Dr. Michael D Shelby
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1st March 2006

Dear Dr. Shelby

The Sanitarium Health Food Company wishes to submit the following comments for consideration in the development of your final conclusions and recommendations regarding the draft expert panel reports on genistein and soy infant formula. The Sanitarium Health Food Company is a leading Australian manufacturer of health foods, and has produced leading brands of soymilks and soy based meals for over 35 years.

We acknowledge the significant amount of work undertaken by the committee to compile and review the large number of the scientific studies in the area of genistein and soy infant formula. Although it is impossible in the timeframe to review all of the information and studies in the reports, there are several areas of concern to us that we wish to draw your attention to.

Paucity of data relating to human subjects
There is very little information or studies in human subjects available regarding toxic effects of genistein. This makes it difficult to extrapolate the remainder of the data in the reports to the likely effects in humans. It would seem to us then that further study with human subjects is a primary area to be examined, as part of the conclusions of the NIEHS reports. The majority of data comes from rodents (rats and mice), which in this area of human infant health and development, do not have a great deal in common with human subjects. The newborn rodent is recognised as approximating a human fetus during the first trimester of pregnancy. Treatment of rodents at the newborn stage with genistein requires a large extrapolation to draw sound conclusions regarding the impacts on human newborns.

Experimental models
A significant number of studies reviewed in the draft report utilise direct injection of genistein into the newborn animal. Genistein does not occur in large concentrations in human plasma/organs when soyfoods are consumed. Genistein is one of the minor components in the complex of isoflavones in soy and does not enter the bloodstream directly, but in first-pass metabolism is converted to the glucuronic acid complex. Therefore, in human plasma, genistein glucuronide is the major form of genistein. Extrapolating data based on genistein directly injected into animals will present difficulties when, in normal plasma the glucuronide is the major form in which genistein appears.

Focus on genistein – a very minor component of the soy isoflavone complex
Genistein represents only a minor proportion of the total isoflavone content of soyfoods. In fact, the major forms of isoflavones, genistin and daidzin represent 98% of the total isoflavones in soy. Because the first-pass metabolism of isoflavones is bypassed, the dosage rate achieved by injection or stomach gavage will be very much higher than that achieved by

normal soyfood intake. This effectively increases the dose rate of genistein in the experimental models compared to normal human consumption.

Experimental data used to extrapolate toxicity studies (and health benefit studies) becomes very difficult when exposure to the active agent occurs in the experimental model much earlier than it would occur during normal food intake. In most of the studies reported in this document, this is a serious error because of the nature of the animal model itself. In the absence of alternative data, there may be no other information to consider, but care needs to be taken on any conclusions drawn based on this limitation.

Wide Use of Soy Food In Asia

The long-term effects of exposure to soy exposure by humans in early age are available from the studying a large section of the Asian population. Soy foods have formed the basis of the diet in many Asian countries for centuries, with exposures in early age through life of populations bordering between 500,000 up to a billion over this period. There has been no evidence of apparent problems with fertility, reproductive health or developmental health among this group. It is possible that the differences between the Asian and Western populations should be investigated in more detail, but the lack of evidence for reproductive unction at this stage needs to be taken into account.

Some recent work has been done in examining infants fed modern soy based infant formulas. There have been an estimated 20 million US infants fed with modern soy infant formula. A study by Strom et al (2001), although retrospective in design, found that there were no delayed developmental or reproductive effects in adults raised on soy infant formula compared to adults raised on cows milk formula provides strong reassurance as to the safety and efficacy of soy foods for humans. The study samples a relatively small number of adults who had been raised on soy infant formula. A recent study by Giampietro and colleagues (2004) also concluded that soy infant formula feeding in early life did not produce hormonal effects in children up to approximately 8 years of age. Although this study again was small, there were no signs of precocious puberty in girls or gynecomastia in boys who had been exclusively fed soy infant formula. Extending these types of studies is warranted and will provide more appropriate data regarding the short and long-term effects of genistein and soy infant formulas.

We trust that these comments are useful for consideration by the committee.

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Strom BL et al, Exposure to soy-based formula in infancy and endocrinological and reproductive outcomes in young adulthood, JAMA 2001;286:807-14.
Giampietro PG et al, Soy protein in children: No hormonal effects, J Ped Endocrin Metab 2004;17(2):191-96.