

Soy and Children's Health: A Formula for Trouble?

Considerable research data has attributed health protective benefits to phytoestrogens, isoflavone chemicals found in soybeans (and soy products) that act as weak estrogens in the body. Reported benefits include protection against several forms of cancer and reduced risks of cardiovascular disease and osteoporosis. While, the research emphasis has been on adult diets, scant data have been collected on the potential short- and long-term effects of phytoestrogens in children. Increasingly, new research is questioning the purported health benefits of soy in adults, as well as raising concerns about adverse effects in children. Defining such effects and determining their significance are the goals of NIEHS researchers Retha Newbold, a biologist in the Environmental Toxicology Branch, and Walter Rogan, a senior investigator in epidemiology.

Research conducted by Kenneth Setchell, a professor of pediatrics at Cincinnati Children's Hospital Medical Center in Ohio, found that infants fed soy formula consume up to 11 mg/kg per day of isoflavones, compared with approximately 1 mg/kg per day taken in by adults eating moderate amounts of soy. Of the isoflavones in formula, genistein accounts for more than 65% of the total and is predominantly linked to sugar molecules. Due to metabolism of the sugar molecules, however, only 1–2% of the circulating phytoestrogens are the bioactive form. However, says Newbold, animal studies show that even low blood levels of bioactive genistein can produce significant accumulation in endocrine-responsive tissues.

According to Rogan, infants fed soy formula are at the highest end of human phytoestrogen exposure because all of their calories are derived from soy. Because soy isoflavones are active as hormones in laboratory animals and are thought to be active in people, there is considerable interest in whether they might be active in babies who are fed soy formula. "The question is," says Rogan, "what would happen if you had a biologically active amount of estrogen going into a baby."

Answers to that question are challenging. Newbold believes that there is cause for concern and is using rodent models and *in vitro* systems to investigate the question more fully. "Someone asked me, 'Do you really think that soy infant formula is really

harmful to kids?' My answer was another question: 'Do you really think excess estrogens are harmful to kids?' That is the issue. I happen to think that they are. There are plenty of examples where excess estrogens are not good. Developmental exposure to diethylstilbestrol (DES) and its well-known adverse effects is just one example. That's been well documented in experimental animals and in humans," she says.

However, Newbold's concern is not universal. The American Academy of Pediatrics supports soy formula as a safe and effective alternative for infants "whose nutritional needs are not being met from maternal breast milk or cow milk-based formulas." In the United States, 20–25% of infants consume soy formula at some point



Food for thought. Researchers are debating the relative safety and risk to infants of consuming soy—a source of environmental hormones—in formula.

during their first year. Soy formula is available off the shelf in the United States, but available only by prescription in Europe. "The bottom line, as we see it, is that soy formulas are safe," says Mardi Mountford, executive director of the International Formula Council. "They've been extensively studied in controlled clinical research. All of this data shows that the [soy-fed] infants grow and develop normally." Setchell asserts that soy formula has an established safety record, and believes that if effects do exist, they may not necessarily be detrimental. "I think there might be subtle effects. If you want my honest opinion, I believe that the subtle effects are more likely to be ones that would demonstrate beneficial effects in the long term," he says.

Animal Studies

Newbold's concern is based in part on findings from a recent study published in the June 2001 issue of *Cancer Research* in which she and her colleagues demonstrate that genistein can trigger reproductive tract abnormalities in aged mice, including uterine adenocarcinoma, a rare form of cancer. In this study, newborn mice were given subcutaneous injections of genistein at a daily dosage of 50 mg/kg. The researchers indicate that although this dosage is higher than the daily amount that infants receive from soy formula (which they estimate at up to 11 mg/kg), it is within an order of magnitude. However, Setchell characterizes the genistein dosage in this study as "massive" and questions

whether the route of administration accurately parallels human dietary exposures. "The route of administration of these compounds has a very big bearing on the action of the compounds. When you inject, you bypass completely the intestinal metabolism of isoflavones, which is quite unique, and it's quite different in rodents than it is in humans," he says.

Newbold agrees that the method of administration is important in animal studies, but further data compiled by Newbold and Dan Doerge, a researcher at the Food and Drug Administration, suggest that in this case it doesn't undermine the findings. These data (slated to be published in an upcoming issue of *Cancer Letters*) arise from a comparison of subcutaneous and

dietary exposures and indicate that both result in very similar serum levels of genistein. Additionally, Newbold reports that these levels and their chemical forms are similar to those reported in humans. "The amount that is actually getting to the target tissue is very similar to what's happening to humans. We're simply not out of the ballpark with our exposures," she says. "I recognize the fact that I'm working with experimental animals and we really have to be very careful when extrapolating data to humans, but I think it's a lot better to be checking this out in an experimental system than testing it on kids," she says.

New information from Newbold's lab (recently accepted for publication in *Biology of Reproduction*) shows that the ovary, in particular, is a target for the developmental effects of genistein. These ovarian effects are consistent with early reproductive aging.

One point on which investigators agree is that epidemiologic studies could provide needed information. "Frankly, there is no animal model that is suitable for the human neonate to really study the effects on development and reproduction," says Setchell. The gold standard would be a prospective long-term study in a very large cohort.

Human Studies

According to Rogan, whether phytoestrogens are biologically active in infants is an open question: "If these things are estrogenic in other systems, [such as] cell receptors and animals, are they estrogenic in kids?" Aside from a small study conducted by Setchell that demonstrated a link between phytoestrogens in soy formula and decreased cholesterol synthesis rates, there are no short-term data in infants. "I think this is something that a lot of people are interested in, but everybody's carrying out discussions in a data-free environment," Rogan says.

Regarding long-term effects, a lone epidemiologic study compares fertility and reproductive end points in young adults who were fed either cow milk formula or soy formula as infants. This study, published last year in *JAMA*, found only subtle effects including slight increases in the length of women's menstrual cycles and the amount of discomfort during menstruation. Still, no epidemiology studies have followed long term outcomes.

Through the upcoming Study of Estrogen Activity and Development (SEAD), Rogan and his colleagues plan to begin filling the void on short-term effects. The SEAD, which is composed of four pilot

investigations, focuses on the development of hormonally responsive tissues and the levels of phytoestrogens and naturally occurring hormones over the first year after birth. "We are reasoning that by examining the hormonally responsive anatomy in infants and watching as maternal estrogen effects wane, the effect of an active estrogen in the child's diet would be to prolong those physical findings," Rogan explains. The investigations will be carried out in three groups of infants grouped by their feeding regimen: soy formula, cow milk formula, and breast milk.

Mountford is unconvinced that this study is necessary. "When we see a proposal like this one from the NIEHS, there does not seem to be any clinical basis for this kind of study that we're aware of. The first question that comes to mind is, why do it?" she says. Mountford points out that pediatricians have seen millions of infants fed soy formula, and it seems that even subtle effects would be apparent. "It seems that it is grasping for straws to think that there might be an effect out there that no one has ever seen," she says. However, Rogan disagrees that subtle effects would be noticed, even given the numbers of children who have been raised on soy formula. "I think that the apparent lack of effect can be taken for the lack of an obvious effect, but subtle changes in the hormonal anatomy have simply not been looked at," he says. "Unless things are really kind of big, they don't just pop out of an unstudied phenomenon," he says.

In the Face of Uncertainty

Researchers agree that a biologic response to phytoestrogens in infants and young children is likely and that a lack of data hinders its characterization. Although Setchell doesn't believe that worry about effects is justified, he agrees that there is a need for more data: "[When] we've had so many infants raised on soy formula and we haven't really seen these horrendous effects that people keep saying these compounds cause, then there's probably no reason for concern. However, I accept that the lack of evidence is not evidence for the lack of effect."

In the meantime, Newbold and Rogan will continue to look for evidence, one way or the other. "I think we just don't have enough information," says Newbold. "I hope I'm wrong, but in case I'm not, experimental animals are telling us this is something to worry about."

Julia R. Barrett

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NIEHS Puts A New Face on Public Service

Beginning in summer 2002, new NIEHS public service announcements (PSAs) will begin appearing on network and cable television stations across the United States. The commercials, produced by the award-winning St. Charles, Missouri—based media company Banyan Communications and shot in Los Angeles, California, have also been shot in Spanish and distributed to Spanish language stations. The new PSAs, developed by NIEHS public affairs specialist Lou Rozier to update ones that have been running since 1999, are intended to promote the NIEHS as an accessible source of information on environmental health.

Targeted at young families, the new PSAs serve to remind everyone that they can be exposed to serious environmental health hazards at home in the form of tobacco smoke, pesticides, and household chemicals such as pesticides, and that protecting themselves is not only important, but also easier than they may realize. The PSAs, whose overall theme is "Your Environment Is Your Health," each focus on one of four areas of risk in everyday household situations, and present easily

implemented tips for people to help them and their children to live healthier.

The PSA that looks at asthma, which was developed with input from Darryl Zeldin, senior scientist in the NIEHS Laboratory of Pulmonary Pathobiology, provides parents with a number of small but effective changes, such as cleaning with HEPA filter—equipped vacuums and removing rugs and other dust-catching items from children's rooms, that they can make to help improve their home environment for their asthma-suffering children.

In the PSA on pesticides, a mother and her baby are playing outdoors when she finds a sign saying that the grass on which her baby is crawling has recently been treated with pesticides. It continues with the announcer saying what should be done if someone is accidentally exposed to pesticides, and shows the mother taking her baby inside quickly and washing both it and its clothes. The third PSA reminds the viewer on the dangers of gasoline vapors, while the fourth, featuring a family at home around the dinner table, depicts a familiar scene—a guest lighting a cigarette at the dinner table. In this case, the guest is asked in a friendly manner to take his cigarette outside, a good example for those people looking for an example of how to politely deal with this often-encountered situation.