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Phytoestrogens and Chow

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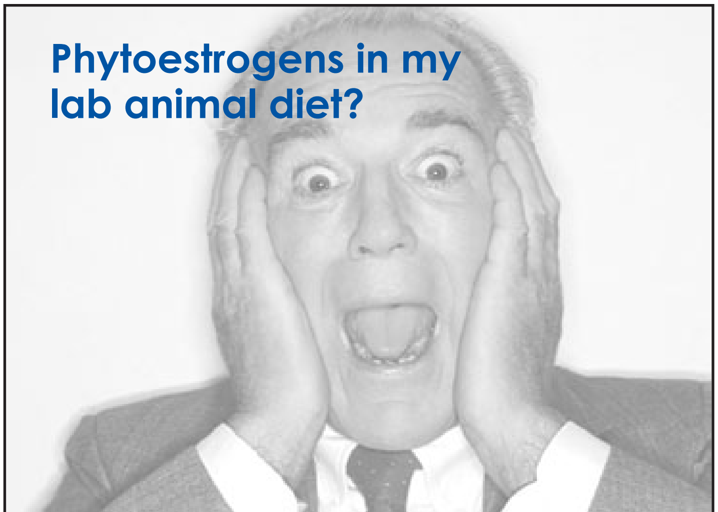

Do you know that grain-based diets contain significant and variable levels of phytoestrogens? If your studies involve pathways which are influenced by estrogenic activity, the diet you feed can have profound effects on your animal model at the molecular and cellular level.

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Phytoestrogens – Uninvited, Troublesome Guests in Scientific Research

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Eliminate variables. It's a fundamental rule in scientific research. Purified diets were designed for this very purpose – to minimize variables so that scientists can be confident they are studying only the nutrient or compound of interest. With the availability of this remarkable tool, it's hard to understand why so many researchers continue to use grain-based chow diets in nutrition studies and even, as we shall see, in studies that are not necessarily nutrition-oriented, such as drug and compound efficacy studies, or behavioral studies.

Perhaps many researchers are unaware of the profound differences between the two diets. Purified diets are made with refined ingredients, such as casein, corn starch, sucrose, corn oil, and a fixed amount of vitamins and minerals. A scientist has complete control over the ingredients added or subtracted (1).

In contrast, grain-based chow diets are made with ground plants, such as corn, wheat, oats, soybean, and alfalfa. There's a problem – plants vary nutritionally from harvest to harvest, and some, including soy and alfalfa, contain significant amounts of biologically active compounds called phytoestrogens, which also vary between harvests (2).

Phytoestrogens in chow add potentially powerful variables to experiments

Phytoestrogens are abundant in soy meal – the major protein source in most commonly-used laboratory chows; and a subclass of chemicals in the phytoestrogen family known as isoflavones are major culprits (3). Isoflavones interact with estrogen receptors and elicit estrogenic or anti-estrogenic effects (4). Therefore, they can interfere with studies influenced by exogenous estrogens. Estrogens regulate a variety of physiological pathways. They are involved in the growth and function of reproductive tissues of both males and females, as well as maintenance of the skeletal, central nervous and cardiovascular systems. Hence, isoflavones can interfere with countless studies and even render the interpretation of results meaningless.

To date, numerous studies in humans and animals leave little doubt that isoflavones in soy affect a variety of experimental endpoints. A brief mention of some examples follows, and extensive reviews on this topic have been published (5, 6, 7) FIG. 1.

Cancer. The low incidence of many cancers in Asian countries, where soy consumption is high, sparked an interest in soy's potential protective effects (8). As partial estrogen antagonists, isoflavones in soy were thought to play a role in preventing cancer. Indeed, laboratory research has confirmed the epidemiological findings. For example, rodents consuming isoflavones have fewer tumors and/or a delay in tumor development in mammary, liver, colon, and prostate cancer (9, 10, 11, 12). Experimental results sometimes conflict and the outcome likely depends on a variety of factors, including the isoflavone amount, duration of feeding, and hormonal state of the animal. Still, the evidence for isoflavones' role in cancer is mounting and must not be dismissed as insignificant in cancer research.

Metabolic Syndrome. Dietary soy has been shown to attenuate the development of hypertension in spontaneously hypertensive rats (13). Soy isoflavones have also been shown to reduce serum cholesterol and triglycerides (14, 15), and prevent the development of fatty liver (16). Rats fed high fat diets with soy as the protein source gained less weight and had less body fat compared with those fed high-fat diets with casein (17). Insulin-sensitivity was also improved in soy-fed mice (18).

Osteoporosis. Studies in both humans (post-menopausal women) and animal models of osteoporosis (ovariectomized rodents) show bone sparing effects of soy isoflavones (19, 20), and the results in animals are remarkably consistent.

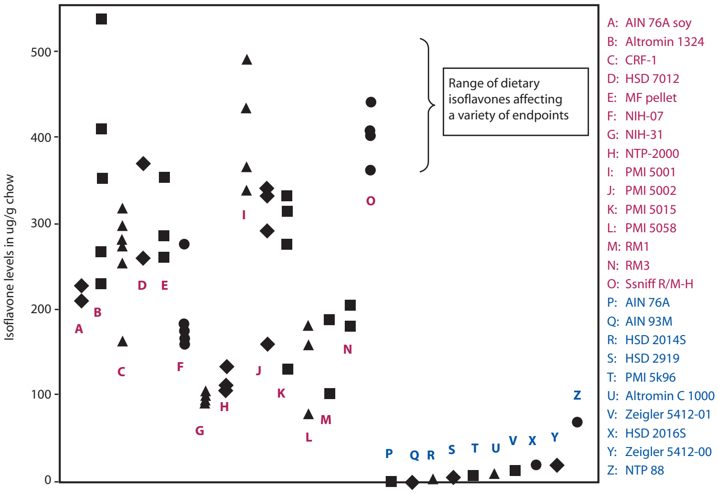

FIGURE 1. Isoflavone content in a number of commonly used laboratory rodent diets. Each data point represents a batch of the diet formulations listed on the right. Diets P-Y are formulated without soy and have negligible amounts of isoflavones. Graphic representation - for details see reference (6).

Reproductive Development. Certain levels of isoflavones are capable of accelerating puberty and stimulating uterine growth in female rodents (21). In male rodents, a decrease in the weight of the prostate gland and sexual organs, as well as a decrease in testosterone, has been reported (22, 23). A literature review reveals inconsistent findings, and, as with other endpoints, likely depends on the dose and other factors. Yet, scientists seem to agree that dietary phytoestrogen content must be considered in studies directly or indirectly involving sexual development.

Behavior. Since estrogen receptors are expressed in the brain, it's no surprise that dietary isoflavones affect behavioral parameters. Effects on learning and memory, social interaction, anxiety-related behaviors, locomotor activity, and pain sensitivity have been reported (6, 24).

A cautionary tale

Mounting empirical evidence to date has implicated isoflavones in a wide range of experimental endpoints, leaving little doubt that, when choosing a diet, careful consideration must be given to the role of these compounds in mammalian physiology. After all, can meaningful conclusions really be drawn if the control diet itself has protective or adverse effects on the phenotype one is studying?

Nutrition scientists who, surprisingly, use grain-based diets as a control for purified diets must be made aware of these differences. In addition, the knowledge must be imparted to scientists studying the efficacy of drugs on a variety of diseases that may be affected by compounds in soy. These include osteoporosis, cancer, heart disease, hypertension, pain sensitivity, and psychiatric disorders. Understandably, many researchers are reluctant to switch from grain-based chows to purified diets. They dare not change the diet in ongoing experiments, since these rely heavily on comparisons to historical data. Yet, a strong argument can be made for a break from the past: Was the "same diet" actually used over the years? The answer is no, since chows vary from batch to batch. Indeed, dietary phytoestrogen variability has likely caused a frustrating variability in data, or a misinterpretation of results, in many studies.

Does removing the phytoestrogen source from grain-based chow fix the problem?

In recognition of the large body of evidence of phytoestrogens' effects, some chow manufacturers now sell chow without soy meal or alfalfa. Instead, the ingredients include ground corn, wheat middlings, and ground wheat. The phytoestrogens in these diets are minimized but not eliminated. Importantly, these ingredients are not refined. Therefore, it is impossible to know which yet-to-be-discovered biologically active compounds are in the diet. Indeed, in 1940, an effect of phytoestrogens was noticed for the first time – when it was observed that sheep grazing on red clover, a phytoestrogen-rich plant, were less fertile (25).

It can certainly be argued that there's no such thing as a perfect diet in laboratory research, but at the very least, for experiments to be meaningful, we should strive to eliminate dietary variables, especially those known to elicit biological responses – namely, phytoestrogens.

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