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Not All Soy Products Are Created Equal: Caution Needed in Interpretation of Research Results

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ABSTRACT  Interest in the health benefits of soy foods has been intense among the research community, health professionals, and the public. At the same time, potential concerns associated with soy consumption, especially as related to soy isoflavones, have tempered the enthusiasm for making public health recommendations. On both accounts, the primary soybean isoflavone, genistein, has received the most attention. Because consumers are becoming increasingly confused by the often conflicting dietary messages, a balanced and accurate view of the risks and benefits of soy foods and soy food components is essential. Even among health professionals, confusion exists about proper nomenclature and about the precise composition of the agents under investigation. Levels of isoflavones are frequently assumed to be constant within categories of soy foods, and intakes are estimated rather than being directly analyzed. Furthermore, all too often research dealing singularly with genistein is interpreted by both health professionals and the media as equating directly with soy. Researchers often fail to fully understand the implications of their research outcomes and the context in which those outcomes should be placed. With the hundreds of publications yearly on soy and isoflavones, it is especially important to consider the literature in its entirety when making pronouncements about health effects. Efforts are needed by all to reduce the public confusion by adapting standardized approaches to the reporting of data. This paper provides a framework for both standardization of nomenclature and appropriate interpretation of data.  J. Nutr. 134: 1229S–1233S, 2004.

KEY WORDS:  • soy  • soy protein  • isoflavones  • genistein

A recent headline from an article typical of those that appear in popular health magazines was “Does Soy Have a Dark Side?” The author first reviewed the positive epidemiologic evidence linking soy food consumption to reduced risk of coronary heart disease and cancer. Then the reader was reminded about the recent approval by the U.S. Food and Drug Administration of a health claim for the cholesterol-lowering effects of soy protein and reduction of risk from heart disease (1). The remainder of the article raised possible negative issues of soy consumption, focusing on the potential increased risk of developing estrogen-sensitive cancers, impaired cognitive function, and reproductive problems. It is most appropriate to consider the possible adverse effects; indeed it is essential for journalists and the scientific community to scrutinize both sides of the risk-benefit continuum for any dietary substance. The author of the article was informed about the issues but was not able to put the different kinds of research results into perspective and was confused about the nomenclature used in different studies.

Confusion regarding the relative merits and potential public health significance of research reports using different research models plagues writers, scientists, and policy makers alike. Even among scientists debate exists about the pros and cons of various research models and approaches. Part of the confusion likely arises because of the lack of standardized nomenclature for referring to soy products and components in the scientific literature. In addition, it is difficult to compare results across a wide range of study designs that often lack biostatistical power and involve poorly defined test substances.

Rather than addressing health and safety of soy foods per se, this paper will provide guidelines for those preparing or inter-
Soy nomenclature and chemical composition

Soy nomenclature has several confusing aspects. It is important to recognize that most epidemiologic studies that have examined the relationship between soy intake and health outcomes have involved Asian populations and therefore evaluated the intake of traditional soy foods, such as tofu or soy milk, that are derived from whole or dehulled soybeans. In contrast, few animal or human intervention studies have involved whole soy foods. Instead, soy concentrates, soy isolates, and grits concentrates Isolates

<table>
<thead>
<tr>
<th>Description</th>
<th>Daidzein</th>
<th>Genistein</th>
<th>Glycitein</th>
<th>Total isolavones</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soy flour, full-fat, roasted</td>
<td>99.27</td>
<td>98.75</td>
<td>16.40</td>
<td>198.95</td>
</tr>
<tr>
<td>Soybean flakes defatted</td>
<td>36.97</td>
<td>85.69</td>
<td>14.23</td>
<td>125.82</td>
</tr>
<tr>
<td>Soy protein concentrate, aqueous washed</td>
<td>43.04</td>
<td>55.59</td>
<td>5.16</td>
<td>102.07</td>
</tr>
<tr>
<td>Soy protein concentrate, produced by alcohol extraction</td>
<td>6.83</td>
<td>5.33</td>
<td>1.57</td>
<td>12.74</td>
</tr>
<tr>
<td>Soy protein isolate</td>
<td>33.59</td>
<td>59.62</td>
<td>9.47</td>
<td>97.43</td>
</tr>
</tbody>
</table>

1 Modified from Jackson and Gilani (5).
2 Values based on mg/100 g edible portion.

Recent research indicates alcohol washing may substantially alter the protein matrix and structure. For example, Gianazza et al. (6) using 2-dimensional electrophoresis demonstrated extensive degradation of the 7S globulin of protein in some soy isolates into proteins and peptides with smaller molecular weights. Peptides formed from the digestion of the α1 constituent subunit from 7S globulin may upregulate hepatic LDL cholesterol receptors and consequently contribute to the cholesterol-lowering effects of soy protein (7). Gianazza et al. (6) also found that some proteins accumulated more in ethanol-treated samples. Researchers often compare ethanol-washed with nonethanol-washed soy protein and then assume that any differences seen in health outcomes are due to the isolavone component when saponins, other alcohol soluble material, and the protein and peptide composition could conceivably contribute or be responsible for the observations.

The composition of specific (standardized) soy foods varies substantially. Setchell and Cole (8) recently evaluated the variations in isolavone levels in soy foods and soy protein isolates. They found a 2–3-fold variation in total isolavones in soy protein isolates over 3 y and fivefold differences in isolavone levels in different commercial soy milks. Figure 1 shows the variations in total isolavones in soy milks (8). The differences among products are due in part to the variety of soybeans, differences in growing and storage conditions, and differential food processing techniques. Clearly, it is important for the scientific community to accurately understand the chemical composition of study products.

Another major source of confusion is the nomenclature used for isolavones. The soybean contains 6 major and 6 minor forms of isolavones. As shown in Table 3, the majority of the isolavones found in soybeans are the β-glycosides, genistin and daidzin, and only small proportions of genistin and daidzin (unglycosylated, or aglycone forms) are present (9). In contrast the hypocotyl, or germ, contains high concentrations of glycitin and some glycine, moderate amounts of daidzin, and relatively small amounts of genistin. Many commercial soy isolavone supplements are made from the soy germ. Those soy isolavone supplements do not contain the same isolavone profile as that obtained from the consumption of soy foods that are produced primarily from the whole or the dehulled soybean. This difference leads to markedly different plasma isolavone profiles (10). Other soy isolavone products derived from whole soy or recovered from the ethanol wash during the preparation of soy concentrates and isolates

as saponins from the product (3,4). Table 2 lists the total and individual isolavone contents of selective soy foods (5).

Prettting research publications in regard to proper nomenclature for the different soy foods and extracts; fair and accurate interpretation of the variety of in vitro, cell culture, animal, and human studies; and accurate translation of research results for public health decision makers and the media. The paper will conclude with recommendations for manufacturers, researchers, and the media.
Expressing isoflavone content

Other constituents.

whereas the entire bean soy milks contain the okara. Modi
okara is removed from whole bean soy milks during processing
Bars represent means of 4 or more replicate analyses. The insoluble
content of a product is expressed. As previously noted, iso
flavones are naturally present in the soybean primarily as glyco-
sides. However, as a result of processing, and especially fer-
mentation, some of the glycosides in soy foods are converted to
aglycones. Researchers often express the iso-
flavones in a product

that the sugar moiety does not con-
tribute to the biological activity, and the amount of the
stated amount refers to the aglycone or glycoside value. This
distinction is critical because the sugar moiety does not con-
tribute to the biological activity, and the amount of the
aglycone present is ~60% of the total weight of the glycoside.
Thus, 100 mg isoflavones may represents anywhere from 60 to
100 mg active isoflavones depending on the type of soy prod-
uct. Simply indicating the form of the isoflavones in a product
is not sufficient. Ideally, all values should be expressed as the
aglycone equivalent. Of course, as noted by Murphy et al. (11),
confusion surrounding isoflavone content could be avoided if
amounts were expressed in molar values, but this has not been
the convention within the scientific community for food la-
beling. In addition, summing of isoflavone intakes may not be
useful because the biological activities of daidzein and
genistein are quite different and the activities of other isofla-

Intpretation of research publications

Even scientists specializing in soy nutrition find it difficult
to synthesize the findings from the hundreds of papers pub-
lished yearly on soy foods, soy isoflavones, and genistein.
These publications range from epidemiologic investigations to
human intervention trials, animal studies, and cell culture
work.

Although several epidemiologic studies involving Western
populations have noted positive associations between soy in-
take and favorable health outcome, some questions remain
about the plausibility of there being a soy-related biological
basis for the reported results because of the very limited soy
intakes noted in these studies. As is always the case with
epidemiologic studies, there is the issue of uncontrolled con-
founding variables. Because soy foods, which are generally
perceived as healthful, are not a traditional part of Western
diets, higher soy consumption may reflect an overall healthful
lifestyle that is not so easily identified or controlled for (12).
Similarly, in Asian countries, soy intake may be more a marker
of a traditional diet and lifestyle (low fat, low red meat, more
green tea, more exercise, etc.) so it is not known, for example,
whether it is the soy or the other components of the tradi-
tional Asian diet and lifestyle that are important.

In Japan and some parts of China, soy foods contribute
~5% of total energy and provide ~8–12 g/d of protein, which
represents ~10% of adult total protein intake (13–16). Not
unexpectedly, recent surveys suggest that daily soy protein and
isoflavone intake among adults of non-Asian descent in West-
countries is quite small, likely being ~1–2 g and 1–3 mg,
respectively (12,17–20). Precise quantification is difficult be-
cause small amounts of soy protein containing variable
amounts of isoflavones are added to literally hundreds of com-
monly consumed processed foods. In contrast to the modern
Asian soy intake, most clinical trials involve feeding between
20 and 50 g/d of soy protein. Although the goals of these trials
are important, we should be mindful that provision of high
amounts of soy protein and isoflavones exceeds habitual in-
takes in soy-consuming populations.

Unquestionably, the population whose soy protein and
isoflavone exposure is greatest is infants consuming 100% of
their diets as soy formula. On a kilogram body weight basis,
isoflavone intake is 4–8 times greater in infants exclusively fed
soy infant formulas when compared with intake of adults. Not
unexpectedly, the concentration of isoflavones in blood and
tissues of infants is 10 times greater than in adults with
comparable daily intakes of soy products, especially because
infants are continually consuming isoflavones throughout the
day (21). Despite these very high levels with their potential for
biological effects, it is worth noting that soy infant formula has
been generally shown to be nutritionally safe and adequate for
normal growth and development.

In animal trials soy protein is typically provided at levels of
10–20% of the diet. Moreover, acute species differences in
colonic metabolism and biotransformation of isoflavones may
influence response to an intervention (22). Although experi-
ments in animals are usually designed to show a difference

1 Modified from Gugger (9).
2 On a dry weight basis hypocotyl, cotyledon, and seed coat are represented by 2.2%, 91.5%, and 6.3% of weight, respectively.
3 Not detected.

TABLE 3
Isoflavone distribution within the soybean

<table>
<thead>
<tr>
<th>Isoflavone</th>
<th>Hypocotyl</th>
<th>Cotyledon</th>
<th>Seed coat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total isoflavones, mg/g</td>
<td>21.54</td>
<td>3.80</td>
<td>0.05</td>
</tr>
<tr>
<td>Daidzin, mg/g</td>
<td>8.38</td>
<td>1.45</td>
<td>0.02</td>
</tr>
<tr>
<td>Daidzein, mg/g</td>
<td>0.35</td>
<td>0.11</td>
<td>—</td>
</tr>
<tr>
<td>Genistin, mg/g</td>
<td>2.46</td>
<td>2.10</td>
<td>0.02</td>
</tr>
<tr>
<td>Genistein, mg/g</td>
<td>0.16</td>
<td>0.14</td>
<td>0.01</td>
</tr>
<tr>
<td>Glycitein, mg/g</td>
<td>10.04</td>
<td>3</td>
<td>—</td>
</tr>
<tr>
<td>Glycitein, mg/g</td>
<td>0.15</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Total soybean isoflavone content, %</td>
<td>11.98</td>
<td>87.94</td>
<td>0.08</td>
</tr>
</tbody>
</table>

FIGURE 1 Total isoflavone content of 85 samples from 40 different brands of commercial soy milks grouped according to milk type. Bars represent means of 4 or more replicate analyses. The insoluble okara is removed from whole bean soy milks during processing whereas the entire bean soy milks contain the okara. Modified from Setchell and Cole (8).
between diet groups, interpretation or translation of those results to humans should be done with the knowledge that these effects may not occur at the lower intake levels typically found in Western or perhaps even in Asian cultures. Studies that use the addition of genistein either by injection or diet provide valuable information about its pharmacological actions, but caution is needed when extrapolating findings to humans consuming soy protein foods, especially because genistein is rarely present in substantial amounts in most human diets.

Specialized animal models are frequently used to study specific health aspects of food components. There are a variety of cancer, diabetes, and coronary heart disease models, usually involving rodents (rats and mice) bred especially to express these diseases. Because no individual animal model is totally comparable with humans with regard to disease progression or metabolism, researchers should consider the strengths and weaknesses of an animal model system when relating the results to humans. This is especially important when investigating the effects of in utero and prepubescent soy exposure.

The microflora in the intestinal tract of rodents and monkeys are more efficient than microflora in humans in producing the isoflavone metabolite equol; in fact, rodents and monkeys are referred to as to equal machines (22). Only ~30–50% of humans can produce equol from daidzein in the gastrointestinal tract and even in those who do, equol levels in serum are relatively modest compared with genistein and daidzein (22–24). Because equol has been suggested to be a particularly potent biologically active isoflavone (22), outcomes of studies with rats and mice may not predict the effect of soy isoflavone consumption by humans.

Perhaps the source of the most confusion and conflicting results is the use of supraphysiological levels of genistein or isoflavone mixtures in cell culture studies. Cell culture studies often use isoflavone concentrations of 10–1000 times higher than physiological levels and provide isoflavones without other soy components. Numerous studies have shown that the half-life of isoflavones in blood after a soy-containing meal is not long (10, 25–30). In healthy adult men and women the terminal elimination half-life of genistein and daidzein ranges from 3 to 9 h after consumption of a soy protein isolate drink (30). Although cell culture studies are aimed at identifying possible isoflavone effects and defining mechanisms, the relevance of these studies to in vivo situations is uncertain. For example, many independent estrogen-receptor-binding effects of genistein that are noted in vitro, such as the inhibition of DNA topoisomerases, tyrosine protein kinases, and cancer cell growth, occur at concentrations that exceed 25 μmol (31). However, peak serum genistein concentrations typically are no higher than 5 μmol and ~95% are conjugated with glucuronic acid and are biologically inactive. The extent to which in vivo observations involving high micromole levels of isoflavones are relevant to humans is unclear.

In vitro studies have an important role, particularly for studying structure-activity relationships and mechanisms whereby soy components may affect cellular or molecular events. However, there is concern that in vitro work may either overestimate or underestimate the in vivo potency of isoflavones. An underestimation may occur because in vitro systems may lack cellular factors that potentiate the effects of isoflavones in vivo or because isoflavone metabolites are produced in vivo that are more potent than the parent compound. In any event, it is quite clear that in vitro data should be interpreted with caution and should be used primarily to help determine the biological actions of individual phytochemicals and to identify the mechanisms underlying those effects.

Conclusions

Confusion regarding soy and health research is not surprising considering the complexity of this field. The confusion often starts when researchers do not provide sufficient details regarding the products and compounds that they use or do not relate the amounts or concentrations used to real-life consumption patterns. Researchers often fail to translate appropriately their results in risk-benefit terms and to compare their findings produced from 1 experimental model with results from relevant research from other types of experimental models. Consequently, the media and health professionals have a difficult time translating the results for consumers and public health messages. Health professionals should place new research into perspective of the entire wealth of published literature when communicating to the public or making public health recommendations.

Recommendations

To reduce the confusion regarding soy and health research, we make the following recommendations:

- Manufacturers who provide information about the isoflavone content on their product labels should express contents as an aglycone amount. In addition, they should provide clear content information on test products to researchers.
- Researchers should provide a detailed and unambiguous description of products, concentrations, and amounts used in their studies.
- Researchers should clearly relate their study conditions to usual soy and isoflavone intakes and/or tissue levels of isoflavones.
- Researchers should consider the risks and benefits of their findings for human health.
- All researchers, but especially those conducting cell culture or animal studies, should outline the benefits and limitations of the model system used.
- The media and public health officials should look at the totality of the evidence when commenting on the potential significance of new findings and demand that researchers be clear on what soy product or extract was used and how any new findings compare with the existing literature.

LITERATURE CITED


