



INTERNATIONAL FORMULA COUNCIL

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Dr. Michael D. Shelby
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Re: Written comments on the NTP-CERHR Draft Expert Panel Reports on the Reproductive and Developmental Toxicity of Genistein and Soy Formula, and request for time for oral public comments during the March 15-17 Expert Panel Meeting (FR Doc. E5-7412)

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 draft NTP-CERHR Expert Panel Reports on the Reproductive and Developmental Toxicology of (a) Soy Formula and (b) Genistein. We also request time for oral public comments during the March 15 Session of the Expert Panel Meeting.

We reiterate the concern expressed in our comments on future evaluations of genistein and soy formula, dated June 11, 2004, that the safety of soy-based infant formulas has been adequately addressed previously and that there is no new information that provides sufficient justification for a reevaluation of soy formula safety. We therefore reaffirm our position that soy-based infant formula safely provides necessary and appropriate nutrition for normal growth and development in term infants. This view is consistent with that 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 position 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 been used 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. They 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.

Many studies support normal growth and development in term infants fed soy infant formula (2, 4-8). Recent concerns raised on the safety of dietary isoflavones in soy infant formulas are based on a relatively small number of animal studies. These animal trials are often characterized by inadequate designs, non-physiological dosages and routes of administration, and conflicting results. The oral-delivery animal studies are inadequate metabolic models for human infants because they generally do not take into account the animal's conversion of oral daidzein to equol, and equol's higher estrogenic potential. Animal data can be suggestive in the absence of human studies, only if the animal models are reliable predictors of effects in humans. The rodent model does not appear to be a reliable model for effects in humans in this particular case. On the other hand, there are many studies in humans that can be used as reliable indicators of safety.

Currently available human infant and adult data show that soy formulas do not adversely affect human growth, development, or reproduction. In a recent review on the safety of isoflavones, Munro et al. (9) stated clearly, "There is no conclusive evidence from animal, adult human, or infant populations that indicates that dietary isoflavones may adversely affect human development or reproduction." Strom et al. (10) evaluated more than 30 developmental and reproductive outcomes in young adults who had been fed soy or milk-based formula in the first 4 months of life. They found similar normal development and reproductive outcomes in both groups with the only differences noted being a slightly prolonged (0.37 day/month) menstrual duration and discomfort with menses, but reproductive outcomes and fertility were not affected. Strom and colleagues note, "Given the large number of comparisons evaluated in these analyses, the few marginally significant findings may be due to chance," and conclude "the findings of the current study are reassuring about the safety of soy infant formula." Based on the scientific evidence, Susan Baker, MD, the 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 Expert Panel's Draft Report on the Reproductive and Developmental Toxicity of Soy Formula

We wish to make the following specific comments regarding the Draft Report on Soy Formula:

Section 1: Chemistry, Use, and Human Exposure:

"We note that the estimated isoflavone intake by infants consuming US infant formula is approximately 8.8 mg/kg bw/day, that the genistein : daidzein ratio in US infant formulas is about 2:1, and that most of the isoflavones in formula are conjugated to sugar molecules to form glycosides which must be deconjugated in order to be biologically active."

IFC Comments

The document provides a useful summary of these data that serve as guidance for clinical and animal model experiments. A conjugated isoflavone oral intake of not more than 10 mg/kg bw/day is a reasonable dosage target for evaluation in animal models of actual human physiology of soy-based infant formulas.

Section 2: General Toxicology and Biological Effects:

"We see that serum isoflavone concentrations of infants consuming soy formula are in the range of 700 µg/L for genistein and 300 µg/L for daidzein, and that these concentrations are 200-250 fold higher than those seen in breast-fed infants, but only about 5 fold higher than Japanese women consuming diets high in soy. A substantial and important difference in isoflavone metabolism is also characterized here: A metabolic pathway for daidzein (mediated by gut micro flora) is conversion to equol. This pathway is

largely inactive in infants and variably active in adults. However, the pathway is highly active in rodents and some primate models where serum equol concentrations are an order of magnitude higher than daidzein. The production of high levels of equol substantially magnifies the estrogenic effects of orally administered isoflavones since estrogen receptor- β has approximately a 25 fold higher affinity for equol versus genistein (ER- β $K_1 = 0.72$ nM vs. 19 nM).

We also note that in rodent models oral doses of isoflavones yield similar serum levels to those seen in soy formula-fed infants but, that IV isoflavone dosage produces serum levels that are more than 100 fold higher than the same dose level given orally."

IFC Comments

Production of high levels of equol from ingested isoflavones in rodent and some primate models makes these models unreliable predictors of biological effects in humans. IV administration of isoflavones further invalidates animal models of oral human isoflavone exposure.

Section 3: Developmental Toxicity Data:

Eighty-four studies are reviewed; 22 evaluated as "Useful", 33 evaluated as having "Limited Utility", and 29 evaluated as having "No Utility".

IFC Comments

(Section 3.1.2.3 Allergy and Immunology) In the review of literature assessing the allergenic potential of soy-based formula, we note the absence of some relevant and important literature. In particular, a study by Halpern (11) where cow milk allergy rates in cow milk-fed infants were compared to soy allergy rates in soy-fed infants. This study demonstrated a 3.6 fold reduction in food allergy in the soy-fed group. Also, studies of the development of soy allergy in milk-allergic infants following soy feeding have been reported by Bock (12), Cantini (13), Zeiger (14), and Kleinola (15). Together these studies show effective management of cow milk allergy with soy-based infant formula in 221 of 247 milk-allergic patients (reviewed by Cordle [16]).

We endorse the use of the Strom study (10, Draft Report references 15, 155) as "best evidence" for the evaluation of developmental and reproductive toxicology outcomes of soy formulas in humans. We believe that this large study of soy formula-fed humans is a much more powerful indicator of potential soy formula toxicity in humans than all of the animal model data. We are concerned that data from this study are often taken out of context or improperly reported. As an example, on page 136 of the Soy Formula Draft Report the "Major findings" for the Strom study are recorded as, "No infant feeding-related differences in adult height, weight, body-mass index, or sexual maturation history; duration of menstrual bleeding was 0.37 days longer and severe menstrual discomfort was more common in women fed with soy formula than with cow-milk formula." This is a (commonly quoted) misrepresentation of the significance of study findings for menstrual bleeding and severe menstrual discomfort as reported by the authors. In the discussion section of their paper Strom and his colleagues comment: "From among the many different factors studied, significant findings were seen only for slightly longer duration of monthly menstruation and for greater discomfort with menstruation. The prolongation of menstrual bleeding was small and was not accompanied by heavier bleeding. Both findings were borderline positive and were 2 of many that were tested. To place this into perspective, if we were to consider a Bonferroni adjustment for the number of hypotheses investigated in this article, neither of these 2 findings would be considered even close to statistically significant at the resulting stricter level of $0.05/30 = 0.0017$. Furthermore, the clinical significance of these findings is not known." We also note that the Draft Report fails to fully acknowledge the lack of differences described by the study in a wide variety of reproductive outcomes (sexual maturation and pregnancy outcomes).

Finally, we find it difficult to assign biological or clinical significance to the animal data reviewed in this section. We agree with the evaluation of the Expert Panel in Section 3.2 that the animal studies reviewed are of limited utility in evaluating the developmental toxicology of soy-based infant formula. We note that of the 27 studies reviewed, 15 were evaluated as having no utility, 12 as having limited utility, and none evaluated as being useful. We also point out that, for the most part, the animal studies failed to account for the presence of daidzein in the animal diets. The rodent chow diet and some of the natural diets often

used as control or breeding diets in these laboratory animal studies contain soy and inherent isoflavones which were most often not considered in the interpretation of the animal data. Unlike human infants, in all of these animal models dietary daidzein is rapidly converted to equol, which has much more potent estrogenic effects compared to daidzein. This makes it impossible to establish dose/response relationships relevant to human infants using these models.

Section 4: Reproductive Toxicity Data:

Twenty-five studies are reviewed; 17 evaluated as "Useful", 5 evaluated as having "Limited Utility", and 3 evaluated as having "No Utility". Generally, we disagree with the Panel's results utility assessments for this literature.

IFC Comment

We question the relevance to the reproductive toxicity of soy-based infant formulas of most of the research reviewed in this section. Studies of the presence or absence of hormonal effects of soy or soy isoflavones in post-pubertal women are not relevant to the use of soy formulas in infants. Aside from the question of relevance, we are concerned that most of these studies did not take into account the equol production status of the study subjects. This literature is confusing and contradictory and may be clarified only in the context of full knowledge of the effects of equol within the study populations. The animal experiments also suffer from a lack of attention to differences in diet daidzein content and equol function. We view the Strom study (10) as the best available assessment of the reproductive toxicity of soy formulas used to feed infants. This study measured 13 outcomes associated with reproductive maturation and function and 12 pregnancy outcomes. Two reproductive function outcomes showed slight differences but, as discussed above, neither was clinically significant nor different by the appropriate statistical test, and there were no differences in any of the pregnancy outcomes.

Specific Comments on Critical Data Needs:

We would like to make some general comments about the incompleteness of the animal data reviewed in the Soy Formula Draft Report. We are disappointed that the Expert Panel did not include any agricultural experts. It should be noted that soy protein, in the form of soybean meal (typically with isoflavone levels exceeding those of soy protein isolates used in human nutrition) is the major protein source in the vast majority of current American agricultural animal starter, grower, and finishing or production rations. The ultimate success of US animal production agriculture requires animal diets that support the highest levels of reproductive efficiency. America produces over 73 million cattle, over 185 million hogs, 93 million turkeys, and about 1.4 billion broiler chickens per year (2002 USDA data). In addition there are approximately 75 million soy-fed dairy cows, and 334 million soy-fed egg-laying chickens annually that contribute to the American food supply. All of these agricultural animal production industries are extremely sensitive to reproduction efficiency or other feeding-related health problems. Soy-based American agriculture is operating at record levels of efficiency and production. Yet, these enormous numbers of soy-fed animals, some of which are much better models of human physiology than isoflavone-treated rodents, were completely ignored in the Expert Panel's evaluation of soy "toxicity".

Summary Comments on the Expert Panel's Draft Report on the Reproductive and Developmental Toxicity of Soy Formula:

Based on our analyses of the information in the Draft Expert Panel Report on Soy Formula and other information reviewed above, it is the position of the IFC that:

Evidence is sufficient to conclude that soy infant formula does not produce developmental toxicity with childhood exposure in boys and girls at levels consumed during normal infant feeding using soy-based infant formulas, as manifested by all practical endpoints clinically tested.

That:

Evidence is insufficient to conclude that soy infant formula produces developmental toxicity in male or female animals at any human-relevant dose, route, or timing of exposure, as manifested by all relevant endpoints. Available experimental animal data and models available are generally not relevant to the assessment of human risk.

That:

Evidence is sufficient to conclude that isoflavones contained in soy infant formulas do not produce reproductive toxicity in men and women fed soy formula as infants at isoflavone levels achieved during normal infant feeding using soy-based formulas, as manifested by all practical endpoints clinically tested.

Finally that:

Evidence is insufficient to conclude that soy infant formula produces reproductive toxicity in male or female animals at any human-relevant dose, route, or timing of exposure, as manifested by all relevant endpoints. The experimental animal data available are generally not relevant to the assessment of human risk.

IFC Comments on the Expert Panel's Draft Report on the Reproductive and Developmental Toxicity of Genistein:

After a thorough review of the contents of the Draft 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 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. Therefore, we conclude that the Draft Report on genistein is not relevant to the current assessment of the developmental and reproductive safety of soy in humans.

To conclude, the general safety of soy as a dietary component, at levels commonly consumed, has been comprehensively and unequivocally established for humans and animals. Artificial laboratory animal models testing dietary components at impractically high doses and by other than dietary exposure routes offer little public benefit in the understanding of practical food toxicology, and should not be supported through continued governmental funding.

The IFC appreciates the opportunity to comment and looks forward to the opportunity to participate in the public discussion of these draft reports on March 15, 2006.

Respectfully submitted,



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