IFC

INTERNATIONAL FORMULA COUNCIL

1100 Johnson Ferry Road, Suite 300 ▪ Atlanta, GA 30342
(404) 252-3663 ▪ Fax (404) 252-0774 ▪ E-mail: info@infantformula.org ▪ www.infantformula.org

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Via Email and U.S. Mail

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

Re: International Formula Council
Comments on the NTP-CERHR Draft Briefs
on Soy Formula and Genistein

Dear Dr. Shelby:

The International Formula Council* (IFC) appreciates the opportunity to comment on the National Toxicology Program (NTP) - Center for the Evaluation of Risks to Human Reproduction (CERHR) Draft Briefs on the Potential Human Reproductive and Developmental Effects of (a) Soy Formula and (b) Genistein. IFC is an association of manufacturers and marketers of formulated nutrition products, e.g., infant formulas and adult nutritionals, whose members are predominantly based in North America, and most of whom manufacture soy protein-based infant formula products. IFC would like to make the following observations and comments on the NTP-CERHR Draft Briefs.

The IFC would first like to reiterate its position regarding the safety of phytoestrogens in soy infant formulas, which were expressed in the following attached IFC documents: (a) June 11, 2004 comments on evaluations of genistein and soy formula; (b) March 1, 2006 written comments on the NTP-CERHR Draft Expert Panel Reports on the Reproductive and Developmental Toxicity of Genistein and Soy Formula; (c) March 15, 2006 oral testimony on the Draft Expert Panel Reports; and (d) June 30, 2006 written comments on the final NTP-CERHR Expert Panel Reports on the Reproductive and Developmental Toxicity of Genistein and Soy Formula. 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. Further, we reaffirm our position that modern soy-based infant formulas safely provide necessary and appropriate nutrition for normal growth and development in term infants. We again 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 (FDA) 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).

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* IFC members are: Mead Johnson Nutritionals; Nestlé Nutrition – Nestlé USA, Inc.; Abbott's Ross Products Division; Solus Products; and Wyeth Nutrition.

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). Since the early 1960s, modern formulas based on soy protein isolates have been fed safely to over 20 million American infants with no higher documented product-related adverse health conditions than for 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. Soy formulas are commonly used in the nutritional management of infants with Type I cow's milk allergy, lactose intolerance, galactosemia, and as a vegetarian human milk substitute.

Based on the scientific evidence, Susan Baker, MD, and 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 Draft Brief (DB) on the Potential Reproductive and Developmental Effects of Soy Formula

We note that, *"The NTP-CERHR monograph is intended to serve as a single, collective source of information on the potential for soy formula to adversely affect human reproduction or development,"* and, *"is intended to provide clear, balanced, and scientifically sound information."* IFC believes the DB on soy formula fails to achieve these goals, as the information contained in it is incomplete and does not represent the written comments and conclusions of the Expert Panel. The DB is confusing, inconsistent, and not balanced. Therefore, these defects invalidate the DB for its stated purpose.

The first section of the DB accurately identifies the biochemical structures and forms of the three major isoflavones contained in soy. The DB notes, *"The sugar-free forms are the biologically active forms,"* and, *"As much as 99% of the phytoestrogen is bound to another molecule in human blood,"* and therefore is biologically inactive. The understanding that up to 99% of human blood phytoestrogen is in a biologically inactive form is ignored in the later discussion of the relevance of animal model data. While the DB differentiates phytoestrogens as free, bound, and total early in the report, this insight is not applied later in the report.

The DB answers "*Possibly*" to the question, *"Can Soy Formula Affect Human Development or Reproduction,"* but indicates that there is, *"Insufficient evidence for a conclusion."* IFC rejects the contention that this answer is "*collective*" or "*clear, balanced, and scientifically sound.*" If NTP-CERHR considers that it has insufficient evidence to assess soy formula safety, why, among other things, has it failed to perform a history of safe use analysis of soy formula? The final statement of the DB reads, *"While the possibility of adverse effects of soy formula on human reproduction or development has not been adequately studied, no such effects have been reported after more than 40 years of soy formula use in the United States."* During this 40-year period more than 20 million infants have been fed soy formulas. This vast experience with soy formula safety and utility is completely inconsistent with NTP-CERHR's answer of

"Possibly." As indicated in our attached June 30, 2006 written comments on the Expert Panel Reports, IFC is deeply concerned that the DB does not include any attempt, nor does it suggest as follow-up research, an analysis of history of safe use (HOSU) data. As pointed out earlier, this vast wealth of human and animal experience seems to meet the National Research Council Institute of Medicine's criteria for valid toxicological analysis (4):

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 very similar.
7. Modern duration of use consistent with historical pattern.
8. Modern indication for use consistent with historical use.
9. Modern target population similar to historical population.

The omission of HOSU data analysis makes it impossible to consider the DB "*collective*" or "*clear, balanced, and scientifically sound.*"

The DB also answers "*Possibly*" to the question, *"Should Feeding Infants Soy Formula Cause Concern?"* First, it is important to understand the magnitude of the unwarranted and unjustified disruption in infant feeding practices that this position will cause. A pronouncement of *"possible concern"* over the safety of soy formula by a federal agency is likely to cause undue concern among parents of infants that have in the past and are currently feeding soy formulas for legitimate medical reasons. Second, there is no credible evidence to support this conclusion. The DB justifies this conclusion based on *"...the similarity in blood levels of total genistein between the rat study in which adverse effects were reported and human infants on soy formula, as well as the effects on the reproductive system of male marmosets fed soy formulas as infants."* This analysis completely ignores the previously stated importance of considering free genistein (which is known to be higher in rodents compared to humans, as indicated in the Expert Panel Report) in determining biological activity. It also fails to account for the increased estrogenic response seen in both animal models associated with the conversion of daidzein to the far more estrogenically potent equol. The DB acknowledges the Expert Panel's position on both the inadequacy of these animal models and the problem in data interpretation associated with metabolism of daidzein to equol (DB page 4, column 1). It also notes the recent publication by Gu et al., which *"...emphasizes the need for studies that utilize an appropriate animal model* [favoring pigs over equol-producing rats and primates] *and/or take into account species differences in metabolism of soy phytoestrogens"* (5). However, the DB ignores these critical scientific elements in explaining its conclusion of possible concern.

The DB indicates, *"The NTP expresses minimal concern for adverse effects in neonates and infants who may consume up to 8 mg/kg bw/day of total genistein in soy formula."* The DB notes that this level of concern is higher than the *"Negligible concern for adverse effects,"* expressed by the Expert Panel. In justifying this discrepancy the DB again cites the data on blood levels of total genistein in rats versus human infants on soy formula, and the marmoset results. These data were essentially dismissed by the Expert Panel and are now further discredited by Gu et al., which is the only additional data included in the DB that was not reviewed by the Expert Panel.

Finally, and now further supported by the data and conclusions of Gu et al., IFC reminds NTP-CERHR that there is a vast yet currently unexplored opportunity to understand the potential health consequences of dietary phytoestrogens by considering information from US animal agriculture. Soy protein with phytoestrogen levels, typically much higher than in the soy protein isolates used in infant nutrition, is by far the most widely used protein source in modern swine nutrition. Further, swine are closer to humans than rats in terms of estrogenic compound metabolism. The vast numbers of swine produced by American agriculture therefore represent an opportunity to understand the potential toxicity of soy phytoestrogens on a very powerful statistical scale.

Specific Comments on the NTP-CERHR Draft Brief (DB) on the Potential Reproductive and Developmental Effects of Genistein

IFC notes that information contained in the DB on genistein, which describes concerns over infant exposure to genistein, follows the same flawed logic used in the DB on soy formula. Therefore, the above comments also apply to the DB on genistein.

In view of these considerations, it is the position of the IFC that the NTP-CERHR Draft Briefs on the Potential Human Reproductive and Developmental Effects of Soy Formula and Genistein, in their current forms, neither reflect a balanced view of the available science, nor the view of the Expert Panel, and fail to serve their stated purpose. Further, the major implications of stating an unsubstantiated "concern of safety" to millions of parents and consumers who have consumed, are giving, or have given soy formula to their infants can not be underestimated. For these reasons issuance of the Briefs in their current form would be a disservice to the public health goals of CERHR.

Respectfully submitted

[Redacted]

Mardi K. Mountford, MPH
Executive Vice President

Attachments: IFC Comments on the April 13, 2004, NTP-CERHR *Federal Register* Notice re future evaluations of Genistein and Soy Formula (June 11, 2004).

IFC Written Comments on the NTP-CERHR Draft Expert Panel Reports on the Reproductive and Developmental Toxicity of Genistein and Soy Formula (March 1, 2006).

IFC Oral Testimony on the NTP-CERHR Draft Expert Panel Reports on the Reproductive and Developmental Toxicity of Genistein and Soy Formula (March 15, 2006).

IFC Written Comments on the NTP-CERHR Expert Panel Reports on the Reproductive and Developmental Toxicity of Genistein and Soy Formula (June 30, 2006).

References

1. American Academy of Pediatrics Committee on Nutrition. Soy protein-based formulas: Recommendations for use in infant feeding. *Pediatrics.* 1998;101:148-53.
2. Merritt RJ, Jenks BH. Safety of soy-based infant formulas containing isoflavones: The clinical evidence. *J Nutr.* 2004;134:1220S-12244S.
3. American Academy of Pediatrics Committee on Nutrition. Pediatric Nutrition Handbook. Elk Grove Village, IL. 1993, pp 190, 360-361.
4. "Dietary Supplements: A Framework for Evaluating Safety." The National Academies Press. 2005, pp 137-41.
5. Gu L, House SE, Prior RL, Fang N, Ronis MJJ, Clarkson TB, Wilson ME, Badger TB. Metabolic Phenotype of Isoflavones Differ among Female Rats, Pigs, Monkeys, and Women. *J Nutr.* 2006;136:1215-21.