Cincinnati Children's

change the outcome®

March 1, 2006

Michael D. Shelby, Ph.D.
NIEHS EC-32
PO Box 12233
Research Triangle Park
NC 27709

Dear Dr. Shelby,

I have read with interest the NTP-CERHR Expert Panel Report on the Reproductive and Developmental Toxicity of Soy Formula and have the related draft report on Genistein. Both of these reports are lengthy reviews of the literature and provide investigators with a useful reference source of this field. I would like to offer some of my own perspectives on this overall and important issue of the safety of soy formula.

Neither of the Draft Reports came to my attention until very recently and there has been insufficient time to make a detailed response to the documents. I want to focus my attention on the Draft Report dealing with soy infant formulas and offer some general thoughts and comments based on my 30 year experience of this field and with reference to my work. Regarding the Genistein Draft Report, in the absence of being able to read this document thoroughly, I have just brief comments at this time.

Genistein is clearly a bioactive molecule, one that appears to display many of the characteristics of selective estrogen receptor modulators (1) and not of estrogens as is so often portrayed by the media. This distinction is important to realize, because it has implications for the potential clinical actions of the molecule. Genistein, with few exceptions is not a major dietary constituent of soy foods unless these have undergone fermentation, as in foods such as tempeh, natto, and to some extent miso, consumed mainly by Asians (2). It accounts for <2% of the isoflavone content of the soybean, soy proteins and most western soy foods, including soy infant formulas (3, 4). The liberal use of genistein in the form of supplements for adults, or food additives should be of some concern, and it is debatable whether it should be regulated as a pharmaceutical, rather than fall under the radar as a dietary supplement. While innumerable studies of genistein in animal models clearly show that adverse reproductive effects can be demonstrated, these findings should be cautiously extrapolated to humans consuming soy foods, and especially to infants feeding on soy formulas.

It is difficult to understand the agenda driving the negative campaign on soy infant formulas, especially given that this is a feeding regimen that has been in use routinely for over 40 years without any solid evidence of toxicity in healthy full-term infants, or in adults later in life. In 2001, at the invitation of the Korean Academy of Pediatrics I was asked to address the issue of the safety of soy infant formula and isoflavones and learned, to my surprise, that unlike other Asian countries, Korean infants (90%) are predominantly bottle-fed, and of these, almost half are fed soy formula and this practice has been in use for over 30 years. One of the leading brands of soy formula in Korea is made from whole soybeans, and its isoflavone content we found to be 5-fold higher than Western soy formulas that are formulated with isolated soy protein (Setchell unpublished data). The earliest soy formulas used in the USA were formulated with soy flour, which would also have had a higher isoflavone content than current formulas. I would estimate that about 20-30 million infants worldwide have been raised on, or exposed to soy infant formulas and their constituent isoflavones. The magnitude of this 'cohort' is such that adverse effects would surely have been noticed, even by default – certainly had this been a drug/pharmaceutical study

spanning 40 years with this statistical power, soy formula would have been considered a completely safe entity. Before alarming the public, it is my view that any perceived negative effects of soy infant formula on reproductive health should be demonstrated by toxicologists and public interest groups leading this 'anti-soy' campaign, and not be assumed based on the biological actions of genistein in animal models, most of which are inappropriate as a model for the human infant.

In considering the published literature, I would recommend that much of what has been shown in immature and adult rodents be disregarded as irrelevant to the human newborn and infant. The stage of reproductive development and neuroendocrine regulation of reproductive aging of a mouse/rat on neonatal days 1-5 is not comparable to a newborn infant but developmentally is considered more like that of the human fetus in the first trimester. Interestingly, outstanding work published by many investigators, including those at NIEHS in the 1980's used the prenatal and neonatal mouse as a model for fetal exposure and development in elucidating the mechanisms of delayed adenocarcinoma in the daughters of women exposed to DES during pregnancy. This was considered an appropriate model for human fetal development, but now, some 20 years later, it is being inappropriately used to extrapolate findings of the effects genistein in the soy formula-fed infant. Without laboring this point, it is well accepted that there is no satisfactory animal model to study reproductive development of the human newborn, unless we use the human infant. Only a long-term large prospective study in infants will help to resolve this issue and that is unlikely to happen for logistical and cost reasons. We clearly do not need further rodent studies since there is more than adequate literature showing deleterious effects of high doses of isoflavones, particularly injected, on reproductive development in newborn rodents. How valid the other animal models are, is also debatable.

Route of administration is probably the most crucial factor to be considered, in reviewing all data on genistein. The pharmacodynamics of genistein is totally different when injected versus given orally (5). Injecting the aglycon, genistein, as has been almost universally done in newborn animal studies is not representative of an infant consuming isoflavones from soy because injection bypasses first-pass metabolism, so crucial in determining the action of a molecule. By contrast, oral administration of isoflavones leads to significant Phase II metabolism and isoflavone glucuronides become the major circulating forms in plasma, not unlike endogenous estrogens (6). This is true for rodents and humans. This conjugation takes place during transport across the enterocyte and also in the liver. The Draft report states that 'human infants may have limited ability to glucuronidate isoflavones because UDPGT is low in the neonate and infant' – referencing studies in mice. However, when isoflavones are delivered at nutritional levels in soy infant formula, they are almost exclusively conjugated to glucuronic and sulfuric acids, in common with endogenous steroids. In the rat/mouse, where relatively huge doses of genistein (up to 50 mg/kg/bw) have been administered in many studies, the K_m and V_{max} for the conjugation reaction is clearly exceeded and genistein then circulates to a large extent in the free (unconjugated) form and therefore will behave biologically differently. Our published study of the deleterious effects of soy on reproduction and liver function in the captive cheetah (7) is often cited as an example of caution for soy foods. I would point out that the cheetah, in common with most feline species, lacks UDP-glucuronyl transferase activity, and therefore cannot conjugate ingested isoflavones and endogenous estrogens. For this reason soy is particularly detrimental to this animal species (7). This a clear example of the need to consider species differences in the metabolic handling of isoflavones when extrapolating findings to humans.

The metabolic transformation on first-pass absorption is crucial, in both the rat and the human, because it is the unconjugated form that is available for receptor occupancy and it is this concentration that has to be considered when making comparisons of the actions of isoflavones. An additional factor to consider is the extent of protein-binding which differs considerably for daidzein, genistein and equol. The intestine provides a key barrier to limiting the biological activity of isoflavones administered orally. Not only does the enterocyte conjugate isoflavones on first pass, but there are also specific intracellular efflux pumps, such as the multidrug resistance protein (MRP2) that shunt isoflavones back into the intestinal lumen. Collectively, events within the lumen and across the enterocyte serve to account for the limited bioavailability of genistein when given orally, which in the rat and the human is typically in the range of 7

-15%. Delivery of genistein directly by injection leads to plasma concentrations that are far higher in concentration than if administered orally, and more importantly differ in qualitative composition as a function of dose. It is frequently and naively stated by many investigators that their study design led to isoflavone concentrations in the rodent comparable to that of human infants fed soy formula, but this is misleading and of little relevance when route of administration differs.

We should ask the crucial question of why studies have not been conducted in the neonatal rat or mouse with oral administration of genistein, or what would be more relevant to soy infant formula, with genistin, rather than genistein. Even though the neonatal rat does not forage for food until about days 15-16 of life, it is still possible to expose the neonatal rodent to isoflavones via the dam since there is adequate transport of isoflavones to the offspring during suckling (8, 9) – after all, infants are exposed to isoflavones orally and not by injection, and it is genistin that is consumed while there are negligible levels of genistein in soy formula. The reasons are clear. No alarming effects would be observed if rodent experiments are designed in this manner. This is because most rodents worldwide are exposed orally to very high levels of isoflavones (80-160 mg/kg body weight; (9) throughout pregnancy and development because the majority of rodent chow purchased by animal breeding houses and Institutional animal facilities is formulated with soy and contains very high levels of isoflavones (9-11). Reared on these rodent chows these animals experience no overt reproductive problems when exposed in this manner, and with doses far higher than those that have been given by injection. This clearly underscores the differences in observed effect subject to route of administration. Soy formula delivers genistin orally to the infant, and if soy formula and its isoflavones were the subject of a pharmaceutical entity then the FDA would require all safety/toxicity studies to be carried out via oral administration, and not by injection and furthermore the formulation tested would have to be genistin and not genistein. To my knowledge few studies have been performed with genistin.

The mouse and rat metabolize isoflavones completely differently from humans. Rodents metabolize soy isoflavones to predominantly equol (12, 13), and are extremely efficient at this biotransformation. Indeed, it has been my contention that equol, and not genistein, is the likely active agent accounting for the actions of soy in rodents. Even the newborn rat pup has mostly equol circulating when suckling on a dam fed a soy-containing rodent chow (9). This is in stark contrast to human adults where the frequency of equol-producers is only 20-30% in Westerners, but much higher in Japanese adults (55%) and vegetarians (59%) (12, 14). By contrast, the human infant fed soy formula fails to synthesize equol early in life (3, 4). This difference may seem subtle but is important because using genistein in rat studies cannot be considered as representative of soy intake by a rodent. In fact, our pharmacodynamic and pharmacokinetic studies in the rat indicate that feeding equol results in a profile that most closely relates to feeding soy in this species (5).

So we are left pondering what all these animal experiments mean. To deny that soy isoflavones have biological effects would be absurd, given a wealth of evidence, from in vitro, in vivo, cellular and molecular studies. Rodent studies are valuable in permitting structure/activity relationships to be probed. Studies of the timing of vaginal opening, or measurement of ano-genital distance (15) that have little meaning to the human but are influenced by isoflavones, merely tell us that these molecules are biologically active and can induce estrogen-like effects in some tissues and at certain periods of time. They do not determine that the effects are necessarily negative, and might even be beneficial in the long-term. This is well illustrated from the studies by Lamartiniere et al that show beneficial effects on rat mammary gland morphology from early exposure to genistein that equate to enhanced chemoprevention for breast cancer (16). Similarly, effects of feeding soy isoflavones on the rat prostate could be considered as a benefit. The endocrine-modulating effect of soy was first demonstrated in Western women by the observation that daily soy food consumption prolonged the length of the menstrual cycle and suppressed the mid-cycle surge of LH and FSH – it did not affect ovulation (17). The much longer menstrual cycle length of Japanese women who consume soy foods regularly (32 days vs 28 days for Western women) is considered a benefit in terms of reducing risk for breast cancer and one could make a case that a 28 day menstrual cycle length in abnormally short when compared with Japanese women. This is a good example of how research studies can be construed differently depending on the yardstick used as the reference.

In my opinion, extrapolating the findings of deleterious effects on reproduction observed in animal studies of genistein, to a human infant fed soy formula, is making a quantum leap of faith and is irresponsible. While many of the findings are interesting, they are not at all surprising, and have absolutely no relevance to this clinical situation. Infants are just not fed or injected with genistein.

Soy infant formulas, and for that matter soy foods, have a long history of safe use and are nutritionally sound (18, 19)). Women throughout Asia are exposed to soy isoflavones through many soy foods throughout pregnancy and isoflavones readily cross the placental barrier and reach the fetus, a critical period for reproductive development. I am unaware of any deleterious effects of feeding soy formula to healthy full-term infants, but rather than suggest that we have not looked for effects, it should be incumbent on toxicologists to present definitive cases of adverse effects of feeding soy formulas to healthy infants before creating the sort of media circus we have seen in recent years. If the hypothesis is that soy formulas are unsafe that should be proven. Save a few exceptions, and these relate to infants with pre-diagnosed disease, there is a paucity of conclusive evidence for negative effects of soy formula on growth and development, pubertal development, reproduction, thyroid function, and cancer of humans. I cannot comment on immune responses since this is outside of my area of expertise, while we are fully aware that allergy to soy, the frequency of which is much lower than allergy to cows milk, is perhaps the only solid concern for soy products.

Only a long-term prospective study in humans will clarify this issue. We clearly do not need further rodent studies which serve little value, other than wasting tax payers money - money that could and should be spent addressing soy formula and human infant studies if this issue is to be successfully resolved. Indeed, it would be my prediction that if a long-term prospective human study was performed we might be surprised to find that there are significant health benefits from early feeding of soy formula, and for that matter soy foods in children and young adults, that relate to longer term disease prevention. Anecdotally, there is evidence showing that as the Japanese are changing the traditional diet and eating less soy foods, there has been a notable increase in the incidence of the chronic diseases of Westerners who generally are not exposed to soy foods. This of course is not proof but interesting association of the potential of including soy foods in the diet for disease prevention. To condemn soy formula based on scant clinical data and animal data that has questionable validity to the human infant would border on irresponsibility and would do a disservice to the pediatric population. In the absence of solid proof to the contrary, common sense should prevail and this panel should look at the bigger picture of soy food consumption worldwide when making a decision on safety.

Sincerely,

Kenneth Setchell. Ph.D.
Professor of Pediatrics
Department of Pathology
Cincinnati Children's Hospital Medical Center
3333 Burnet Avenue
Cincinnati, Ohio 45229

E-mail address: Kenneth.Setchell@cchmc.org

Acknowledgments: I wish to point out that my colleagues and I first identified equol in human urine more than two decades ago and we showed that it was derived by the action of intestinal bacteria on isoflavones present in soy. This led to our proposal that these non-steroidal estrogens may be helpful in the prevention and/or treatment of many hormone-dependent diseases. This early research, conducted in London, England, was exclusively funded by the Medical Research Council, London, UK. Over the last 20 years, financial support for my research has come from Cincinnati Children's Hospital Research Foundation, and since 1986, I have been awarded collectively > $5 million in funding from the National Institutes of Health (R-01 CA56303-03; R01-CA73328-03; R01AT002190; R01AT003313), the Food

Standards Agency (FSA # grant T05019) and the Ministry of Agriculture Fisheries and Food (MAFF Project FS2903) in collaboration with Dr. Aedin Cassidy (presently at the University of East Anglia, UK), the American Cancer Society, and the American Institute of Cancer Research (in collaboration with Stephen Barnes, at the University of Alabama in Birmingham). By comparison, over this period a negligible amount of funding (<2%) has been obtained from industry; indeed had my research program depended on industry funding it would be non-existent. I have no investment in soy formulas, or any conflict of interest related to my expressed views on this issue. None of my research is funded or influenced by the soy infant formula industry.

References:

1. Pike AC, Brzozowski AM, Hubbard RE, et al. Structure of the ligand-binding domain of oestrogen receptor beta in the presence of a partial agonist and a full antagonist. Embo J 1999;18:4608-18.
2. Coward L, Barnes NC, Setchell KDR, Barnes S. Genistein and daidzein, and their b-glycosides conjugates: anti-tumor isoflavones in soybean foods from American and Asian diets. Journal of Agricultural and Food Chemistry 1993;41:1961-1967.
3. Setchell KDR, Zimmer-Nechemias L, Cai J, Heubi JE. Exposure of infants to phyto-oestrogens from soy-based infant formula. Lancet 1997;350:23-7.
4. Setchell KDR, Zimmer-Nechemias L, Cai J, Heubi JE. Isoflavone content of infant formulas and the metabolic fate of these phytoestrogens in early life. Am J Clin Nutr 1998;68:1453S-1461S.
5. Brown NM, Setchell KDR. Efficient transplacental passage of isoflavones. Presented at 5th International Symposium on the Role of Soy in Preventing and Treating Chronic Disease. 2003;September 21-24, Orlando, FL.
6. Setchell KDR, Brown NM, Zimmer-Nechemias L, et al. Evidence for lack of absorption of soy isoflavone glycosides in humans, supporting the crucial role of intestinal metabolism for bioavailability. American Journal of Clinical Nutrition 2002;76:447-53.
7. Setchell KDR, Gosselin SJ, Welsh MB, et al. Dietary estrogens--a probable cause of infertility and liver disease in captive cheetahs. Gastroenterology 1987;93:225-33.
8. Fritz WA, Coward L, Wang J, Lamartiniere CA. Dietary genistein: perinatal mammary cancer prevention, bioavailability and toxicity testing in the rat. Carcinogenesis 1998;19:2151-8.
9. Brown NM, Setchell KDR. Animal models impacted by phytoestrogens in commercial chow: implications for pathways influenced by hormones. Lab Invest 2001;81:735-47.
10. Thigpen JE, Setchell KDR, Ahlmark KB, et al. Phytoestrogen content of purified, open- and closed-formula laboratory animal diets. Lab Anim Sci 1999;49:530-6.
11. Thigpen JE, Setchell KDR, Saunders HE, Haseman JK, Grant MG, Forsythe DB. Selecting the appropriate rodent diet for endocrine disruptor research and testing studies. Ilar J 2004;45:401-16.
12. Setchell KDR, Brown NM, Lydeking-Olsen E. The clinical importance of the metabolite equol-a clue to the effectiveness of soy and its isoflavones. J Nutr 2002;132:3577-84.
13. Setchell KDR, Clerici C, Lephart ED, et al. S-equol, a potent ligand for estrogen receptor beta, is the exclusive enantiomeric form of the soy isoflavone metabolite produced by human intestinal bacterial flora. Am J Clin Nutr 2005;81:1072-9.
14. Setchell KDR, Cole SJ. Defining equol producer status and its high frequency among vegetarians. Journal of Nutrition 2006;submitted.
15. Thigpen JE, Haseman JK, Saunders HE, Setchell KDR, Grant MG, Forsythe DB. Dietary phytoestrogens accelerate the time of vaginal opening in immature CD-1 mice. Comp Med 2003;53:607-15.
16. Lamartiniere CA, Murrill WB, Manzolillo PA, et al. Genistein alters the ontogeny of mammary gland development and protects against chemically-induced mammary cancer in rats. Proc Soc Exp Biol Med 1998;217:358-64.

17. Cassidy A, Bingham S, Setchell KDR. Biological effects of a diet of soy protein rich in isoflavones on the menstrual cycle of premenopausal women [see comments]. Am J Clin Nutr 1994;60:333-40.
18. Setchell KDR, Radd S. Soy and other legumes: Bean around a long time but are they the 'Superfood' of the millenuium and what are the safety issues for their constitutent phytoestrogens. Asia Pacific Journal of Clinical Nutrition 2000;9:S13-S22.
19. Setchell KDR. Soy isoflavones--benefits and risks from nature's selective estrogen receptor modulators (SERMs). J Am Coll Nutr 2001;20:354S-362S; discussion 381S-383S.

January 24, 2006

Wendy N Jefferson, Ph.D.
Mail Drop E4-02
NIEHS
111 Alexander Drive
South Campus
P.O. Box 12233,
Research Triangle Park
NC 27709

Re: Article in Biology of Reproduction 2006; Vol 73: pages 798-806

Dear Dr. Jefferson:

I have read with some interest your recent publication relating to experimental studies of genistein in newborn rodents. While I accept that your data are no doubt sound, I would point out that from an experimental design perspective, these findings have little relevance to infants consuming soy formula. I am therefore astounded by press release comments attributed to yourself, and supported by your NIEHS Director, Dr. Schwartz, implying that soy infant formulas may be unsafe. Such comment does nothing but a disservice to a nutritional regimen that has been used in more than 30 million infants world-wide over the last 40 years and furthermore is of considerable benefit to a specific proportion of infants that cannot for clinical or other reasons be breast fed. Before making such comments to media I would suggest that you might consider some of the facts surrounding soy formula and isoflavones and at least point out the limitations of your experimental design rather than misguide the public.

It is well known that genistein when injected early in life to rodents causes abnormalities in the ovaries. Coral Lamartimiere in the 1990's showed that injecting genistein into rats on days 2, 4 and 6 caused abnormalities in the ovaries, some of the type reported in your paper for mice However, early exposure to genistein, as with estrogen, also leads to a marked resistance to chemically-induced breast cancer late in life, which now forms the basis of the theory that early exposure to isoflavones is highly protective against breast cancer later in life – a potential benefit. The major problems with interpreting your findings to human infants are as follows:

Your study design injected the genistein at massive doses into newborn mice (up to 50 mg/Kg body wt) – adults consuming soy are typically exposed to 0.5 – 1.0 mg/kg and infants 6-11 fold higher exposures on a body weight basis, of which only 1% represents genistein (Setchell, et al. Lancet 1997; 350:23-27; and Setchell, et al. AJCN 1998; 68:1453S-1461S.). Indeed a key statement in your manuscript and accompanying press release is factually incorrect – genistein is not the primary isoflavone in soy as stated. It is daidzin and genistin that are the major isoflavones of soy formula, accounting for about 98% of the total isoflavones consumed by the infant.

The pharmacodynamics of genistein is totally different when injected versus oral administration. Injecting the aglycon, as you did, totally bypasses first-pass metabolism that takes place when infants are fed isoflavones derived from soy formula. Oral feeding leads to significant Phase II metabolism and isoflavone glucuronides become the major circulating forms in plasma, not unlike endogenous estrogens (Setchell et al. AJCN 2002;76:447-453). Indeed, this first pass metabolism is crucial where isoflavones are concerned because glucuronidation takes place during intestinal uptake. This is not the case when genistein is injected.

The mouse and all rodents, metabolize soy isoflavones completely differently from that of the infant. Rodents metabolize soy isoflavones to predominantly equol, they are 'equol-producing machines' including the newborn rat pup which has mostly equol circulating even when suckling on a dam fed a soy-containing rodent chow (Brown & Setchell Laboratory Investigation 2001; 81: 735-747). By contrast, the human infant fed soy formula fails to synthesize any equol until about 1 year of life. The route of administration and the pharmacodynamics of a molecule are crucial to influencing its physiological

actions. If this were a drug development study the FDA would never require such experiments to determine the safety of a compound given orally. Your contention, that the levels of genistein in the rodent reflect those in the human infant are irrelevant, given the different modes of action.

The stage of reproductive development of a mouse on neonatal days 1-5 is not comparable to a newborn infant – as you know, developmentally it can be considered more like a human fetus in the first trimester. Indeed, save the infant, there is no satisfactory animal model to study reproductive development of the human newborn.

I would ask of you the obvious question - why did you not expose animals to genistein orally, since this is possible via the dam – after all, infants are exposed to isoflavones orally. I believe you would find no significant effects had you designed the experiment in this manner. Most rodents worldwide are exposed orally to very high levels of isoflavones (80-160 mg/kg body weight; Brown & Setchell Laboratory Investigation 2001; 81: 735-747) throughout pregnancy and development. This is because the majority of rodent chow purchased by animal breeding houses and Institutional Animal Facilities is formulated with soy and contains very high levels of isoflavones (Thigpen et al. Laboratory Animal Science 1999; 49:530-536; Brown & Setchell Laboratory Investigation 2001; 81: 735-747; Thigpen, et al. ILAR Journal 2004; 45: 401-414. These animals experience no reproductive problems when exposed in this manner – indeed there are investigators, including industry, who insist that isoflavones in rat chow pose no reproductive problems.

In my opinion, to make extrapolations from the findings of your study to human infants fed soy formulas is grossly irresponsible. While the findings are interesting, and not at all surprising, they have absolutely no relevance to this clinical situation. Infants are just not injected with genistein, nor are they exposed orally to such high levels.

Soy infant formulas have a long history of safe use, and are nutritionally sound (Setchell, J. Am. Coll. Nutr 2001; 20: 354S-362S). Women throughout Asia are exposed to soy isoflavones through soy foods consumed throughout pregnancy. I am unaware of any deleterious effects of feeding soy formula to healthy full-term infants, and believe it should be incumbent on the toxicologists to present definitive cases of adverse effects of feeding soy formulas to infants before creating a media circus. Save a few exceptions, and these relate to infants with pre-diagnosed disease, I doubt you will find any documented cases.

Only a long-term prospective study in humans will sort this issue out. We clearly do not need further rodent studies since there is more than adequate literature showing deleterious effects of high doses of isoflavones, particularly injected, on reproductive development in newborn rodents. In my opinion, these types of experiments serve little value other than wasting tax payers money - money that could and should be spent addressing soy formula and human infant studies if this issue is to be successfully resolved. Indeed, It would be my prediction that if a long-term prospective human study was performed we might be surprised to find that there are significant health benefits from early feeding of soy formula, and for that matter soy foods in children and young adults, that relate to longer term disease prevention. Anecdotally, there is evidence showing that as the Japanese are changing the traditional diet and eating less soy foods, there has been a notable increase in the chronic disease of Westerners who generally are not exposed to soy foods. Finally, I would suggest that if you feel compelled to speak to media on this issue you point out the only relevant fact from your study, and that is, if you are a rodent it is perhaps advisable to avoid being injected with genistein!

Sincerely,

Kenneth Setchell. Ph.D.
Professor of Pediatrics

P.S. I should point out I have no investment in soy formulas, or any conflict of interest related to my above expressed views and none of my research is funded by the soy infant formula industry.

Supporting references:

Setchell KDR, Zimmer-Nechemias L, Cai J, Heubi JE. Exposure of infants to phyto-oestrogens from soy-based infant formula. Lancet 1997; 350:23-27
Setchell KDR, Zimmer-Nechemias L, Cai J, Heubi JE. Isoflavone content of infant formulas and the metabolic fate of these phytoestrogens in early life. American Journal Clinical Nutrition 1998; 68:1453S-1461S.).
Brown NM, Setchell KDR. Animal models impacted by phytoestrogens in commercial chow: implications for pathways influenced by hormones. Laboratory Investigation 2001; 81: 735-747.
Setchell KDR, Brown NM, Zimmer-Nechemias L, Brashear WT, Wolfe B, Kirschner AS, Heubi JE. Evidence for lack of absorption of soy isoflavone glycosides in humans, supporting the crucial role of intestinal metabolism for bioavailability. American Journal of Clinical Nutrition 2002;76:447-453).
Setchell KDR. Soy isoflavones – benefits and risks from nature's selective estrogen receptor modulators. Journal of American College of Nutrition 2001; 20: 354S-362S.
Thigpen JE, Setchell KDR, Ahlmark KB, Locklear J. Spahr T, Caviness GF, Goelz MF, Haseman JK, Newbold RR, Forsythe DB. Phytoestrogen content of purified open- and closed-formula laboratory diets. Laboratory Animal Science 1999; 49:530-536.
Thigpen, JE, Setchell KDR, Saunders HE, Haseman JK, Grant MG, Forsythe DB. Selecting the appropriate rodent diet for endocrine disruptor research and testing studies. ILAR Journal 2004; 45: 401-414.

CC. Dr. David Schwartz Director of the National Institute of Environmental Health Sciences (NIEHS)