Isoflavone Content of Breast Milk and Soy Formulas: Benefits and Risks

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To the Editor:

A recent editorial (1) properly credited Franke and Custer (2) for an important study of urinary and breast milk concentrations of isoflavones in women consuming soybeans. This editorial cited literature concerning potential health benefits of phytoestrogens and, to a much lesser extent, potential toxicity. In the accompanying letter below, Franke points out that infants consuming soy-based formula are exposed to high concentrations of phytoestrogens.

Estrogens are two-edged swords in humans; both risks and benefits can be demonstrated in the same person. Two examples are oral contraceptives (benefit: fertility control; risk: increased incidence of breast cancer (3)) and unopposed estrogen replacement therapy (benefit: reduction in mortality due to heart disease and osteoporosis and relief of menopause symptoms; risk: increased incidence of endometrial cancer (4)). Given this characteristic of estrogens generally, what do we know of risks from phytoestrogens?

Adverse effects of phytoestrogens on reproduction and development in wildlife (5), livestock (6), and experimental animals (7) have been documented. Developmental exposure to phytoestrogens results in toxicities similar or identical to those of other estrogens. Neonatal rodents have long been used as a model of human prenatal diethylstilbestrol (DES) exposure on the basis of developmental staging and similar outcomes from exposure (8). However, the neonatal rodent and postnatal human are not at equivalent morphological stages of development (9) and the neonatal rodent does not model the infant human. In addition to lacking a rodent estrogen model of the human infant, we also have little clinical experience with human infant exposure to estrogens generally. Although the data are limited for developmental effects of phytoestrogens, the similarity of DES and phytoestrogen effects in newborn rodents should be considered a cautionary note for the developmentally later exposure that occurs with soy infant formula. As the editorial points out, the beneficial effects of soy-based formulas or of milk from mothers consuming phytoestrogens is speculative. The same is true for potential risks.

Phytoestrogen exposure is quite high; ~20% of American infants receive an isoflavonoid dose from soy formula (expressed as mg/kg) that is about five times higher than the dose that lengthened the follicular phase of the menstrual cycle and lowered lutropin and follitropin concentrations in adult women (10). To my knowledge, only one study is underway in soy formula-exposed infants, despite our great uncertainty concerning benefits and risks of isoflavone exposure.

While metabolism and disposition data are important in both animals and humans, another crucial need is to define appropriate animal models and to explore phytoestrogen effects in these models; to characterize biological effects of phytoestrogens in infants, particularly those consuming soy-based infant formulas; and to be able to compare results across animals and humans. These studies need to define effects as either beneficial or adverse, and to explore a large variety of effects. They should also consider dose response, age at exposure, and length of exposure. Only after completion of such studies can we know the benefits and risks of infant phytoestrogen exposure and thus be able to provide the best advice to parents concerning infant exposures from breast milk and soy-based formulas.

In the meantime, this large, uncontrolled, and basically unmonitored human infant experiment continues unabated.

To the Editor:

The editorial by Slavin (1) summarizes the effects of isoflavones and recent research on human isoflavone exposure, including our studies on breast milk concentrations after soy

consumption (2). Some brief comments may be helpful to add to the current knowledge in the area of isoflavonoid research.

Extensive analyses of isoflavone concentrations in legumes showed that exclusively soy foods contained considerable amounts of these agents, whereas other legumes such as lentils, beans, and chickpeas contained trace or nondetectable amounts (3). A recent study confirmed these results by reporting isoflavone concentrations in lentils, beans, and chickpeas to be lower by a factor of 50 to 5000 relative to soybeans (4).

The higher urinary isoflavone recovery after consumption of fermented vs nonfermented soy foods (5) needs to be verified because the protocol applied resulted in differential isoflavone doses, which might explain the effects observed.

Soy-based infant formulas are known to contain appreciable amounts of isoflavones (6). Unpublished studies in our lab reconfirmed this by showing average concentrations in four soy-based infant formulas of 77 (±25), 18 (±5), and 122 (±35) mg/kg of daidzein, glycitein, and genistein, respectively. Following dosing directions on the label leads to a daily average isoflavone exposure of 6 mg/kg in an infant, which is 4–6 times greater than in adults consuming soy foods regularly. Whether this relatively high exposure results in a beneficial or adverse effect in the infant remains to be determined. Except for legume allergies (7) and one report of three cases of goiter (8), however, acute toxicities and chronic adverse effects in infants fed soy-based formula have not been observed.

Slavin's editorial mentions correctly that further studies are needed to evaluate effects of soy exposure by accurate determination of isoflavone bioavailability, particularly in infants. As pointed out earlier (2), differential conjugation patterns of isoflavones present in soy foods (glucosides) vs breast milk (glucuronides/sulfates) may lead to differential efficiency of systemic uptake of these phytoestrogens in the newborn.

To the Editor:

We were puzzled by the statement in a recent editorial (1) "that infants who consume soy formulas do not receive isoflavones and that the only way they can receive isoflavones is through breast milk."

Franke and Custer (2) use HPLC methods to show that lactating women consuming a diet with a high phytoestrogen content will produce breast milk containing the two isoflavones genistein and daidzein at ~20 μg/L, although there is a large variation between individuals. This is in good agreement with the recently published GC/MS data of Morton et al. (3), who report isoflavone concentrations of ~4 μg/L in the breast milk of Hong Kong women. A typical infant weighing 7 kg and consuming 0.8 L of breast-milk per day should thus have an upper range of isoflavone consumption of ~4 μg/kg body weight per day.

To our knowledge, there have been three reported determinations of the phytoestrogen content of formulas. Nguyenle et al. (4), using HPLC, reported concentrations of the glycoside conjugates equivalent to ~9000 μg/L for daidzein and 24000 μg/L for genistein, averaged over four different formulas. Morton et al. (3) analyzed one formula by GC/MS and found daidzein at 13 000 μg/L and genistein at 8690 μg/L. Dwyer et al. (5) also used GC/MS and found lower values, but still in the range 200-1400 μg/L for daidzein and 600-3100 μg/L for genistein—despite stating in their results that the formulas were nearly/virtually devoid of these compounds.

Even considering these lower values, infant formulas clearly contain at least 10-fold the amount of phytoestrogens found in breast milk—and the other data indicate that the difference may be as much as 1000-fold. This means that the phytoestrogen intake of the infant described above would increase to a minimum of 90 μg/kg body weight per day, up to 4000 μg/kg body weight per day when fed infant formulas (6). This is to be compared with the intake of an adult consuming a daily ration of 50 g of soy protein, i.e., 700 μg/kg body weight per day of isoflavones, an amount known to cause hormonal effects in premenopausal women (7).

Very little of the isoflavones exists in their free form in either breast milk or soy formulas. The isoflavones in the soy products are in the form of glycosides; those in breast milk, as glucuronides. The bioavailability of these compounds may be a function of the conjugating group as well as the gut microflora of the individual, but the absorption and subsequent metabolism of these compounds by infants has not been fully investigated. The possibility that infants may be being exposed to phytoestrogens at concentrations greater than those found in breast milk is cause for concern, given the evidence that hormonal imbalance early in life can affect the sexual development of some animal species (8)(9)(10)(11)(12)(13).

A recent statement has recommended that breast milk and cow's milk formulas should be preferred to soy-based formulas for feeding infants in the absence of other factors that preclude the use of nonsoy protein (6). From the point of view of phytoestrogen content, we think that breast-milk *is* to be favored for infant nutrition, not because it is the sole source of these compounds for infants but because it is relatively free from them.

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The author of the Editorial referred to replies to the above Letters:

Joanne Slavin

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To the Editor:

In reply to the comments regarding my editorial on phytoestrogens in breast milk (1), I appreciate the clarification on isoflavone content of soy-containing infant formulas. As I mentioned recently (2), I relied on a research article that stated that soy formulas were devoid of isoflavones, whereas as described by Bluck and Bingham above, soy formulas are rich sources of isoflavones, and the calculations of Franke show that infants fed soy-containing formulas are exposed to much higher concentrations of isoflavones than are breast-fed infants.

We know little about the bioavailability of isoflavones in breast milk and soy-containing infant formulas. Isoflavones in breast milk are in the form of glucuronides, whereas those in infant formulas are in the form of glycosides. Further, breast milk is a rich source of oligosaccharides, and breast-fed infants have a higher concentration of bifidobacteria in their guts than do formula-fed infants. Because phytoestrogens are metabolized in the gut by the microflora before absorption, these differences in gut microflora need study in assessing the exposure of infants to phytoestrogens.

As discussed above by Sheehan, adverse effects of phytoestrogens in animals argue for a careful study of phytoestrogen metabolism in human infants. Lack of a rodent estrogen model for the human infant limits research in this area. Although Bluck and Bingham mention studies that support that hormonal imbalance early in life can affect the sexual development of some species, Franke points out that the long history of successful feeding with soy infant formulas argues that soy consumption is safe for infants. In fact, soy-containing infant formulas have been fed to human infants for >40 years without any reports of adverse effects of phytoestrogens. Londitudinal studies of infants fed soy formulas should be conducted to document that there are no signs of increased disease risk in this population.

The uncertainty in this area has prompted the UK Ministry of Agriculture Fisheries and Food to recommend that breast milk and cow's milk formulas should be preferred to soy-based formulas for feeding infants in the absence of other factors that preclude the use of nonsoy protein (4). The research to support this recommendation is not compelling, but

infant feeding practices always support a conservative approach. This area awaits the results of clinical trials of soy infant formulas to support whether the phytoestrogens in soy are at least neutral or perhaps even have a positive effect on health status.

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