NTP BRIEF ON SOY INFANT FORMULA:

PEER-REVIEW COMMENTS AND NTP RESPONSE

SEPTEMBER 2010

National Institute of Environmental Health Sciences

National Institutes of Health

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

On October 2, 2008 (73 FR 57360), the National Toxicology Program (NTP) Center for the Evaluation of Risks to Human Reproduction (CERHR) announced its intention to conduct an updated review of soy infant formula in order to complete a previous evaluation begun in 2006. The preliminary outcome of this evaluation, the draft NTP Brief on Soy Infant Formula, was peer-reviewed by the NTP Board of Scientific Counselors (BSC) on May 10, 2010 at a public meeting. The NTP provided BSC members with this charge:

"To determine whether the scientific information cited in the draft NTP Brief on Soy Infant Formula is technically correct, clearly stated, and supports the NTP's conclusions regarding the potential for soy infant formula to cause adverse developmental effects."

The draft NTP Brief concluded there is *minimal concern* for adverse effects on development in infants who consume soy infant formula. This level of concern represents a "2" on the five-level scale of concern used by the NTP that ranges from *negligible* concern ("1") to *serious* concern ("5"). The BSC voted in favor of the *minimal* concern conclusion with 7 yes votes, 3 no votes, and 0 abstentions. One member thought the conclusion should be *negligible* concern and 2 members thought the level of concern should be higher than *minimal* concern. This report contains a summary of the peer review comments as well as the NTP's response to major comments and recommendations made during the peer review. Summary minutes of the May 10, 2010 BSC meeting are available at *http://ntp.niehs.nih.gov/go/9741*. The final results of the NTP evaluation are published in the NTP Monograph on Soy Infant Formula, available at the CERHR website (*http://cerhr.niehs.nih.gov/)* under "Evaluations." The NTP Monograph contains the final NTP Brief on Soy Infant Formula as well as an expert panel report prepared to assist the NTP in reaching conclusions on soy infant formula.

NTP BSC members in attendance:

Tracie Bunton, Eicarte LLC
Edward Carney, The Dow Chemical Company
Russell Cattley, Amgen
David Eastmond, University of California - Riverside
Elaine Faustman, University of Washington
William Janzen, The University of North Carolina at Chapel Hill
Stephen Looney, Medical College of Georgia
Raymond Novak, Wayne State University (Chair)
Ruthann Rudel, Silent Spring Institute
James Sherley, Boston Biomedical Research Institute

NTP BSC members not in attendance
Janan Eppig, The Jackson Laboratory
Mitzi Nagarkatti, University of South Carolina School of Medicine
Gina Solomon, Natural Resources Defense Council
Justin Teeguarden, Pacific Northwest National Laboratory

The following comments, grouped by topic (in bold type), were presented during the peer review meeting. The NTP's responses to the comments (in italic type) follow each set of comments:

Usage and Exposure

- The NTP Brief should provide more information on what is known about factors associated with individual differences in equol production, including diet and life stage.
- The NTP should consider use of existing physiologically-based pharmacokinetic (PBPK) models in the evaluation.

The NTP added a comment to the NTP Brief directing readers to Section 2.1.1.2 of the final expert panel report for additional information on equol production.

A delayed nonlinear PBPK model for genistein dosimetry in adult rats has been developed that focuses on simulating genistein's ability to suppress biliary excretion (Schlosser et al. 2006; Zager et al. 2007). However, this model does not seem suited to address the major issues related to internal dosimetry identified during peer-review of the draft NTP Brief on Soy Infant Formula, i.e., the conjugation profile of genistein during infancy or the ability of infants to produce equol from daidzein.

Weight of Evidence Conclusions for Adverse Effects on Development

- The NTP Brief should modify the visuals and descriptors used to convey "hazard conclusion" and "level of concern" conclusions.
- The NTP Brief should include better summaries of key information such as the results of animal experiments, be more consistent in the discussion of statistics and provide power calculations for the epidemiology studies, focus on the quality and design of studies rather than the number of studies, explain the rationale for highlighting a conclusion of *some evidence for no adverse effects* on growth in health full-term infants fed soy formula, and include more comparisons with estrogen levels to allow comparisons on the exposure level with the biological effects level.
- The NTP should consider the information from domestic livestock fed soy-based diets.

The NTP concurs that the similar graphics used to present "weight of evidence" and "level of concern" conclusions can be confusing. The NTP is currently in the process of revising how it communicates weight of evidence conclusions and expects that schematics used in future NTP monographs will be more visually distinct, including the usage of different colors and overall layout.

The NTP has modified text in the section entitled "Can Soy Infant Formula or its Isoflavone Contents Adversely Affect Human Development?" Traditionally, the NTP includes a response to this question using one of the following words: Yes, Probably, Possibly, Probably Not, No, or Unknown. The NTP concurs that use of "possibly" may be confusing in light of the overall

conclusion of "minimal concern" but does not feel that a different descriptor would be more appropriate. Thus, NTP has deleted the response "possibly" to minimize confusion.

Most of the scientific support for the conclusions presented in the NTP Brief is based on scientific findings and conclusions presented in more extensive detail in the final CERHR Expert Panel Report on Soy Infant Formula released January 15, 2010 (75 FR 2545, available at http://cerhr.niehs.nih.gov/evals/genistein-soy/soyformula/soyformula.html). The expert panel considered both the quality and quantity of human and laboratory animal studies in reaching its overall conclusion of "minimal" concern for adverse effects on development in infants who consume soy infant formula. In brief, each study is summarized in the expert panel report, including information on statistical analyses. The expert panel assesses the strengths and weaknesses of each study in order to categorize the study as to its utility in the evaluation, i.e., "no," "limited," or "high" utility). The statistical power of studies was a major factor considered by the expert panel and led to many of the human studies being considered as "no" or "limited" utility. Only studies considered of "limited" or "high" utility were used to reach conclusions on potential health effects. The integration of findings from these studies is presented in Section 3.6 of the final expert panel report ("Summary of Developmental Toxicity Data"). Tables 153 to 157 in the final expert panel report summarize the findings in the studies considered to be of "limited" or "high" utility. The summary tables of laboratory animal studies are quite long (~40 pages) and not presented again in the NTP Brief. Instead, the draft and final NTP Briefs direct the reader to the tables in the final expert panel report in the sections on "Supporting Evidence" based on human and laboratory animal studies.

With regard to the conclusion on growth in human infants, the NTP concurred with the expert panel and the American Academy of Pediatrics (AAP) that there is no indication of impaired growth in infants fed soy infant formula. The weight of evidence for this conclusion was stronger compared to other health parameters based on human data ("some evidence for no adverse effects" versus "insufficient evidence for a conclusion"). The NTP agreed with the expert panel that it was important to highlight this conclusion on growth to express concurrence with a similar conclusion presented in the recent AAP policy statement on the use of soy infant formula (Bhatia and Greer, 2008). Text has been added to the NTP Brief to address comments on comparing the levels of estrogenic isoflavones in infants to those of estradiol, the main endogenous estrogen in blood or breast milk.

The NTP considered whether information on domesticated animals, namely pigs, could be considered in reaching conclusions related to use of soy infant formula. However, the literature on livestock pigs was considered of very limited utility because (1) soy protein as an amino acid source is not typically introduced into the diet of pigs until after weaning, and (2) no specific safety assessments of soy isoflavones in diets fed to swine appear to have been conducted (December 3, 2009 public comment received from Dr. Hans H. Stein of the National Soybean Research Laboratory in Urbana, IL available at http://cerhr.niehs.nih.gov/evals/genistein-soy/SoyFormulaUpdt/pubcom/HansStein12-02-2009.pdf)

References

Bhatia, J., and Greer, F. (2008). Use of soy protein-based formulas in infant feeding. *Pediatrics* **121**, 1062-8.

Schlosser, P. M., Borghoff, S. J., Coldham, N. G., David, J. A., and Ghosh, S. K. (2006). Physiologically-based pharmacokinetic modeling of genistein in rats, Part I: Model development. *Risk Anal* **26**, 483-500.

Zager, M. G., Schlosser, P. M., and Tran, H. T. (2007). A delayed nonlinear PBPK model for genistein dosimetry in rats. *Bull Math Biol* **69**, 93-117.