of the esophagus, stomach, thyroid, pancreas and liver in those countries.[1] Solae has not addressed these important statistics either in its initial petition or in its August 17, 2004 response to the comments submitted by the Weston A. Price Foundation.

1. Harras A., et al. Cancer Rates and Risks (4th edition 1996 National Institutes of Health, National Cancer Institute).

Meta-analyses

Solae states that meta-analysis "is widely accepted by the medical research community" and that "There has been a sharp increase in the number of publications in medical journals using meta-analysis as a tool of assessment in recent years." This sharp increase is primarily due to the numbers of studies being sponsored by food processors which have much to gain by using meta-analysis to "average out" adverse findings in order to obtain a desired outcome. Many bio-statisticians have warned against the increasingly common use of meta-analyses to demonstrate the existence of an effect in

the sponsor's direction of interest and to circumvent the obscuring of the desired results as found in a large number of small studies. Meta-analyses are also used inappropriately to provide simple, commercially viable answers to complex clinical problems such as the use of soy to prevent cancer. Meta-analysis is most useful where the primary literature is of good quality, there is little heterogeneity in the response to treatment, the interest centers on estimation of a specific, critical parameter of outcome, and the meta-analyst is deeply expert in the subject matter. Other uses have produced results that may be seriously misleading.[1-3] We submit that no health claim should be made for a product based on averages whenever adverse findings exist that put at least some members of the public at risk.

1. Jones, DR, Meta-analysis: weighting the evidence. *Statistics in Medicine*, 1995, 14, 137-149.

2. Nicolucci A, Tognoni G. Should we trust results of meta-analyses? *Lancet,* 2004, 364, 9443, 1401.

3. Bailar JC 3rd.The practice of meta-analysis, 1995 *J Clin Epidemiol,* 48, 1, 149-157.

Cell Culture Studies

Solae states that "cell culture work does not accurately depict the impact of dietary soy intake and cancer development in humans. Therefore publications from *in vitro* studies on individual components of soybeans such as isoflavones (e.g. genistein) were not reviewed for this health claim petition." We agree that cell culture work does not provide definitive answers. However, adverse findings – particularly those that coincide with adverse findings documented in epidemiological and laboratory studies -- raise serious questions about safety. We hold that these safety issues must be fully resolved before a cancer claim for soy protein should be considered by the FDA.

Estrogen-Dependent MCF-7 Tumor Model Studies in Ovariectomized Mice

Solae states that it failed to include research led by William Helferich, M.D., at the University of Illinois, Urbana/Champaign, because "soy food was not used as a

treatment" in these studies. In fact, these studies used soy protein isolate-based feeds containing increasingly high concentrations of the soy isoflavone genistein. We hold that these studies must not be ignored; they link soy protein – and especially the constituents of soy protein known as genistein – to the acceleration of breast cancer in women who have already been diagnosed with the disease.

Solae acknowledges that these studies establish the fact that soy phytoestrogens support the growth of estrogen-dependent tumors, but states that this only occurs in the absence of endogenous estrogens. Despite the fact that most postmenopausal women show low levels of endogenous estrogen, Solae rejects the obvious conclusion that soy protein containing genistein is potentially dangerous for this group of consumers. Instead, Solae chooses to focus on the possibility that soy genistein can inhibit cancer growth when endogenous estrogens are present. Because women have different levels of endogenous estrogens during different phases of their life cycle, increased consumption of soy protein cannot safely be recommended to all women, much less to men and children. Furthermore, a soy protein/cancer health claim would encourage many women to purchase soy isoflavone supplements even though the claim would only be made for soy protein. On this, Dr. Helferich is clear: "Our preclinical laboratory animal data suggest that caution is warranted regarding the use of soy supplements high in isoflavones for women with breast cancer, particularly if they are menopausal."[1]

Solae's remarks regarding Tamoxifen also deserve comment. Solae states that the chemical structure of Tamoxifen is "similar to that of genistein," that genistein has "no more effect" than Tamoxifen and that the FDA has approved Tamoxifen for for breast cancer prevention in women who are at high risk of developing breast cancer." These statements are true but they leave out the fact that the FDA approved Tamoxifen as a *drug* and not as a food. The FDA has not recommended that the entire population – male and female, adults and children – be medicated with this pharmaceutical in the interest of cancer preventive. We hold that soy genistein like Tamoxifen may have promise as a pharmaceutical drug, not as a food, and that it should be carefully administered, monitored and recommended as such.

Solae cites a study involving postmenopausal monkeys, in which epithelial proliferation and progesterone receptor expression in the breast and uterus are significantly higher in the estrogen group compared with isoflavone-deleted and isoflavone-containing soy protein groups and where researchers found no significant difference between the isoflavone-depleted and isoflavone-containing groups. The authors concluded that "these findings suggest that high dietary levels of isoflavones do not stimulate breast and uterine proliferation in postmenopausal monkeys and may contribute to an estrogen profile associated with reduced breast cancer risk."[2] We hold that this study is not relevant because the estrogen group received equine estrogen. Unnatural conjugated equine estrogens are used in conventional HRT therapy and have been proven unsafe. The fact that soy protein might be relatively safer than HRT should not be construed to mean soy protein is indeed absolutely safe. Later in this document, the Weston A. Price Foundation will discuss studies that have linked soy to epithelial cell proliferation.

1. Helferich, William. As quoted by Barlow, Jim. Estrogen found in soy stimulates human breast-cancer cells oon normal premenopausal breast. University of Illinois/Champaign pres release, December 17, 2001.

2. Wood CE, Register TC, et al. Breast and uterine effects of soy isoflavones and conjugated equine estrogens in postmenopausal female monkeys. J Clin Endocrinol Metab, 2004, 89, 33462-3468.

Genistein and Tamoxifen Interaction

Weston A. Price Foundation submitted evidence that genistein may negate the Tamoxifen effect, thus proving hazardous to women undergoing treatment. To address this issue, Solae presents several studies indicating that dietary soy is synergetic with Tamoxifen. Solae states that chemical structure of both Tamoxifen and genistein are similar to that of estrogen and that "these compounds can inhibit, have no effect, or even support the growth of estrogen-dependent tumors depending on doses used and the estrogen status of a given model." In other words, both the prescription drug and the non-prescription soy isoflavone can have many possible effects, some of strong potency and none entirely predictable. Instead of proving safety, we maintain that these studies

suggest that genistein should sometimes be recommended by a licensed physician to be given in conjunction with Tamoxifen as a prescription drug, with the dose carefully calculated and the patient's progress carefully monitored. We hold that it is inappropriate and irresponsible for Solae to encourage women to eat increased amounts of genistein-containing soy protein at will. Such haphazard dietary use of soy protein could prove especially hazardous to women with breast cancer.

Short-Term Feeding Studies in Women

Solae criticizes the Weston A. Price Foundation's decision to submit three studies suggesting risk to breast tissue. We do not claim that these studies prove extreme or definitive danger but pointed out that caution is advised until safety has been proven. As long as any women in such studies experience estrogen-related changes in their nipple aspirate, women should not be advised to increase their consumption of soy protein as a breast cancer preventive. Petrakis concluded: "In view of the increasing use of soy protein food products in Western populations, more detailed investigations of the effects of soy on the physiology of the female breast appear highly desirable."[1]

Solae states that "soy consumption is inversely related with serum estrogen levels in premenopausal and postmenopausal women. Although reduced serum estrogen levels are widely assumed to be beneficial for women, this is an unproven theory. Indeed many leading clinicians are now prescribing bio-identical hormone therapies including 17 β estradiol (as opposed to equine estrogen) because cancer is rarely present in young women (who naturally have high levels of endogenous estrogens).

Solae concludes "Moreover, findings by Petrakis et al (1996) are contrary to epidemiological studies from Asia and soy-consuming populations in the United States. These studies demonstrate that soy consumption is related to a lower risk of breast cancer As we have previously stated, the evidence that soy consumption alone is linked to a lowering of breast cancer risk remains unconvincing. And if we credit soy foods for lower rates of breast and prostate cancers in Asia, then the same logic requires us to

blame soy for the higher rates of cancer of the esophagus, stomach, thyroid, pancreas and liver in those countries. [2]

1. Petrakis NL, Barnes S, et al. Stimulatory influence of soy protein isolate on breast secretion in pre-and postmenopausal women. *Cancer Epidemiol Biomarkers Prev,* 1996, 5, 785-794.

2. Harras A., et al. *Cancer Rates and Risks* (4th edition 1996 National Institutes of Health, National Cancer Institute).

Data Interpretation – Epidemiological Studies

Solae states that it evaluated all the studies in "descending order of persuasiveness as per FDA criteria." We hold that few of these studies are persuasive. They indicate the fact that many dietary and lifestyle factors appear to be protective against breast, prostate and GI tract cancers. Again, if soy can be credited with lowered rates of breast and prostate cancer then also must be blamed for the higher rates of cancer of the esophagus, stomach, thyroid, pancreas and liver in those countries. Solae has failed to address this important issue.

Inclusion of Animal Studies

Solae reviewed animal studies that assessed soy protein as a component of diet and the preventive effect of such diets in experimentally induced tumorigenesis. However Solae claimed that studies using "crude mixture of compounds or a pure compound" were "irrelevant." We hold that these compounds are constituents of soy protein and could indicate safety problems with soy protein.

Solae chose not to address the Weston A. Price Foundation's concerns about "early studies on trypsin inhibitors and/or raw soy flour on biochemical changes or pre-neoplastic lesions in pancreases in rats." Rather, Solae dismisses them with the words "Studies on an individual chemical compound in any form do not evaluate the intake of a soy diet in animals and humans and therefore these studies were not reviewed for this petition."

We hold that these early studies are relevant, that they are backed by recent data and that they raise serious questions about the safety of soy protein. Trypsin inhibitors are a constituent of soy protein that cannot be fully deactivated by cooking and other processing methods (See Section 2 above). When the level of trypsin in the small intestine is reduced – as is the case every time a person eats food such as soy with a high level of trypsin inhibitors – the hormone CCK (cholecystokinin) stimulates the pancreas to secrete and manufacture more digestive enzymes When this occurs only occasionally, the pancreas responds to the crisis, rests and recovers. When it happens day after day – as it does for people who deliberately include several servings of soy protein in their daily diets -- pancreatic hypertrophy and hyperplasia result.[1]

Growth depression occurs because the pancreas uses up amino acids that would ordinarily be used for growth and repair processes in order to produce extra digestive enzymes. Studies using radioactive methionine show an increased conversion of methionine to cystine occurring in the pancreas or blocking of the needed enzyme cystathione synthetase. This causes a shortage of the methionine needed for growth and repair.[2] Trypsin inhibitors also affect other amino acids needed for health and growth, notably threonine and valine. Both are routinely added to rat and other animal chows to achieve proper growth. The extra amino acids, however, do not prevent ongoing damage to the pancreas, which continues to react with an immune system response that causes enlarged pancreatic cells.[3]

The extent of pancreatic hypertrophy and hyperplasia varies widely from species to species in the animal kingdom. In some soy-fed animals the pancreas swells quickly, in others more slowly and in some not at all. Rats and chicks, which have large pancreases for their size, are the most likely to show changes in the organ as well as in their digestive capacities. Because their requirements for the sulfur-containing amino acids needed for the synthesis of pancreatic enzymes are higher than animals with a smaller pancreas (in proportion to their body weight), they are highly susceptible to trypsin-inhibitor damage.[4,5] Though hypertrophy and hyperplasia are less likely to occur in calves, dogs, pigs and adult guinea pigs, these animals suffer from the loss of their ability to secrete sufficient enzymes. In addition, increases in RNA and protein correspond with hypertrophy and increases in DNA with hyperplasia.[6]

Two recently published studies by Larry H. Garthoff and other researchers at the FDA's Division of Toxicological Research and Nutritional Product Studies in Laurel, MD[7,8] are widely cited as proof that "dietary trypsin inhibitor at levels once shown to cause morbidity in swine and neoplasia in rats produced near normal, growth, health and behavior over a period of 39 weeks."[9] However, this statement fails to mention the fact that the pigs experienced ongoing diarrhea and occasional vomiting and that the study – originally planned as a two-year study – was cut short at 39 weeks, long before precancerous or cancerous lesions would be likely to occur. Even so, there were changes in body weight, organ weights, pancreatic protein concentration and amylase activity, as well as evidence of macrocytic anemia.

Cancer, however, is the issue most germane to Solae's health claim petition. Where trypsin inhibitors cause cell proliferation (hyperplasia), cancer becomes a distinct possibility. Furthermore, trypsin inhibitors potentiate two known pancreatic carcinogens, azaserine and nitrosamine. Though azaserine is a pancreatic cancer-causing chemical that is more likely to be found in the laboratory than in the average diet, nitrosamine is a byproduct of food processing found in most modern soybean products (See Section 1 above). Cancer has also occurred in soy protein-fed animals that have not been exposed to known carcinogens. Trypsin inhibitors alone can cause adenomatous nodules on the pancreas of rats, with cancer rates rising in step with the levels of trypsin inhibitors. Although similar cancers were not induced in mice and hamsters using the same strategies, caution is certainly advised.[10-19]

As yet, human studies do not clearly connect soy protease inhibitors to pancreatic cancer. However, short-term studies on human subjects show that protease inhibitors stimulate pancreatic secretions, suggesting that long-term ingestion might lead to the development of pancreatic lesions similar to those observed with rats.[20-23] and premature infants fed soy formula show increased levels of digestive enzymes compared to dairy formula-fed babies, indicating low digestibility of the soy formula and stress on the pancreas.[24]

It may not be coincidental that pancreatic cancer recently moved up to fourth place as a cause of cancer deaths in men and women in the United States.[25] In the 1970s and 1980s, researchers studying protease-inhibitor damage on the pancreas noted that pancreatic

cancer had then moved up to fifth place and wondered whether there might be a soybean-protease inhibitor connection.[26-28] The fact that this ongoing rise has occurred along with a rise in the human consumption of soybeans does not prove cause and effect. However, looking at the increase in pancreatic cancer cases alongside pertinent animal studies is suggestive – and sobering. Whether trypsin inhibitors alone or some other soybean factor (such as lectins) must share the blame, the human animal appears to be at risk. Safety has yet to be proven and health claims should not be made. In fact, in 1998, Irvin E. Liener, Ph.D, expert specialist in protease inhibitors warned the FDA: "Soybean trypsin inhibitors do in fact pose a potential risk to humans when soy protein is incorporated into the diet."[29]

1. Liener IE, Kakade ML. Protease inhibitors. In Irvin E. Liener, ed. Toxic Constituents of Plant Foodstuffs (NY Academic Press, 2nd ed, 1980) 7-71.

2. Liener, Kakade, 46, 49.

3. Rackis. Biological and physiological factors in soybeans. *J Am Oil Chemists Soc*, 1974, 51, 165A-166A.

4. Liener, Kakade, 42-43

5. Struthers BJ, MacDonald JR. Effects of raw soy flour feeding in weanling pigs: comparison with rats and monkeys. *Qual Plant Foods Hum Nutr*, 1985, 35, 331-338.

6. Struthers, MacDonald

7. Garthoff LH, Henderson GR et al. The autosow raised miniature swine as a model for assessing the effects of dietary soy trypsin inhibitor *Food CHem Toxicol*, 2002, 40, 487-500.

8. Garthoff LH, Henderson GR et al. Pathological evaluation, clinical chemistry and plasma cholecystokinin in neonatal and young miniature swine fed soy trypsin inhibitors from 1 to 39 weeks of age. *Food Chem Toxicol*, 2002, 40, 501-516.

9. Messina, Mark. Letter to Vicki Nelson of *Mothering* magazine, February 26, 2004.

10. Liener IE. Possible adverse effects of soybean anticarcinogens. *J. Nutr*, 1995, 125, 744S-750S

11. Levison DA, Morgan RG et al Carcinogenic effect of di(hydroxypropyl)nitrosamine (DHPN) in male Wistar rats: promotion of pancreatic cancer by a raw soya flour diet. *Scand J Gastroenterol,* 14, 217-224.

12. Morgan RGH, Levison DA et al. Potentiation of the effects of the action of azaserine on the rat pancreas by raw soya bean flour. *Cancer Lett*, 1977, 3, 87-90.

13. McGuiness EE, Morgan R et al. The effects of long-term feeding of soya flour on the rat pancreas. *Scand J Gastroenterol*, 1980, 15, 497-502.

14. Rackis JJ, Gumbmann MR Liener IE. The USDA Trypsin Inhibitor Study, I. Background, objectives and procedural details. *Qual Palnt Foods Hum Nutr,* 1985, 35, 213-242.

15. Liener IE, Nitsan Z et al. The USDA Trypsin Inhibitor Study, II. Timed release biochemical changes in the pancreas of rats. *Qual Plant Foods Hum Nutr*, 1985, 35, 243-257.

16. Spangler WI, Gumbmann MR et al. The USDA Trypsin Inhibitor Study, III. Sequential development of pancreatic pathology in rats. *Qual Plant Foods Hum Nutr*, 1985, 35, 259-274

17. Gumbmann MR, Spangler WI et al. The USDA Trypsin Inhibitor Study, IV. The chronic effects of soy flour and soy protein isolate on the pancreas in rats after two years. *Qual Plant Foods Hum Nutr*, 1985, 35, 275-314.

18. Roebuck BD. Trypsin inhibitors: potential concern for humans? *J Nutr*, 1987, 117, 398-400.

19. Myers BA, Hathcock J et al. Effects of dietary soya bean trypsin inhibitor concentrate on initiation and growth of putative preneoplastic lesions in the pancreas of the rat. *Food Chem Toxic,* 1991, 29, 7, 437-443.

20 Liener IE. Effect of a trypsin inhibitor from soybeans (Bowman-Birk) on the secretory activity of the human pancreas. *Gastroenterol,* 1988, 94, 419-427.

21. Holm H, Reseland JE et al. Raw soybeans stimulate human pancreatic proteinase secretions. *J. Nutr*, 1992122, 1407-1416.

22. Calam J, Bojarski JC , Sringer CJ. Raw soya-bean flour increases cholecystokinin release in man. *Br J Nutr,* 1987, 58, 2, 175-179.

23. Liener IE, Letter to the editor. Soybean protease inhibitors and pancreatic carcinogenesis. *J. Nutr*, 1996, `26, 582-583.

24. Lebenthal E, Chooi TS, Lee PC. The development of pancreatic function in premature infants after milk-based and soy-based formulas. *Pediatr Res,* 1981, 15, 9, `2240-1244.

25. American Cancer Society Cancer Reference Information, 2003, How Many People Get Pancreatic Cancer? www.cancer.org.

26. Roebuck BD. Trypsin inhibitors potential concern for humans? *J Nutr*, 1987, 117, 398-400.

27. Myers BA, Hathcock J et al, 437.

28. Morgan RGH, Womrsley KG. Cancer of the pancreas. *Gut,* 1977, 18, 580-596.

29. Liener IE. Letter to Dockets Management Branch, Food and Drug Administration, December 31, 1998.

Solae also declined to address the concerns we raised about the effect of soybean lectins on the intestines in animals "because studies on an individual chemical compound in any form do not evaluate the intake of a soy diet in animals and humans, these studies were not reviewed for this petition." We hold that these compounds are constituents of soy protein, that their safety must be proven and that their potential roles in carcinogenesis or cancer acceleration must not be ignored.

Solae also declined to address our concerns about two publications that "did not meet our definition of studies investigating cancer growth and development as an endpoint measurement and therefore were not reviewed for the petition. The publication by Lephart et al (2001) is a study on brain structure and aromatatse activity in rats and that by Govers et al (1992) is a study on colonic epithelial proliferation" We maintain that both of these studies are significant. Lephart et al showed that soy phytoestrogens significantly decreased prostate weights – a fact that is clearly relevant to a health claim related to soy protein and prostate cancer – and warned of possible side effects on the sexually dimorphic brain region, which pertains to gender differences. Govers et al showed that soy protein increases colonic epithelial proliferation, an early biomarker of colon cancer risk. This is clearly pertinent if soy protein is to be proposed as a preventer of colon cancer.

Prostate Tumor Animal Model Study

Solae states that the Weston A. Price Foundation unjustly "criticized Solae's interpretation of the study by Pollard and colleagues (2001) that assessed diet and duration of testosterone-dependent prostate cancer in Lobund-Wistar rats." Solae has still not addressed those concerns, but reemphasizes the reduced tumor incidences from a soy protein isolate/isoflavone diet. Solae chose to omit the bad news from this study, namely that "dietary soy protein promoted PC tumorogenesis but only in Lobund-Wistar rats." Given the fact that Solae has petitioned for a health claim for all forms of soy protein, this is a serious error of omission. L-W rats were developed as "a unique model of spontaneous prostate cancer (PC) that shares many of its characteristics with the natural history of PC in man, including (a) inherent predisposition, high production of testosterone and aging risk factors, (b) endogenous tumorigenic mechanisms and (c) early stage testosterone-dependent and late stage testosterone-independent tumors."

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Maternal and Perinatal Genistein Exposure

Solae objects to our citing studies showing adverse effects from the estrogenic constituent of soy protein known as genistein. Yet, throughout this section Solae attempts to establish a claim that genistein exposure during pregnancy, the neonatal period and puberty has inhibited experimentally induced mammary tumorigenesis in female rats. Solae notes that Hakkak et al (2000) have demonstrated that feeding female rats a soy protein over two generations significantly inhibits chemically induced mammary tumor development compared to casein-fed animals" but fails to address our concerns about advancement of vaginal opening, a sign of premature puberty.

Solae also favorably cites the studies of Coral A. Lamartiniere, Ph.D., who has proposed giving shots of genistein to female fetuses in the womb to preprogram them for reduced susceptibility to breast cancer later in life. Dr. Lamartiniere's experiments on rats have yielded "enhanced mammary gland maturation" and accelerated uterine weight gain. In other words, premature breast development and early puberty. However, these early sprouting breasts have fewer terminal end buds and more lobules, changes that indicate greater differentiation and (possibly) decreased susceptibility to carcinogens.[1-4] Other researchers, including Hilakivi-Clarke whom we cited in our original document –

see less cause for optimism. Their work shows that perinatal genistein is an endocrine disrupter that contributes to or causes breast cancer."

In its discussion of how soy genistein exposure during pregnancy might benefit baby girls, Solae also fails to address the effects the estrogenic substance might have on an unborn baby boy. Birth defects such as hypospadias and cryptorchidism caused by excess prenatal exposure to either environmental or dietary estrogens have been documented. When less extreme exposure to estrogens occurs, the consequences might not manifest until puberty or adulthood and might include reduced sperm production, poor sperm quality, small penis size and a greater propensity to develop testicular cancer in early adulthood.[7,8] Exposure to excessive soy isoflavones *in utero* may also put males at risk for the later development of benign prostatic hypertrophy and prostate cancer in that prostate cells sensitized to estrogen during fetal development are more responsive to estrogens later in life and less responsive to the normal controlling mechanisms of prostatic growth.[9] Thus boys born to mothers who consume excessive amounts of soy protein during pregnancy may be predisposed to prostate cancer. A soy cancer health claim would encourage such excessive consumption.

Finally, the FDA should consider the finding by North et al that vegetarian mothers were 4.99 times more likely to give birth to a boy with hypospadias than a mother on an omnivorous diet because of a greater exposure to phytoestrogens.[10] Although this study falls far short of proving that soy protein in the diet is the culprit, soy is the only phytoestrogen source with a major role in the diet.[11] The link is strong enough a European commission has mandated a study of 3,000 babies to determine what might be causing the epidemic of hypospadias.[12]

Solae correctly notes that "the route and quantity of genistein administered to animals in a given model play an important role in determining the outcome of an experiment. We agree that these factors should be considered when extrapolating the impact of dietary soy to women's health from these laboratory findings." However, this does not mean that unfavorable findings can be disregarded. Soy protein – complete with its genistein component – has the potential for harm at high levels of consumption. The establishment of a soy protein/cancer health claim would encourage many health-

conscious consumers to increase their dietary intake of soy protein in a reckless manner, with no knowledge of what would constitute proper dosage in the light of bioindividuality, gender differences, or special "windows of vulnerability" such as pregnancy, lactation and puberty.

1. Lamartiniere CA, Zhang JX, Cotroneo MS. Genistein studies in rats: potential for breast cancer prevention and reproductive and developmental toxicity. *Am J Clin Nutr,* 1998, 68, 6 Suppl, 1400S-1405S.

2. Lamartiniere CA. Protection against breast cancer with genistein: a component of soy. *Am J Clin Nutr,* 2000, 71, 6, 1705S-1707S.

3. Lamartinine CA. Timing of exposure and mammary cancer risk. *J Mammary Gland Biol Neoplasia,* 2002, 7, 1, 67-76.

4. Lamartiniere CA, Cotroneo MS et al. Genistein chemoprevention: timing and mechanisms of action in murine mammary and prostate. *J Nutr*, 2002, 132, 3, 552S-558S.

5. Yang J, Nakagawa H et al. Influence of perinatal genistein exposure on the development of MNU-induced mammary carcinoma in female Sprague-Dawley rats. *Cancer Lett*, 2000, 149, 1-2, 171-179.

6. Hilakivi-Clarke L, Cho E et al. Maternal exposure to genistein during pregnancy increases carcinogen-induced mammary tumorigenesis in female rat offspring. *Oncol Rep,* 1999, 6, 5, 1089-1095.

7. Baskin, Laurence, ed. *Hypospadias and Genital Development: Advances in Experimental Medicine and Biology,* vol 545 (NY Kluwer Academic/Plenum Publishers, 2004).

8. Colborn, Theo. Endocrine disruption overview: are males at risk? In Baskin, 193-194.

9. Santii R, Newbold RR et al. Developmental destrogenization and prostatic neoplasia. *Prostate,* 1994, 24, 2, 67-78.

10. North K, Golding J. A maternal diet in pregnancy is associated with hypospadias *BJU Int,* 2000, 35, 107-113.

11. Price KR, Fenwick GR. Naturally occurring oestrogens in foods – a review. *Food Add Contam,* 1985, 2, 73-106.

12. Gray E Jr, Ostby J et al. Toxicant induced hypospadias in the male rat. In Baskin, 234.

Studies Reporting Data on Bio-Markers

Solae writes "Weston A. Price cited studies that measured a change in a particular biomarker (e.g. serum level of prostate specific antigen or insulin-like growth factors) and "These studies were not reviewed for this petition" We maintain that all of the studies involving biomarkers were properly included and that they significantly undermine Solae's claims that soy protein is safe and should be used to prevent cancer. Solae comments that a "study by Probst-Hensch et al (2003) measured insulin like growth factor is not a study on soy." This statement is true, but insulin-like growth factor (IGF) has been implicated in the etiology of chronic diseases including breast, prostate, colon and lung cancers and we cited proof that researchers have shown that soy increases circulating levels of IGF, especially in men.

Genistein and Uterine Tumor Model

Solae states that "results from a multi-generation feeding study showed that there was no difference in uterine weight in offspring in a study comparing diets based on soy protein or casein, and there was no uterine tumor development in either group." (Badger et al, 2001). However, Solae neglects to add that this study reported the fact that soy protein isolate accelerated puberty in the female rats.

Solae also cites the work of Strom et al (2001) as evidence of no significant differences in cancer, reproductive organ disorders, libido dysfunction, sexual orientation and birth defect in offspring" between groups fed soy formula and cow's milk formula during infancy. Indeed Strom announced only one adverse finding: longer, more painful menstrual periods among the women who had been fed soy formula in infancy and he concluded that the results were "reassuring." We maintain that the data in the body of the report was far from reassuring. Mary G. Enig, PhD, President of the Maryland Nutritionists Association; Naomi Baumslag, MD, Clinical Professor of Pediatrics at Georgetown University and President of the Women's International Public Health Network; Lynn R. Goldman, MD, MPH, Environmental Health Sciences, Johns Hopkins University; and Retha Newbold, PhD, National Institute of Environmental Health Sciences, Research Triangle Park, NC have identified many problems

with this study, including:

- Failure to include mention of statistically significant, higher incidences of allergies and asthma in the study's abstract – the only part read by most busy health professionals and media reporters.
- Glossing over or omitting from the main body of the report gynecological problems such as higher rates of cervical cancer, polycystic ovarian syndrome, blocked fallopian tubes, pelvic inflammatory disease, hormonal disorders and multiple births.
- Manipulation of statistics by not evaluating still births or failure to achieve pregnancy (higher in the soy-fed women) but evaluating miscarriages (slightly higher in the dairy-formula fed group).
- Excluding thyroid function as a subject for study (although thyroid damage from soy formula has been the principal concern of critics for decades). Nonetheless, thyroid damage can be surmised by the fact that the soy-fed females grew up to report higher rates of sedentary activity and use of weight loss medicines.
- Conducting the entire study by telephone interviews, asking subjective questions, and performing no medical examinations, laboratory tests or other objective testing.
- Providing no information on the ages at which formula feeding ended, the dose length or the quantity of the soy isoflavones (all of which are basic requirements of valid toxicology studies).
- Following up infants who were given soy formula as infants for just 16 weeks (though serious damage can occur for at least the first nine months in boys and the first six months in girls) and omitting any information about whether the subjects in the study took soy formula after the initial 16-week study period or ate soy foods during childhood.
- Using a study group of 282 soy-fed persons that was too small for most of the negative findings to become "statistically significant."

Solae also criticizes our inclusion of a study assessing neonatal genistein on uterine tumor development in mice (Newbold et al, 2001). We maintain that this study from the National Institute of Environmental Health Sciences, Research Triangle Park, NC is relevant and that its lead author Retha Newbold, Ph.D., has publicly questioned the safety of soy infant formula.

Solae concludes this section by citing studies showing that consumption of soyfoods is associated with a significantly lower risk of endometrial cancer in women. In fact, Goodman et al (1997) show that high consumption of all legumes (not just soy) are associated with a decreased risk of endometrial cancer and that similar reductions in risk were found for increased consumption of whole grains, vegetables, fruits and seaweeds. Furthermore, soy and legumes only improved the risk of women who were never pregnant or had never used unopposed estrogen.

Finally, Solae cites a study by Balk et al (2002) in which consumption of soy cereal for six months did not cause any stimulation to the endometrium in post-menopausal women. Solae failed to report the fact that improvement in hot flushes, night sweats and vaginal dryness occurred in the placebo group, not the soy group, and that insomnia was more frequent in the soy group. Solae has also omitted a recent study that showed that soy isoflavones cause "significant increases in the occurrence of endometrial hyperplasia," a precursor of cancer. The researchers concluded: "These findings call into question the long-term safety of phytoestrogens with respect to the endometrium."[1] Although this warning applied to the use of soy isoflavone supplements, soy protein products contain isoflavones.

1.Unfer V, Casini ML et al. Endometrial effects of long-term treatment with phytoestrogens randomized, double-blind, placebo-controlled study. *Fertil Steril*, 2004, 82, 1, 145-148.

Prostate Tumor Growth

Solae discounts the negative findings of Cohen et al 2003 with the words "explanations for these findings remain speculative." We maintain that the results speak for themselves, that sure explanation is not needed and that we should heed the warning of researchers who wrote that their study "cast doubt on the effectiveness of isoflavone-

rich soy protein isolates as adjuvant therapy in the treatment of advanced hormone-refractory prostate cancer."

Thyroid Hormones

Solae states "It is important to note that flavonoids are not constituents of soy." This statement is not true. We quote the first paragraph of Section III of the British Committee on Toxicity's Phytoestrogen report:

> "Some naturally occurring compounds present in plants have been found to possess oestrogenic properties, these chemicals have been termed 'phytoestrogens'. The majority of phytoestrogens belong to a large group of substituted phenolic compounds known as flavonoids. Flavonoids are present in many plants and it has been estimated that they can constitute up to 7% of the dry weight of some plants . . Three classes of flavanoid, the coumestans, prenylated flavonoids and isoflavones, are phytoestrogens that possess the most potent oestrogenic activity. A class of non-flavonoid phytoestrogens, the lignans has also been identified."[1]

Solae objects to the fact that we presented *in vitro* as well as *in vivo* studies from the National Laboratory for Toxicological Research. We believe these studies are all relevant and agree with the conclusions of FDA expert Daniel R. Doerge, Ph.D., who writes "The possibility that widely consumed soy products may cause harm in the human population via either or both estrogenic and goitrogenic activities is of concern. Rigorous, high-quality experimental and human research into soy toxicity is the best way to address these concerns."[2]

Solae suggests that the FDA ignore the work of its own laboratory in favor of several industry-sponsored studies. According to Solae, Duncan et al (1999a) and Duncan et al (1999b) prove the safety of an isoflavone-rich diet. In fact, the data in these studies show evidence of soy-induced endocrine disruption along the pituitary/hypothalamic/thyroid axis. The researchers reported a decrease in T3 concentrations in premenopausal women receiving 128 mg isoflavones/day but concluded that because no effects were seen on total or free T4 or TSH, the results were "unlikely to be physiologically important." In the second Duncan study, postmenopausal women on high soy isoflavones diets (132 mg/day) showed higher

thyroid binding globulin (TBG) levels while those on the lower isoflavones diet (65 mg/day) showed decreased TBG levels. These confusing results led the team to conclude that "while the changes are significant, they may not be physiologically relevant." Similarly, in another study cited by Solae, Persky et al (2002) found "small effects on thyroid hormone values that are unlikely to be clinically important."[77] While neither Duncan nor Persky have proved adverse effects on the thyroid, these studies cannot be appropriately used to establish safety.

These weak thyroid studies cited by Solae do not overpower the evidence of a major human study carried out at the Ishizuki Thyroid Clinic in Japan, where 30 grams of pickled soybeans per day given to healthy adult men and women, induced thyroid disruptions after only 30 days.[3] All the subjects consumed seaweed daily to ensure adequate iodine intake. Compared to non-soy-eating controls, TSH levels increased significantly in a group of 20 adults fed soy for one month and in a second group of 17 fed for three months. Two individuals shot up from an optimum level of 1 uU/mL to a pronounced hypothyroid state of 7uU/mL. Thyroxine levels decreased slightly. The second group experienced a significant increase in free thyroxine, indicating improved thyroid function, after they stopped eating the soy. Goiter and hypothyroidism appeared in three members of the first group and eight of the second. Many of those in the three-month group also suffered from symptoms associated with hypothyroidism: 53 percent from constipation, 53 percent from fatigue and 41 percent from lethargy. One case of subacute thyroiditis (inflammation of the thyroid) appeared in the first group. Although 9 of the 11 subjects saw a reduction in goiter size after they stopped eating the soy, goiter persisted in two subjects. These received thyroxine treatments and their goiters subsided in another two to six months.

The subjects in the Ishizuki study started out healthy. During the course of the study, all had adequate iodine and did not eat very much soy – only 30 grams per day. The levels of isoflavones in this amount was approximately 23 mg/g total genistein and 10 mg/g of total daidzein. This study showed that soy isoflavones exert harmful effects in healthy adults at levels far below the levels of isoflavones administered to babies fed soy infant formula. [4] This finding – and its significance to infants – was of such concern to the United Kingdom's Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT), that it concluded: "Even allowing for differences in absorption the large differences in exposure would be expected to cause significant effects." COT identified several

populations at special risk for soy-induced thyroid disease – infants on soy formula, vegans who use soy as their principal meat and dairy replacements, and men and women who are self medicating with soy foods and/or isoflavone supplements in an attempt to prevent or reverse menopausal symptoms, cancer or high cholesterol.[5]

Solae buttresses its claim that soy is safe for the thyroid by referencing studies showing that soy protein proved goitrogenic for iodine-deficient animals but not to those replete in iodine. We maintain that the solution of adding iodine to the diet is a simplistic and partial solution to the thyroid damage caused by soy protein. The first report in medical journals of enlarged thyroid glands in rats and chickens caused by soybean rations appeared in the 1930s.[6] In 1961, researchers discovered that spiking chow with iodine could prevent goiter, but rats and chickens required twice as much iodine to prevent enlarged thyroids as animals fed soy-free diets. Even then, their thyroid glands showed abnormal cell proliferation.[7] When iodine is largely absent, soy can provoke malignant hyperplastic goiter.[8] Thyroid specialist Dr. Mieko Kimura of Kyoto University writes: "It is well known that a goiter is induced by simple iodine deficiency, but it was noteworthy that hyperplastic goiters can be induced in rats in a high percentage by the administration of soybean factor(s) under iodine-deficient condition, together with accurate signs of malignancy such as invasiveness and metastasis formation in the lungs.[9]

Solae also fails to mention a recent industry-sponsored study that concluded that soy isoflavones do not affect thyroid function in individuals who are "iodine replete." The women in this study received the RDA of 150 ug per day of iodine in addition to iodine in their diet. Although this was a study on soy isoflavones, the authors conclude with the general recommendation, "It is important for all individuals regardless of their soy intake to consume adequate iodine" and urged those who consume large amounts of soy to make sure they consume "sufficient iodine."[10] Many parts of the world are iodine depleted and levels have also been decreasing in the American diet. The National Center for Health Statistics reports that median iodine intake decreased by more than 50 percent between the National Health and Nutrition Examination Surveys (NHANES) of 1970-1974 and 1988-1994. The Center also reports that several recent surveys have shown that the proportion of the U.S population with low iodine levels is increasing.[11]

Finally Solae states that recently published epidemiological studies show that consumption of soyfoods is related to a reduced risk of thyroid cancer in women. Solae however, ignores National Cancer Institutes figures showing that thyroid cancer rates are higher in Asia than in western countries with lower soy food consumption. Yet, elsewhere in its petition Solae credits high consumption of soy protein for the lower rates of breast, prostate and gastrointestinal cancers in Asia.

1. Committee on Toxicity (UK) Draft Report of the COT Working Group on Phytoestrogens. 3. Chemistry and Analysis of Phytoestrogens.

2. Doerge DR, Goitrogenic and estrogenic activity of soy isoflavones. *Environ Health Perspect,* 2002, 110, Suppl, 3, 340-353.

3. Ishizuki Y, Hirooka et al. The effects on the thyroid gland of soybeans administered experimentally in healthy subjects. *Nippon Naibundi gakkai Zosshi*, 1991, 67, 622-629. Translation by Japan Communication Service.

4. Fitzpatrick M. Soy formulas and the effect of isoflavones on the thyoird. *NZ Med J,* 2000, 113, 1102, 24-26.

5. Committee on Toxicity (UK) Draft Report of the COT Working Group on Phytoestrogens, 4. Sources and concentrations of phytoestrogens in foods and estimated dietary intake and 10. Effects of phytoestrogens on the thyroid gland and thyroid function.

6. Patton AR, Wilgus HS, Harshfield GS. The production of goiter in chickens. *Science,* 1939, 89, 162.

7. Block RJ, Mandi RH et al. The curative action of iodine on soybean goiter and the changes in the distribution of iodoamino acids in the serum and in the thyroid gland digests. *Arch Biochem Biophysics*, 1961, 93, 15-21.

8. Kay T, Kimura M et al. Soyabean, goire and prevention. *J Trop Pediatr*, 1988, 34, 110-113.

9. Kimura S, Suwa J et al. Development of malignant goiter by defatted soybean with iodine-deficient diets in rats. *Gann,* 1976, 76, 763-765.

10. Bruce B, Messina M, Spiller GA. Isoflavone supplements do not affect thyroid function in iodine-replete postmenopausal women. *J Med Food*, 2003, 6, 4, 309-316.

11. National Center for Health Statistics, Iodine Level, United States, 2000.

12. Harras A., et al. *Cancer Rates and Risks* (4th edition 1996 National Institutes of Health, National Cancer Institute).

Immune Function

Solae dismisses Yellayi et al (2002), the study the Weston A. Price Foundation submitted on subcutaneous injection of genistein and thymic changes in overaiectomized mice because "It is important to note that injection of genistein is not related to dietary exposure to soy. " However, Yellayi concluded "These results raise the possibility that serum genistein concentrations found in soy-fed infants may be capable of producing thymic and immune abnormalities."

Solae cites Regal et al (2000) as proof that soy enhances anti-inflammatory responses in animals. However Regal concludes this study with a warning: "However, this beneficial anti-inflammatory effect of dietary phytoestrogens is accompanied by a potentially detrimental increase in antigen-induced leakage of protein into the airspace, suggesting that other components of the immune-mediated inflammatory response are enhanced." This conclusion raises concerns because many studies, including Strom et al (2001) cited earlier by Solae, have associated soy infant formula with higher risk of allergies and asthma.

Equol Production from Daidzein

Solae chooses to make no comment on findings by Akaza et al (2002) that showed that, to fully benefit from soy protein, the American human body should be better producers of equol. Solae also dismisses Miyanaga et al (2003) as "a study on green tea." This study suggests that green tea might be needed if Americans are to improve their ability to produce equol. The limited ability of Americans to produce equol suggests that soy protein alone may not be as effective for everyone as Solae has claimed.

Reviews, Editorials and Letters to Editors

Solae declines to review reviews, editorials and letters to edotors because they are not "individual studies" and do not meet the criteria for substantiation for health claims.

We submit that these documents refute Solae's contention that there is "consensus among experts qualified by scientific training and experience" to evaluate such claims regarding the relationship between soy protein products and a reduced risk of certain cancers.

Additional Citations

Solae indicates that it is improper to cite publications that provide data on miso and soybean paste. Although the Solae claim is for products containing higher levels of soy protein, these studies are relevant because they raise concerns about the safety of soy.

Solae also rejects five publications cited by Weston A. Price Foundation because they are not related to soy foods and cancer. We cited Nomura et al (2003) and Chyou et al (1990) as evidence that green vegetables are more appropriate to a gastrointestinal health claim than soy protein. We cited Velicer et al (2004) because Ingram et al (1997) show that high excretion of both equol and enterolactone are associated with a lowering of breast-cancer risk and that there were no associations with the parent phytoestrogens daidzein and matairesinol. This suggests that metabolism of these compounds by the gut microflora is critically important and that soy protein intake alone would not be the most relevant factor in the lowering breast cancer risk.

Finally, we cited Fuchs et al (2002) because a low intake of the essential amino acid methionine is associated with an increased risk of colon cancer in women and Giovannucii et al (1993) linked a methyl deficient diet to early stages of colorectal neoplasia. Soy protein contains all the essential amino acids, but is low in methionine as well as other sulfur-containing amino acids. These facts provide additional concerns that soy can contribute to cancer.

In conclusion, Solae states "To the extent that the studies are not addressed in Soale's petition, we have concluded that they are not relevant or significant to our petition for a qualified health claim." We maintain that all publications we cited are relevant because they establish the fact that neither the safety nor cancer preventive effect of soy protein has been proven and that some evidence exists linking soy protein to the

genesis or acceleration of cancer. Accordingly, soy protein cannot appropriately be recommended for a cancer health claim.

* * * * *

Solae concludes it document with the words "We urge FDA to expedite publication of their ruling so food manufacturers can convey this important dietary health information to consumers on food labels." Rather, we urge the FDA to protect the American consumer and to promptly reject Solae's soy protein/cancer health claim.

Sincerely,

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