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Arkansas Children's Nutrition Center is an Agricultural Research Service program that is affiliated with Arkansas Children's Hospital and the University of Arkansas for Medical Sciences

Dr. Michael Shelby
CERHR Director, NIEHS
PO Box 12233, MD EC-32
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Re: Draft NTP Briefs on Genistein and Soy Formula.
A public comment.

Dear Sir

It is very disappointing that the NTP decided to publish the two reports in the manner they did and that they also changed the conclusions after the closure of the open panel meetings.

I have the following comments related to the report on Soy Formula

1. Phytoestrogens are really not of similar biological activity to the female hormone estradiol. They have properties similar to SERMs like tamoxifen or raloxifene. They are not complete ER agonists like estradiol. In addition, they affect many other cell signaling pathways in an ER independent fashion.

2. If there is sufficient evidence to conclude minimal concern, then how can there be insufficient evidence? There are no data to suggest concern about safety in soy-fed infants.

3. To think that animals fed genistein-containing diets (or injected with genistein) and that have developmental effects represents a valid model because the blood genistein levels of those animals is similar to those of soy-fed humans is ridiculous. This does not mean that soy-fed infants could possibility have adverse effects. This is a completely specious argument: a) the genistein metabolite profile in rodents and humans is completely different; b) SPI is a complex mixture of protein matrix and phytochemicals. Mixtures may have completely different effects than pure compound in isolation and other components could easily cancel out genistein effects; and c) exposure of neonatal humans to genistein in soy and rats to free genistein in the referenced studies is different.

4. The Marmoset studies do not add evidence that soy may affect human development. Monkeys metabolize phytoestrogens differently than humans and are a bad model for the reproductive effects. Therefore, one cannot conclude anything about humans from these data. It is now known that infants fed soy formula do not make equol; whereas, monkeys make huge amounts.

5. The conclusion in the report that feeding soy formula is cause for concern is based on the false premise that SPI = genistein. This is simply wrong. No adverse effects on reproduction or development reported after > 40 years of soy

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formula feeding to millions of babies! If there was something there we would have picked it up long ago.

I have the following comments related to the report on Genistein:

Infants consume 1-8 mg/kg/d genistein mainly as inactive genistin. Infants never consume free genistein as a pure chemical! And they never will. Therefore to use genistein data to justify any concern about infants fed soy formula is ridiculous. In addition, genistein is conjugated as it crosses the gut wall to mainly inactive glucuronides. Circulating free genistein are much lower in babies (< 10% of dose, c. 200-300 nM) than rats which make more less glucuronide and more sulfate and are much higher in rats fed pure genistein than in rats fed genistin in SPI. Despite this, it requires 35-44 mg/kg/d free genistein to produce adverse developmental and reproductive effects in rodents. Therefore, for genistein to have toxic effects in infants, their consumption would have to be at least 100 x higher than actual limits of consumption. Therefore NTP conclusions about genistein in infants on soy formula as minimal risk is excessive: should be negligible concern.

Exposure pattern in NTP multi-generation study dose do not reflect exposure of infants to genistein as genistin in soy formula just during 0-6 months of life. The NTP study examines the wrong exposure periods to the wrong chemical in the wrong species in an inappropriate context. It is not possible to extrapolate these studies to human infants on formula

Data on coat color changes with genistein in agouti mice are NOT reproducible when SPI is fed during pregnancy in data from my own lab using many more animals than the original Jirtle study referenced.

Concerns about total levels of free genistein in infants fed soy formula are unfounded. The pattern of active vs. inactive metabolites in rats and humans differ substantially even if total levels are similar: rats have far more free aglycone and sulfate than humans where > 90% of total genistein is inactive glucuronide.

Thank you for allowing me to make comments.

Since [Redacted]

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