IFC

INTERNATIONAL FORMULA COUNCIL

5775 Peachtree-Dunwoody Road, Bldg. G, Ste. 500 ■ Atlanta, GA 30342
(404) 252-3663 ■ Fax (404) 252-0774 ■ E-mail: ifc@kellencompany.com ■ www.infantformula.org

June 30, 2006

Dr. Michael D. Shelby
CERHR Director, NIEHS
P.O. Box 12233, MD EC-32
Research Triangle Park, NC 27709

Re: Written comments on the NTP-CERHR Expert Panel Reports on the Reproductive and Developmental Toxicity of Genistein and Soy Formula

Dear Dr. Shelby:

These comments are submitted on behalf of all U.S. infant formula manufacturers by the International Formula Council (IFC)[*], an international association of manufacturers and marketers of infant formulas whose members are predominantly based in North America.

We wish to make the following observations and comments on the NTP-CERHR Expert Panel Reports on the Reproductive and Developmental Toxicology of (a) Soy Formula and (b) Genistein.

We reiterate the concerns expressed in our earlier comments dated June 11, 2004, on future evaluations of genistein and soy formula, our written comments on the Draft Expert Panel Reports filed on March 1, 2006, and our oral testimony on the Draft Reports presented on March 15, 2006. The IFC believes the safety of soy-based infant formulas has been adequately addressed and there is no new information that provides sufficient justification for a reevaluation of soy formula safety. We therefore reaffirm our position that modern soy-based infant formulas safely provide necessary and appropriate nutrition for normal growth and development in term infants. We wish to remind NTP-CERHR that this view is consistent with the position expressed by the 1997 National Institutes of Health/U.S. Food and Drug Administration Panel Meeting on the significance of phytoestrogens in infant soy formulas, and with the statement of the American Academy of Pediatrics (AAP) that the use of soy-based infant formula is a safe and effective alternative to provide appropriate nutrition for normal growth and development in term infants (1).

Soy protein has played an important medical role in infant feeding for nearly a century. During this period, soy protein-based infant formulas have evolved to become safe and effective alternatives for infants whose nutritional needs are not met with human milk or formulas based on cow's milk (2). From the early 1960s, modern formulas based on soy protein isolates have been fed safely to over 20 million American infants with no higher documented adverse health conditions than breast-fed or cow's milk formula-fed babies. Modern soy formulas meet all nutritional requirements and safety standards of the AAP Committee on Nutrition (AAP-CON) (3) and the Infant Formula Act of 1980 and its 1986 amendments (4). Soy formulas are commonly used successfully in infants with Type I cow's milk allergy, lactose intolerance, galactosemia, and as a vegetarian human milk substitute.

[*] IFC members are: Mead Johnson Nutritionals; Nestlé USA, Inc., Nutrition Division; PBM Products; Ross Products Division, Abbott Laboratories; Solus Products; and Wyeth Nutrition.

Based on the scientific evidence, Dr. Susan Baker, Chair of the AAP-CON in 2001, commented, “Parents can feel confident that soy-based infant formulas are safe. For over 50 years, millions of babies have grown and developed normally on soy-based formulas. Mother’s milk is the best nutrition for babies. The American Academy of Pediatrics policy is that soy formulas are safe and effective for babies who are not being breast-fed and cannot tolerate a cow’s-milk formula.” In conclusion, the long history of safe use, the acceptance of soy infant formula feeding by the FDA and the AAP, and long-term human studies indicating an absence of adverse health effects all clearly demonstrate that soy infant formula is safe and supportive of normal growth, development, and reproduction.

Specific Comments on the NTP-CERHR Expert Panel Report on the Reproductive and Developmental Toxicity of Soy Formula

The IFC reiterates its specific written comments on the Draft Expert Panel Report on the Reproductive and Developmental Toxicity of Soy Formula, submitted on March 1, 2006, and believes they are applicable to the Expert Panel Report on the Reproductive and Developmental Toxicity of Soy Formula. In addition, we wish to make the following general comments:

We note the analysis of the literature has been modestly modified from the Draft Expert Panel Report. Several references have been added to make the analysis more complete. We see the representation of results of the Strom study was made more accurate by clarifying the lack of statistical significance of differences seen in pair-wise comparisons when appropriate multiplicity corrections were included.

Regarding interpretation of the animal data, we wish to make NTP-CERHR aware of a recent publication by Gu et al., (5, attached) which is not cited in the Expert Panel Report. The Gu et al. paper supports and extends our understanding of the differences in metabolism of dietary isoflavones between rodents, pigs, monkeys, and women. These authors conclude, "Thus, there were significant interspecies differences in isoflavone metabolism, and the overall metabolic profile of pigs was closer to that of women than that of rats or monkeys."

The IFC is concerned that the Expert Panel Report does not include any attempt, nor does it suggest as follow-up research, to analyze history of safe use (HOSU) data, despite a vast wealth of human and animal experience that seem to meet the criteria for valid toxicological analysis. For example:

1. Soy formula is used in a traditional medical system.
2. Extensive HCP monitoring of infants assures clinical AEs would be detected and reported.
3. Soy formulas have been and are now ingested.
4. Current and past soy protein isolate ingredients are the same, or similar.
5 .Current and traditional soy formula intakes are the same.
6. Current and traditional soy formula compositions are very similar.
7. Modern duration of use is consistent with historical pattern.
8. Modern indication for use is consistent with historical use.
9. Modern target population is similar to historical population.

HOSU analysis was proposed during the public discussion of the Draft Expert Panel Report in March 2006, yet the strategy is not mentioned or acknowledged in the current Report. When considering the apparent comprehensive nature of the Expert Panel’s analysis, this omission is very difficult to understand, especially the Expert Panel’s conclusion, "Evidence is insufficient."

This continued oversight raises questions about the objectivity and diversity of approach of the Expert Panel. An examination of the composition of the Expert Panel shows a predominance of toxicologists and an underrepresentation of pediatric clinical experts. Also, there were no representatives from veterinary medicine, food animal nutrition, or animal agriculture. These factors make it difficult to understand the Expert Panel's conclusion, "There are insufficient human or experimental animal data available to permit determination of developmental or reproductive toxicity of soy infant formula." Further, the items listed as critical data needs seem to address our earlier concern.

More specifically, we wish to address weaknesses in the below recommended Critical Data Needs:

"Data are needed to describe more carefully human infant exposure to isoflavones in soy infant formula using biomarkers of exposure."

A vast amount of data is currently available to address this issue. Section 1.2.3 of the Expert Panel Report provides an excellent review of much of these data. Table 3 of the Report shows similar isofalvone content of soy infant formulas available in the United States, and the relationships between formula consumption and age are well known. Growth rates and other biomarker results are also well known. The IFC agrees with the conclusion in section 1.3 of the Expert Panel Report, "The available data provide a good foundation for estimating approximate exposure and dose within broad populations or within individuals when the soy formula and infant's weight and age are known," and see no need for further research in this area.

"Another case-control study to examine premature breast development in females and exposure to soy infant formula is needed."

This recommendation is presumed to be triggered by the Freni-Titulare et al. study (Expert Panel Report, reference 162). This study describes a substantial increase in rates of premature thelarche in Puerto Rican children. This is a public health anomaly isolated to Puerto Rico that has been followed since 1978. In a subset of patients, soy formula use was associated with premature thelarche with an odds ratio of 2.2, (90% CI = 1.0-5.2. P = 0.05). However, in the same study, chicken consumption showed a premature thelarche odds ratio of 4.9 (95% CI = 1.1-21.9, P = 0.039). The authors indicated that their multivariate analysis showed no significant associations overall. They also noted that in more than 50% of the thelarche patients, there was no exposure to any of the risk factors (including soy formula consumption) for which statistical associations were found. Monitoring of premature thelarche in Puerto Rico has continued. By 1995, Puerto Rico's Premature Thelarche and Precocious Sexual Development Registry contained 2,716 case reports. Analyses of these data by Colon et al. (6) showed the incidence of premature thelarche in Puerto Rico was 10-15 times the rate in "Olmsted, Minnesota" (note that the soy infant formulas used in Puerto Rico are typically the same brands and have the same compositions as those used the United States). These authors also reported that serum samples of most (68%) thelarche patients contained endocrine-disrupting phthalates, presumed to be from the local environment. IFC believes that the premature thelarche seen in Puerto Rico is an isolated public health problem, is not reproduced in like-fed U.S. populations, and has nothing to do with use of soy infant formulas. We also note that the increase in premature thelarche incidence was quickly identified by the normal health care delivery system as a serious problem. If a similar problem appeared in the United States, it also would be rapidly identified. At least in Olmsted, this was not the case. Taken as a whole, these data do not justify funding new clinical studies to examine premature breast development in females exposed to soy infant formula. Concern about this issue could be fully addressed by a HOSU analysis.

"A longitudinal cohort study to examine postnatal growth and neurobehavioral development of healthy full-term infants fed soy infant formula; these infants should be compared to breast-fed or cow milk formula-fed infants, with particular attention paid to exposure conditions."

Such a study has been underway at the Arkansas Children's Nutrition Center, Little Rock, for some time. While there are some concerns about the design of this study, results could contribute significantly to our understanding of the use of soy infant formulas. IFC does not endorse funding additional cohort studies to examine postnatal growth and neurobehavioral development of healthy full-term infants fed soy infant formula beyond the ongoing trial at ACNC.

"Case-control studies are needed to examine reproductive endpoints, such as age at the beginning of puberty, early age at onset of menopause, endometriosis, uterine leiomyomata, and reproductive organ carcinogenesis and neonatal exposure to soy infant formula and other soy products. These studies should be large enough to ensure sufficient statistical power to detect meaningful differences. Longitudinal cohort studies should be identified that have the potential to evaluate exposure to soy infant formula in relation to these outcomes, including age of onset of menopause."

The IFC sees little practical value in these recommendations. Additional longitudinal studies (beyond those already underway) of sufficient size would be extremely costly and difficult to perform. Study designs aimed at determining age of the onset of menopause endpoints might last more than 50 years. The IFC views analyses of HOSU data as the best and most practical way to generate this kind of information. We reiterate our earlier concerns that there has been no serious attempt by the Expert Panel to gain information from the more than 20 million American infants who have used modern soy formulas. We also note that data from countries with high rates of soy infant formula use, particularly in South Korea, may be useful in understanding the use of soy formula.

Finally, the IFC urges NTP-CERHR to develop a much stronger understanding of the production agriculture uses of soy protein in food animal nutrition. According to Gu et al. (5) the pig represents the animal model closest to human metabolism of soy isoflavones. Soy protein is by far the most widely used protein source in modern swine nutrition. The vast numbers of swine produced by American agriculture therefore represent an opportunity to understand the animal toxicity of soy on a very powerful statistical scale. We recommend NTP-CERHR develop a detailed understanding of the lessons learned by American agriculture about soy nutrition over the last 50 years.

IFC Comments on the Expert Panel Report on the Reproductive and Developmental Toxicity of Genistein

After a thorough review of the contents of the Expert Panel Report on the Reproductive and Developmental Toxicity of Genistein, it is the position of the IFC that this report does not contain information useful in directly evaluating the human reproductive and developmental toxicity of soy-based foods that may contain genistein and other plant isoflavones. The report is restricted to considerations of the effects of genistein by itself. Purified genistein is not equivalent to the mixed isoflavones found in foods, and is not consumed in a food matrix comprised of other components. Validation of this position is found in the fact that the Expert Panel reported no relevant *in vivo* human data evaluating genistein reproductive or developmental toxicity. The data reviewed for genistein contained no clinical data and were almost entirely obtained from animal studies. In many of the animal models used, isoflavone metabolism is substantially different compared to humans. The Expert Panel conclusion that genistein produces developmental toxicity in rats seems valid, but the IFC strongly disagrees with the Expert Panel contention that the experimental animal data are assumed relevant to the assessment of human risk. Much of the testimony given during the March Expert Panel meeting discredited the use of the rodent and monkey models as relevant to soy isoflavone toxicity in humans. The difficulty in applying rodent and monkey data to human genistein toxicity is also documented in the recent Gu et al. publication. Despite these shortcomings it is interesting to note the comment made in section 5 of the Expert Panel Report: "The Expert Panel expresses negligible concern for adverse effects in neonates and infants who may consume up to 0.01-0.08 mg/kg bw/day of genistein aglycone contained in soy formula."

Conclusion

It is the position of IFC that the general safety of soy, and in particular soy infant formula, at levels commonly consumed, has been comprehensively and unequivocally established for humans by extensive clinical research and a very long history of safe use by many millions of people, both in the United States and around the world.

The IFC appreciates the opportunity to comment on the Expert Panel Reports.

Respectfully submitted,

Mardi K. Mountford, MPH
Executive Vice President

Attachment: Gu et al. publication

References:

1. American Academy of Pediatrics Committee on Nutrition. Soy protein-based formulas: Recommendations for use in infant feeding. Pediatrics 1998;101:148-153.
2. Merritt, R.J., Jenks, B.H. Safety of soy-based infant formulas containing isoflavones: The clinical evidence. J. Nutr. 2004; 134: 1220S-1224S.
3. American Academy of Pediatrics Committee on Nutrition. Pediatric Nutrition Handbook. Elk Grove Village, IL: American Academy of Pediatrics, 1993, pp 190, 360-361.
4. The Infant Formula Act of 1980. Public Law No. 96-359, 94 Stat. 1190 [codified at 21 U.S.C. §350(a), 301, 321 (aa), 331, 374(a)]. September 26, 1980.
5. Gu,L., House, S.E., Prior, R.L., Fang, N., Ronis, M.J.J., Clarkson, T.B., Wilson, M.E., Badger, T.B. Metabolic Phenotype of Isoflavones Differ among Female Rats, Pigs, monkeys, and Women. J. Nutrition 2006; 136: 1215-1221.
6. Colon, I., Caro, D., Bourdony, C.J., Rosaro, O. Identification of phthalate esters in the serum of young Pureto Rican girls with premature breast development. Environ. Health Perspect. 2000; 108(9): 895-900.