Dietary phytoestrogens, a source of research variation.

Ask a Nutritionist Series: Impact of phytoestrogens on research, Volume 1.

- Soybean meal, a common ingredient in laboratory animal diets, contains variable levels of phytoestrogen known as isoflavones
- Isoflavones are selective estrogen receptor modulators (SERM) because of both estrogenic agonistic and antagonistic effects
- Dietary isoflavones can affect a variety of research endpoints
  - No simple absolute threshold for physiological effects
  - Tissue responses can differ
  - Magnitude and direction of response varies
  - Responses are model dependent

Laboratory diets containing soybean meal should be avoided in research studies if the end point may be affected by dietary isoflavones.

Challenge:

Dietary isoflavones impact research.

Solution:

Envigo's minimal isoflavone Teklad Global Rodent Diets lead to reliable, repeatable research results.

Dietary soy: a natural and variable source of phytoestrogens

Phytoestrogens are plant-derived compounds which mimic both the structure and function of estrogens in mammals and can impact research results (1, 2). The main phytoestrogens (and their primary sources) include: isoflavones (mainly genistin and daidzin found in soybean protein), coumestans (mainly coumestrol found in alfalfa) and lignans (from flax and sunflower) (1). Isoflavones are glycosylated in soybean meal but will be converted within the gastrointestinal tract to the active aglycone forms, genistein and daidzein (**Figure 1**). Since analysis of isoflavones typically involves converting to the aglycone form, data are routinely reported as genistein and daidzein as they are in **Figure 2**.

Soybean meal is a common ingredient in standard laboratory animal diets, supplying primarily protein, but it also adds the isoflavones genistein and daidzein.

The isoflavone content of soybean meal can fluctuate (2 – 6 fold) due to genetics and growing conditions (3-6). Regional sourcing practices can restrict isoflavone variation to 2-fold, as demonstrated by the internal data shown in **Figure 2A** for soybean meal sourced from the upper Midwest. This same variation is then reflected in diets containing soybean meal. Dietary isoflavone level is a function of the amount of soybean meal present and the content in the source material (**Figure 2B**).

Diets containing soybean meal in typical amounts will have isoflavone levels ranging from 100 – 700 ppm (sum of genistein + daidzein, aglycone form) (7-12). Fixed formulation (adding the same amount of soybean meal in each diet lot) and regional sourcing can minimize variation in dietary isoflavones within a crop year, while year to year differences are responsible for the majority of variability.

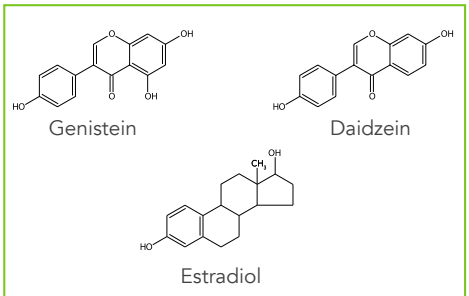

Figure 1. Structural similarity of genistein and daidzein to estradiol confers activity at the estrogen receptor.

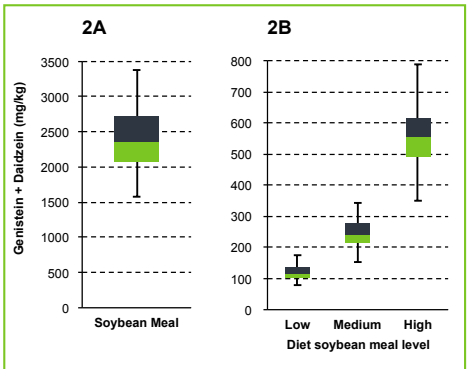

Figure 2. Box and whisker plots showing the distribution of isoflavones (genistein + daidzein) in **2A:** Soybean meal regionally sourced from the upper Midwest by Envigo from 2006 – 2016.

In **2B:** Envigo diets containing low (~5%), medium (~10%) and high (~25%) amounts of soybean meal during the same time period.

Physiological actions of isoflavones

Isoflavones may have estrogenic agonistic or antagonistic effects and are therefore termed selective estrogen receptor modulators (SERM). Structural similarities to 17 β-estradiol allow isoflavones to bind to estrogen receptors with preference for the β receptor (1, 13). Although relative potency is significantly lower than endogenous estrogens, isoflavones are able to exert multiple physiological effects due to higher circulating concentrations relative to endogenous estrogen (8, 14). Estrogen receptors are widely distributed among body tissues and various cell types, affecting a wide range of physiological systems, including the cardiovascular (15), immune (16-18), reproductive (19-21), endocrine (22, 23), and central nervous systems (24-27). While much attention has been paid to the effects of isoflavones acting through the estrogen receptor, isoflavones also have estrogen independent mechanisms such as acting as PPAR agonists (22, 28-32), activation of the cAMP/PKA pathway (33-37) and via antioxidant activity (25, 38-42).

In general, isoflavones seem to have a protective effect in animal models, modulating pathological conditions such as cancer, metabolic syndrome, and neurodegeneration.

By feeding soy-containing diets, the consequent 'protective' effect of isoflavones is likely to diminish the phenotype of animal models developed or manipulated to exhibit such pathology.

Isoflavones may also confound the effects of putative or potential therapeutic compounds.

Dietary isoflavones result in research variation

Predicting the impact of dietary isoflavones on research outcomes is difficult. Isoflavones do not illicit a classic dose response, thus there is no simple absolute threshold for the physiological effects of isoflavones and some effects have been demonstrated at low levels of phytoestrogens. For example, feeding a diet with 100 ppm genistein reduced lung metastases in athymic BALB/c mice implanted with prostate cancer cells by ~50% (43). Likewise, the proportion of TRAMP mice exhibiting prostate tumors dropped significantly with the addition of 100 ppm genistein to the diet, reducing the effectiveness of the animal model (44). Therefore, diets containing < 20 ppm have been recommended for endocrine disrupter studies because this level is thought to have only negligible endocrine effects (14).

Specific tissues respond differently to the same dose of genistein, making it difficult to define a no effect level for dietary isoflavones. In ovariectomized mice, feeding 300 ppm genistein increased uterine weight, while decreases in adipose tissue were only seen at dietary levels of 500 ppm or more and effects on body weight were only significant at 1500 ppm (45). Additionally, the magnitude and direction of isoflavone effects can vary. Similar levels of dietary genistein (~1000 ppm) suppressed (46) or enhanced (47) the action of tamoxifen in models of ectopic breast cancer in the presence of estradiol. Response to dietary isoflavones is also model dependent. In Fischer 344, but not Sprague-Dawley® rats, vaginal opening date was affected by changes in dietary isoflavone levels ranging from 7 – 431 ppm (7).

With so much uncertainty, the precautionary principle would dictate that laboratory diets that contain soybean meal should be avoided for those research studies in which the end point may be affected by dietary isoflavones.

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Phytoestrogens limit translation of preclinical results to clinical outcomes

Ask a Nutritionist Series: Impact of phytoestrogens on research, Volume 2

- Isoflavone consumption is higher in rodents fed soybean meal containing lab diets than humans.
- Rodents have higher proportion of circulating unconjugated isoflavones than humans. Unconjugated soy isoflavones have greater activity.
- Rodents are consistent producers of equol, a more physiologically active isoflavone metabolite, while humans are inconsistent equol producers.
- In order to improve translation of rodent results to human outcomes, strong consideration should be given to the avoidance of soybean meal-containing lab animal diets.

Challenge:
Dietary isoflavones limit translation of preclinical results to clinical outcomes.

Solution:
Envigo's minimal isoflavone Teklad Global Rodent Diets lead to reliable, repeatable research results.

Dietary phytoestrogens exert both estrogen dependent and independent effects and have been shown to have broad effects on research outcomes in rodent models (Table 1).

Rodents fed soy containing diets consume higher levels of isoflavones than humans

Rodents fed soybean meal containing laboratory diets consume higher levels of isoflavones than human populations. Dietary isoflavone level is dependent on the soybean meal inclusion rate and is influenced by soy genetics and growing conditions. Isoflavone levels in rodent diets containing soybean meal can range from approximately 80 – 790 ppm (genistein + daidzein) resulting in an isoflavone intake range of 8 – 118 mg/kg body weight per day (**Table 2**). This intake range is more than 10 times higher than adult Western populations even when scaled for body surface area[1-6] (**Table 2** dark grey columns).

Isoflavone intake levels for infants fed soy formula approach levels consumed by rodents fed diets containing 5 – 10% soybean meal[7], however differences in metabolism and pharmacokinetics of isoflavones likely result in differences in physiological responses to consumed isoflavones.

Research area	Effects described in the literature
Oncology	Modulate tumor growth, latency, multiplicity, metastasis; diminish action of drugs such as tamoxifen and letrozole
Reproductive	Increase uterine weight; accelerate vaginal opening; affect response to exogenous estrogens/xenobiotics
Endocrine	Differences in body composition (weight, adiposity), glucose and insulin homeostatsis, bone density and blood pressure
Neuroscience	Performance differences on tests measuring anxiety behaviors and response to pain stimuli
Immunology	Modulate immune organ development; display anti-inflammatory and antioxidant actions

Table 1. Research areas affected by isoflavone consumption in rodents[25].

Species effects on phase II metabolism results in differences in isoflavone bioactivity

The primary forms of isoflavones consumed by rodents and humans are the glycosides genistin and daidzin. These glycoside forms are poorly absorbed, so once ingested the glycoside moiety is removed via endogenous and microbial β-glucosidases[8-10]. Upon uptake by the enterocyte and liver the majority of free aglycone forms (genistein and daidzein) undergo conjugation via Phase II metabolism for circulation[11]. Glucuronic acid is the primary Phase II conjugate followed by sulfides[12].

Phase II metabolism of isoflavones affects binding and activation of the intracellular estrogen receptor. Conjugated isoflavones are relatively hydrophilic and it is unclear if these compounds can readily pass through the cell membrane to access the intracellular estrogen receptor[11, 13]. An *in vitro* study found binding of murine uterine cytosol estrogen receptors was weaker with conjugated isoflavones compared to unconjugated forms[11]. Once activated, the ER receptor translocates into the nucleus, binding DNA to regulate gene expression. Conjugation of isoflavones limits the downstream binding of nuclear receptors *in vitro* reducing relative potency for the β-ER by ~15 fold for genistein and ~4400 fold for daidzein[13]. Conjugated genistein and daidzein have limited effects on growth of the human MCF-7 cell line compared to aglycone forms[14]. In a transfected cell line with ERα/ERβ ratios mimicking healthy breast cells conjugated isoflavones were found to not be estrogenic[13].

The ability to activate isoflavones via deconjugation at the tissue level differs between species, with rat breast tissue having a ~30 fold higher deconjugation capacity compared to human breast tissue[15]. Isoflavone conjugation influences physiological effects and conjugation ratios differ between rodent strains and sexes as well as between rodents and humans.

In general, the proportion of circulating unconjugated isoflavones is ranked mice > rats > humans[16-18]. Compared to C57BL/6 mice and Sprague-Dawley rats, nude mice and the transgenic mouse model Angptl4b6 have higher proportions of unconjugated circulating isoflavones[16]. While sex does not appear to affect conjugation patterns in humans, sex and hormonal changes do affect conjugation patterns in rodent models[17]. Hormone status in Sprague-Dawley rats affected both oral bioavailability of genistein and circulating conjugated isoflavones[19]. The ability to deconjugate isoflavones at the tissue level has also been shown to differ between rodents and human models[15].

Differences in conjugation patterns between humans and rodents influence isoflavone activity and physiological effects.

Equol production differs in humans and rodents

Equol is a metabolite of daidzein that is exclusively produced by bacteria[20-22]. This metabolite has a greater affinity for the estrogen receptor (ER) and higher biological activity than the parent compound daidzein[20, 23]. Microbial production of equol can be affected by a number of variables in rodents and humans. Feeding a soy containing diet to conventionally raised rodent results in the production of equol but not in germ-free rats[22]. While conventional rodents are consistent equol producers when fed soybean meal, equol production varies in humans. Only 25 – 30% of the adult Western population is considered "equol producers" while 50 – 70% of adults in Japan, China and Korea produce equol[23, 24]. Differences in equol production may be related to differences in nutrient intake and lactase phlorizin hydrolase activity, the enzyme responsible for both the hydrolysis of lactase and deglycosylation of isoflavones[20, 24]. Differences between rodents and humans in circulating levels of equol can affect the translation of preclinical results to clinical outcomes.

Taken together rodents have higher circulating concentrations of isoflavone metabolites with greater affinity for the β-estrogen receptor, thus leading to more pronounced effects than seen in humans. Feeding lab diets containing soybean meal should be avoided in preclinical research studies in order to improve translation of rodent results to human outcomes.

Translating Isoflavone Intakes from Human to Rodents				Typical Rodent Isoflavone Intakes from Soybean Meal in Laboratory Rodent Diets		
Population	**Isoflavone intake, mg/day**	**Human isoflavone intake, mg/kg/day**	**Equivalent rodent intake, mg/kg/day[a]**	**Dietary soybean meal level**	**Typical dietary isoflavone range[b], ppm**	**Rodent isoflavone intake[c], mg/kg/day**
Western adults	1 - 3[(1)]	0.01 - 0.05	0.1 - 0.6	Low	80 - 175	8 - 26
East Asian adults	15 - 50[(4-6)]	0.2 - 0.8	1.4 - 10.2	Medium	150 - 340	15 - 51
Infants fed soy milk	20 - 45[(7)]	6 - 11	20 - 55	High	350 - 790	35 - 118

Table 2. Comparison of consumption of isoflavones in humans and rodents.

a Equivalent Rodent Intake = Human Isoflavone Intake/((animal weight in kg/human weight in kg)$^{0.33}$)[(25)]. Unless provided by the original reference, adult human body weight is assumed to be 60 kg, mouse weight 20 g and feed intake 3 g, rat weigh 150 g and feed intake 15 g.

b Envigo diets containing low (~5%), medium (~10%) and high (~25%) amounts of soybean meal during the same time period[(25)].

c Assuming mice weigh 20 g and consume 3 g diet/day and rats weigh 150 g and consume 15 g diet/day.

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