Rebuttal on Isoflavones in Soy-Based Infant Formulas

Sir: I will reply to the letters you received regarding our paper (Murphy et al., 1997). Both letters appear to be objecting to one sentence only in the introductory paragraph. The sentence reflects my knowledge of the soy foods and, in particular, the soy isoflavone, field for the past 18 years. I am not an endocrinologist and, therefore, am not an authority on hormone interactions with estrogen receptors. However, the sentence objected to reflects my reading of the scientific literature, papers given by scientists from New Zealand at the Second International Symposium on the Role of Soy in Preventing and Treating Chronic Disease in September 1996 in Brussels (forthcoming in *Am. J. Clin. Nutr.*), and the results of a meeting called by the National Institutes of Health (NIH) May 15, 1997. The pertinent topic of the paper, however, is to report the level of isoflavones found in soy-based infant formulas. My paper reports no new biological information on isoflavones.

Soy-based infant formulas have been consumed by infants in the United States over the past 60 years. Soy foods including soy milk have been consumed by all age groups in most Asian populations for centuries with few reports of hormonal effects (Barnes, 1998; Quak et al., 1998).

The first international citation of the New Zealand controversy was presented by Dr. J. Birkbeck at the above-mentioned Second International Symposium on the Role of Soy..., describing its origin with a breeder of parrots in New Zealand following death and disease of some of the flock. According to Birkbeck, this incident apparently escalated to formation of the "Soy Information Network" and attempts to ban soy formulas and resulted in a 35% reduction of soy-based infant formula sales in New Zealand. Attempts have apparently been made to ban other soy foods. These events have occurred in the face of no new knowledge or indication that soy or its isoflavones cause the deleterious effects.

The May 1997 meeting at the NIH most likely parallels the meetings referred to by James in New Zealand, Switzerland, and the United Kingdom. The NIH meeting, called by Dr. Ephraim Levin (National Institute of Child Health and Development) and chaired by Dr. Frederick Naftolin (Yale), was titled "Significance of phytoestrogens in infant soy formula". I was invited by the NIH to present a summary of what is known about the levels of isoflavones in soy-based infant formula. Dr. Samuel Fomon, internationally recognized infant specialist, presented data showing about 25% of U.S. infant formula market is soy-based, which is in contrast to Europe where soy-based formulas account for only 8% of the formula market share. Thus, one can assume that one-fourth of all U.S. infants over the past 50 years have been consuming soy-based formula. Comparing the size of this population and the small number of reported cases of adverse effects due to soy formula feeding led to my conclusion that there are few adverse effects related to soy formula consumption throughout this population cohort. This mirrors the conclusion of the majority of attending pediatricians from NIH that "isoflavones in formulas are a toxicant in search of a disease".

The American Academy of Pediatrics citation deals with allergic responses to soy feeding which would involve a protein-mediated response. Protein allergies are quite common in young children and involve the proteins of highest consumption, usually cow's milk protein, eggs, and peanuts (Taylor, 1995). The American Academy of Pediatric statement and accompanying citations do not identify isoflavones as the causative agent.

It is true that isoflavones have been included as toxicants in publications prior to 1985. However, recently, the health-protective effects of isoflavones and other constituents in soy have gained favor with over 1600 citations in 1997 related to their health-protective effects. There have been a few citations of infertility problems in exotic species at lower doses and numerous older citations for ruminant livestock consuming large amounts of isoflavones. James's citation of the Cassidy paper (1990) may be premature since it represented an experimental protocol over only one ovulatory cycle, which is considered too short by most endocrinologists. Changes in the menstrual cycle suggested by Cassidy et al. (1990) would most likely be beneficial rather than harmful.

Fitzpatrick's reference to the Sheehan paper (1998), the results of the Third International Conference on Phytoestrogens in 1995 but published only in March 1998, is interesting in that it is one of two papers discussing deleterious effects of isoflavones, with six papers citing the health-protective effects of isoflavones for adults and potential protective effects for infants. The other paper in this symposium describing negative effects of isoflavones is co-authored by Fitzpatrick (1998) and cites support by Richard and Valerie James.

References cited by Fitzpatrick (Markiewicz et al., 1993; Collins et al., 1997; Hoffman, 1995; Dees et al., 1997) are in cell systems, not intact organisms. The bioavailability issue is very important. In adults, reports on plasma concentrations have not exceeded 5 μM, whereas most in vitro observations for phytoestrogens' effects exceed 10 μM (Barnes et al., 1996). Bioavailability of isoflavones in infants has not been explored and should be. Barnes (1998) and Messina et al. (1997) both suggest that phytoestrogens have biological properties different from those of steroid hormones and cite evidence that early exposure to phytoestrogens may have protective effects toward certain types of cancer later in life.

Finally, the mention in my paper of 1−2 μM isoflavones in human milk reflects unpublished results from our laboratory, which should have been cited in that manner, and are from an analysis of one lactating subject who routinely consumed soy. Our results are higher than those reported by Franke et al. (1998) and Setchell et al. (1997) probably due to the dose consumed or bioavailability of the subjects. Our statement on finding isoflavones in human milk was mentioned only to indicate that we have observed that isoflavones are present in human milk. The statement in no way suggests soy-based infant formula is better for infants than human milk.

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Thank you for the opportunity to respond to these letters. It appears that the letter writers may be looking for a disease caused by isoflavones or other soy components with minimal evidence when contrasted with the considerable amount of evidence for positive health effects of soy and little, if any, reason to suspect increased disease risk of any kind in the large cohort of soy infant formula consumers in the United States over the past 50 years. Readers must make their own judgments based on the peer-reviewed publication record.

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Patricia A. Murphy
Department of Food Science and Human Nutrition, Iowa State University, Ames, Iowa 50011-1061

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