

March 1, 2010

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*Submitted electronically to thayer@niehs.nih.gov*

Dear Dr. Thayer,

The following comments are submitted on behalf of the more than two million members and supporters of People for the Ethical Treatment of Animals (PETA) in response to the Final CERHR Expert Panel Report on Soy Infant Formula published January 15, 2010. PETA is the world's largest animal rights organization and is committed to using the best available science to protect animals from suffering and to promoting the acceptance of human-relevant methods for risk assessment.

In its 2006 report on genistein, the CERHR Expert Panel expressed "negligible concern" for its reproductive and developmental effects in adults and for its effects in infants (CERHR, 2006a). In its 2006 report on soy formula, the Expert Panel concluded that there were "insufficient human or experimental animal data available to permit determination of developmental or reproductive toxicity of soy infant formula" (CERHR, 2006b). In its 2008 Federal Register notice announcing plans for updated evaluations of genistein and soy formula, CERHR stated that it had not completed these evaluations and that it had determined that updated evaluations were needed claiming that "since 2006, a substantial number of new publications related to human exposure or reproductive and/or developmental toxicity" had been published for these substances (CERHR 2008).

In the current report, the CERHR Expert Panel recommended animal experiments examining the effects of:

- soy formula as opposed to individual compounds;
- isoflavones other than genistein;
- soy in the most relevant period of development;
- early life exposures to soy proteins and isoflavones on animal susceptibility to subsequent chemical insults in later life;
- soy or isoflavone exposure during infancy on puberty including additional measures of puberty such as ovulation, gonadotropin secretion and onset of estrus cyclicity;
- soy or isoflavone exposure during infancy on fertility, reproductive senescence, and life span; and
- soy or isoflavone exposure from birth to weaning on non-reproductive behaviors.

As the International Formula Council (IFC) observed in its 2009 comments on the draft Expert Panel report, "concerns raised on the safety of dietary isoflavones in [soy infant formula] are



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mainly based on a relatively small number of animal studies” showing adverse effects (IFC, 2009). Yet in this final report, CERHR has again recommended numerous new animal studies to address effects that are irrelevant to human exposures when human experience and human-relevant studies have clearly affirmed the safety of soy formula for use with infants.

### **Human experience and human-relevant studies**

Soy-based formulas have been used to feed more than 20 million infants in the U.S. since the early 1960s, and the number of adverse effects reported has been no greater than that reported for cow’s milk-based formulas (IFC, 2009). As recently as 2008, the American Academy of Pediatrics stated that “[l]iterature reviews and clinical studies of infants fed soy protein-based infant formulas raise no clinical concerns with respect to nutritional adequacy, sexual development, thyroid disease, immune function, or neurodevelopment” and specifically that “there is no conclusive evidence from animal, adult human, or infant populations that dietary soy isoflavones may adversely affect human development, reproduction, or endocrine function” (Bhatia et al., 2008). The U.S. Food and Drug Administration has also found soy formulas to be safe for use with infants.

Data evaluated by the Expert Panel for its 2006 report show that soy formula does not adversely affect human reproduction or development. In a retrospective cohort study published in 2001, Strom et al. evaluated 952 adults aged 20 to 34 years who had participated as infants in controlled feeding studies conducted at the University of Iowa in 1965-1978. These researchers observed no statistically significant differences between those fed soy formula and those fed cow’s milk formula as infants for more than 30 outcomes. No statistically significant differences were noted for adult height, weight, body mass index, or any of the indexes of pubertal maturation. In addition, no statistically significant differences were noted for a large number of other outcomes including cancer, reproductive organ disorders, hormonal disorders, libido dysfunction, sexual orientation, and birth defects in offspring. The study had sufficient statistical power to detect clinically significant differences between the groups in most outcomes. The authors concluded that their study results were “unequivocally negative across a large number of outcomes that potentially may be influenced by the estrogenic or antiestrogenic activity of phytoestrogens” and were “reassuring regarding the long-term effects of phytoestrogen exposure of this type.”

More recently, Gilchrist et al. (2010) used ultrasonography to assess the size of breast buds, uterus, ovaries, prostate, and testes in 120 human infants exclusively fed breast milk, cow’s milk formula or soy formula. There were no feeding group differences in gestational age at birth; birth weight, length or age; or weight or length at sonography. Among girls, there were no significant feeding group differences in breast bud volume; uterine volume, length or shape; or numbers and mean size of ovarian cysts. Among boys, there were no feeding group differences in breast bud, prostate, or testicular volumes. The authors concluded that their data do not support major diet-related differences in reproductive organ size. In addition, there was no evidence that feeding soy formula exerts any estrogenic effects on reproductive organs studied. Interestingly, there was some evidence that ovarian development may be advanced in infants fed cow’s milk formula, indicating that it may have developmental effects that differ from breast milk.

## **Irrelevance of experiments in animals**

While administration of isoflavones has been shown to adversely affect development in rodents (Gilchrist et al., 2010), such experiments have no relevance to human exposures. Most experiments in rodents differ from typical human exposures in that rodents are administered isolated genistein rather than soy formula at doses far in excess of human exposures via dissimilar exposure routes. Most importantly, rodents have a completely different metabolic profile for isoflavones than do humans.

Results obtained in experiments with isolated genistein have little relevance because soy formula is a complex mixture, the effects of which may be influenced by other components. Moreover, less than 2% of the total content of this isoflavone is present in soy formula as the aglycone. Instead, it is the more prevalent glycosylated form, genistin, to which infants are primarily exposed. Since each is metabolized differently, the ultimate toxicological effects may not be comparable (Badger, 2009). Regarding exposure route, Thomas M. Badger, director of the Arkansas Children's Nutrition Center and principal investigator in the above mentioned study of Gilchrist et al., commented that "[r]odents have limited use (utility) in identifying the effects of soy formula because it is very difficult to 'bottle feed' a newborn rat or mouse." Dietary exposure limits the availability and activity of isoflavones. When injected, genistein bypasses first-pass metabolism resulting in plasma concentrations far higher than when it is administered orally, especially at high doses (Setchell, 2006).

Experiments using oral administration in rodents are also inadequate, however, because rodents convert genistein to equol, which has a much higher estrogenic potential than genistein. Gu et al., (2006) measured the concentrations of isoflavones and their metabolites in serum and urine from rats, monkeys, pigs, and humans after each had consumed diets containing soy protein isolate. Serum from rats and monkeys had equol concentrations of 77% and 52% of total isoflavones plus metabolites, respectively, whereas serum from humans and pigs had undetectable levels of equol. Similarly, urine from rats and monkeys had equol concentrations of 69% and 51% of total isoflavones plus metabolites, respectively. Urine from pigs had an equol concentration of only 2% and equol was again undetectable in urine from humans. Humans and pigs excreted the majority of soy isoflavones as glucuronides and sulfates. The authors concluded that there are significant interspecies differences in isoflavone metabolism with human subjects producing no or little equol compared with rats and monkeys. As Kenneth Setchell, Professor of Pediatrics in the Department of Pathology, Cincinnati Children's Hospital Medical Center, wrote in his 2006 guest editorial for *Environmental Health Perspectives*, "The only appropriate model for postnatal human reproductive development is the human infant."

## **Additional experience with animals**

Soybean meal is an important source of protein in most rodent diets used by breeding and research facilities as well as in diets fed to farmed animals. Rodent chows are typically based on soybean meal with total isoflavone concentrations between 80 and 160 mg/kg body weight per day – higher than doses of purified genistein used in many rodent toxicological experiments and

also orders of magnitude greater than human dietary exposures. Soybean meal is also the basis of diets fed to billions of farmed animals including pigs and egg-laying chickens. Obviously, the success of these industries depends on high reproduction efficiency and would be extremely sensitive to any adverse reproductive and developmental effects of soy (IFC, 2009). As IFC observed, “American farmers have been performing a pig-soy isoflavone feeding experiment more than 200 million times per year for more than half a century.”

### **Conclusions and recommendations**

The absence of adverse effects reported for soy formula during its 40-year history of use with more than 20 million infants is clear evidence of its safety. This has been confirmed by recent human data. There is no justification for more animal studies that are likely to show the same adverse effects already seen in previous animal studies and shown to be irrelevant to human exposures. Instead, retrospective research and clinical studies in humans is the only relevant approach to further examining the safety of soy formula.

Thank you for your attention to these comments. I can be reached at (757) 622-7382, ext. 8001, or by e-mail at josephm@peta.org.

Sincerely,

*[Redacted]*

  
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