

1 May 1998

Office of Premarket Approval (HFS-200)  
Center for Food Safety and Applied Nutrition  
Food and Drug Administration  
200 C Street SW  
WASHINGTON DC 20204  
**UNITED STATES OF AMERICA**

**Attention:** Dr AM Rulis

Dear Dr Rulis

I have corresponded with Linda Kahl of your office regarding the recognition by the Archer Daniels Midland (ADM) Company that soy isoflavones are generally recognised as safe (GRAS). I have also received ADM's support document entitled 'An information document reviewing the safety of soy isoflavones used in specific dietary applications'.

I understand that the FDA's procedure for evaluating ADM's notice does not involve rulemaking and that there is no formal mechanism for submission of comments within the context of 'notice and comment' rulemaking. However, I also understand that the FDA welcomes fact-based information on food safety issues.

With regard to GRAS Notice Number GRN 000001, and acting on instructions from a client, I would like to submit the attached information to your office for your consideration

Yours faithfully

**KINGETT MITCHELL & ASSOCIATES LTD**

Mike Fitzpatrick PhD MNZIC

cc Dr L Kahl

## **1 INTRODUCTION**

The Archer Daniels Midland Company (ADM) have provided the Food and Drug Administration (FDA) with notice that it has determined that the substance soy isoflavone is generally recognised as safe (GRAS). This notice was made in accordance with the FDA proposed rule 'Substances Generally Recognized as Safe' 21 CFR Parts 170, 184, 186 and 570.

In support of this notice, ADM have provided a document entitled 'An information document reviewing the safety of soy isoflavones used in specific dietary applications'.

In my opinion soy isoflavone (or more correctly, the soy isoflavones) should not be granted GRAS status. In fact given the current state of knowledge in the body of scientific literature it would make more sense, in terms of risk assessment, to prohibit the addition of soy isoflavones to foods. Further, manufacturers should act to minimise the exposure of the human and animal population to these compounds that appear to occur in all foods that contain soy protein. This opinion is based on my understanding of the scientific literature on soy isoflavones and some experience as a researcher in the field.

I have read the ADM supporting document and have found that, as a scientific document, it is seriously lacking. Firstly, the document contains several important factual errors. Some of these errors were so blatant that it caused me to reflect on ADM's moral and legal obligation to present an accurate case to the FDA. Secondly, I noted that the references cited in the ADM document frequently misrepresented, and sometimes bore no relation to, the conclusions made by the authors cited. Thirdly, the ADM document does not present the full body of current scientific evidence regarding soy isoflavones. Several notable omissions exist in relation to the potential for soy isoflavones to cause breast cancer and thyroid disease. Finally, many of the conclusions reached in the ADM document are not based on factual evidence and logic but rather assumption and belief. As such the ADM document does not represent good science.

These scientific deficiencies in the ADM document, and counter arguments, are detailed in the sections below.

## **2 SOY ISOFLAVONES: HISTORY OF USE**

In order to prove the GRAS status of soy isoflavones it is critical for ADM to demonstrate that soy isoflavones have enjoyed a long and safe history of use. Hence ADM claim that 'these isoflavone components...have been consumed by millions of humans for over two thousand years'. However, their claim is not based on fact and neither is there any evidence provided to substantiate their claim.

The claim that isoflavones have been consumed for thousands of years has become quite common in isoflavone scientific literature, however it is no more than an assumption

and appears based on the general perception that historical soybean consumption was widespread in Asia.

Although soybean products have been consumed in some parts of Asia for many hundreds of years (1) they did not form a significant part of the diet (2). Also, the traditional soybean was quite different to the soybean as we know it today.

*Glycine soja*, the wild soybean, is found in northern, north-eastern and central China, adjacent areas of the former USSR, Korea, Taiwan and Japan. *Glycine soja* is the species of soybean that was consumed traditionally and is the ancestor of the modern cultivar, *Glycine max* (3).

The isoflavone content of *Glycine max* was first reported about 60 years ago (4) but it is impossible to know with certainty whether *Glycine soja* contained isoflavones. It is well established that *Glycine max* is, compositionally, quite different to *Glycine soja*. For example, *Glycine max* contains approximately 21.0% oil compared with 9.8% in *Glycine soja* and *Glycine max* also contains more protein (3). This is quite expected because *Glycine max* has been cultivated to have maximised economic potential.

It has also been shown that plants such as that as *Glycine max* produce phytoestrogens such as the soy isoflavones as a defence mechanism in response to pests (5). Increased disease resistance has been a consistent goal of soybean breeders and it is quite conceivable that this goal has served to increase the levels of isoflavones, and other naturally occurring toxins, in *Glycine max*.

It is also well established that different cultivars of *Glycine max* can contain widely variable levels of isoflavones (6). If this is so then it is not implausible that the traditional Asian soybean, *Glycine soja*, contained quite low levels of isoflavones, or perhaps none at all.

Therefore, a counter argument to the ADM claim of long and safe use could be that isoflavones have entered the human food chain only in relatively recent times. It has been the cultivation of *Glycine max* coupled with mass production technology and incorporation of soy protein into numerous foods that has resulted in these compounds being almost unavoidable in the human diet. This mass exposure has only occurred in the last 30 years and it is still undetermined whether isoflavones are safe or not.

In summary, ADM cannot show a long and safe history of use because there is no evidence to substantiate their claim 'that isoflavones have been consumed by millions of humans for over two thousand years'.

### **3 SOY ISOFLAVONES: SAFETY OF USE**

ADM claim 'a long safe history of consumption for soy products and soy foods'. The issue of the safety of soy products in relation to isoflavone toxicity and risk:benefit considerations has been the subject of a recently published paper (7) by a senior scientist at the FDA National Center for Toxicological Research (NCTR), Dr Daniel Sheehan.

Sheehan is 'unconvinced that the long history of apparent safe use of soy products can provide confidence that they are indeed without risk' and likens soy products to herbal medicines stating that the 'confidence that soy products are safe is clearly based more on belief than hard data'.

Even if ADM'S claims in relation to soy isoflavones, 'no toxic effects at normal dietary levels', were correct (which they are not, see Section 4) this does not provide evidence that soy products are safe. This is because the potential harmful effects of soy isoflavones have never been thoroughly investigated.

There have been several studies that attempt to define the acute toxicity of soy isoflavones in various experimental animals and these are cited in the ADM document. However, the prime concern in relation to estrogenic compounds such as the soy isoflavones is the potential for chronic endocrine system and reproductive toxicity and alterations to the immune system (8,9). As such the harmful effects of soy isoflavones would not have been obvious if they did exist. A compelling example is the estrogenic drug, diethylstilbestrol (DES). Treatment with DES continued for over 20 years before physicians fortuitously made the association between its use and the incidence of a rare type of malignancy in DES daughters (10). In the case of soy isoflavones, however, the fact that estrogenic compounds are present in soy foods has not been general knowledge to health professionals until quite recently. Therefore, any link between effect and cause is unlikely to have been made.

Until more extensive epidemiological studies are undertaken with clearly identified endpoints (such as breast cancer, thyroid disease or immune system dysfunction) it must be concluded that there is no certainty that soy isoflavones are safe at all.

#### **4 SOY ISOFLAVONES: ADVERSE EFFECTS**

ADM argue that 'these isoflavone components...have been consumed by millions of humans for over two thousand years with no recorded adverse effects'. Furthermore ADM claim that 'published epidemiology and feeding studies in both animals and humans indicate no toxic effects at normal dietary levels' and that 'soy isoflavones, as part of a soybean based diet, are not associated with reports of adverse health effects'.

It is difficult to reconcile these statements with published scientific literature which is replete with reports of adverse effects and toxicity of isoflavones at dietary levels. In fact it was the toxicity of dietary levels of isoflavones to animals that first raised the awareness of the scientific community to the fact that soy isoflavones were endocrine disrupters (11).

Reproductive effects, infertility, thyroid disease or liver disease due to dietary intake of isoflavones had been observed for several animals including cheetah (12), quail (13), mice (14), rats (15), sturgeon (16) and sheep (17).

With regard to sheep toxicity ADM claim that the ‘adverse effects were attributed to feeding on subterranean clover and are associated with coumestrol and the isoflavone formononetin’. This is another example of misinformation in the ADM document. In fact it is generally accepted that sheep metabolise formononetin to the soy isoflavone daidzein. Daidzein is, in turn, metabolised to equol which is believed to be responsible for the type of infertility referred to as ‘clover disease’ (18). There can be no doubt that if sheep were fed a diet supplemented with soy isoflavones they would, depending on dose and duration, develop clover disease.

In another study it has also been reported that 9 out of 20 young calves died when fed a soybean milk replacer (19). The authors implicated ‘phenolic compounds’ as the reason of increased prostaglandin synthesis, gastrointestinal disorders, tachycardia, bronchoconstriction and death. Soy isoflavones have the potential to interfere with normal prostaglandin synthesis and are, therefore, a likely explanation for this toxicity in calves. It should be noted that in a control group of calves fed an ethanol extracted soybean milk replacer, only 4 out of 20 deaths occurred. Ethanol extraction reduced the amount of phenolics, which would have included isoflavones, in the soybean milk replacer 2.18% to 1.00%.

ADM claim that ‘infertility effects are not general to all animals’ citing work by Lundh (20). However, this author does not even investigate inter-species differences in reproductive toxicity due to isoflavones. Rather, his work shows how different species metabolise isoflavones differently. Although not all animals become infertile after consuming soy isoflavones at normal dietary levels for restricted periods, feeding at such levels does result in profound endocrine effects in all animals species studied to date.

ADM also claim that ‘soy isoflavones have been widely consumed and are recognised to be non-toxic’ citing Petrakis et al. (21) and Setchell et al. (22). In fact, nowhere in either of these papers do the authors state that soy isoflavones are recognised as non-toxic.

Petrakis et al. found that consumption of soy protein has a stimulatory effect on the premenopausal breast. Although Setchell et al. state that ‘there is no evidence to suggest that ingestion of isoflavones...has adverse effects in human beings’, they acknowledge ‘the potential effect that these bioactive compounds may produce...is unknown’.

It is incorrect to state that there is no evidence of harmful effects of soy isoflavones on humans. In fact there is mounting evidence that dietary levels of soy isoflavones cause thyroid disease and may increase the risk of breast cancer.

Goitre and hypothyroidism were reported in infants fed soybean diets until the early 1960’s (23). In fact recent reports indicate that thyroid disorders may be attributable to feeding soy-based infant formulas (24-25). Further, a study on 37 adults showed that diffuse goitre and hypothyroidism appeared in half of the subjects after consuming 30 g per day of pickled roasted soybeans for three months (26). These findings are consistent

with the recently proposed mechanism by which soy isoflavones affect thyroid hormone synthesis (27).

It is concluded that soy isoflavones can be the cause of thyroid disorders in soy consumers and, hence, there is every indication that cases of goitre and hypothyroidism in infants were caused by the soy isoflavones. Unless diets that include soy isoflavones are adequately supplemented with iodine, goitre will result. In this regard Kay et al. discuss the minimum safety iodine requirement for a soybean diet (28).

However, even if iodine supplementation does occur, under conditions of high chronic doses of isoflavones persistent inhibition of thyroid hormone synthesis could potentially lead to thyroid cancer (27).

With regard to breast cancer, Dees et al. have shown that dietary concentrations of genistein may stimulate breast cells to enter the cell cycle; this finding led these authors to conclude that women should not consume soy products to prevent breast cancer (29). This work is consistent with an earlier report by Petrakis et al. who expressed concern that women fed soy protein isolate have an increased incidence of epithelial hyperplasia (21).

There is no doubt that soy isoflavones are biologically active in humans. The first report of a definitive experiment which showed this involved the consumption of 60g of soy protein per day for one month by pre-menopausal women (30). The soy isoflavones disrupted the menstrual cycle during, and for up to three months after, administration. With regard to this study the ADM document claims 'no adverse effects were noted' but the authors of the original paper did not state this. It is appreciated that there are varying opinions in the scientific community as to what constitutes toxicity. In recent times, however, there has evolved a greater understanding of endocrine disrupters and their effects. Many now view the multiplicity of effects that endocrine disrupters can induce as toxic effects (8).

The inclusion of endocrine disrupters in human diets should not be taken lightly. With specific reference to soy-based infant formulas the high soy isoflavone intake of this population group has led Dr Sheehan to note that infants fed soy-based formulas have been placed at risk in a 'large, uncontrolled, and basically unmonitored human infant experiment' (31). If soy isoflavones are granted GRAS status this experiment would spread to the greater population and millions would be exposed to compounds which are increasingly being shown to have adverse effects.

Also, the synergistic effects that soy isoflavones may induce when combined with other xenoestrogens that the human population are exposed are beyond the scope of this document. However, there is a general thesis that because of the potential for synergistic effects, human exposure to all endocrine disrupters, such as the soy isoflavones, requires urgent reduction (8).

## **5 SOY ISOFLAVONES: BENEFITS**

In recent times there have been numerous claims that isoflavones prevent hormone related diseases such as breast cancer. Under some conditions genistein has been found to inhibit breast cancer cell growth (32). However, there is no consensus amongst scientists that isoflavone ingestion reduces breast cancer risk.

Recently the UK government published a definitive review assessing the effects of phytoestrogens in the human diet (33). This study found that there was almost no evidence linking health benefits from foods containing isoflavones to the isoflavones themselves.

Similarly in their review of phytoestrogens and western diseases, Adlercruetz and Mazur assert that any benefits from soy products are not due to isoflavones specifically. They conclude that the combination of a high phytoestrogen intake with a western diet may not be beneficial (34).

ADM state that ‘epidemiological studies between Western and Far Eastern populations suggest that components of soybeans may contribute to important health effects’. However an epidemiological study in China has shown that high soy intake is not protective against breast cancer (35).

Based on evidence to date it is concluded that there is little evidence for the beneficial effects of soy isoflavones. Indeed authorities in the field do not support the ADM thesis that soy isoflavones ‘provide positive health maintenance benefits’.

## **6 SUMMARY AND CONCLUSIONS**

In conclusion, the recognition by the Archer Daniels Midland Company that soy isoflavones are generally recognised as safe (GRAS) is seriously flawed. The supporting document entitled ‘An information document reviewing the safety of soy isoflavones used in specific dietary applications’ contains factual errors, misrepresents cited authors and does not present the full body of current scientific evidence. The conclusions reached in the ADM document are not based on fact:

- There is no evidence of a long and safe history of use or that ‘these isoflavone components...have been consumed by millions of humans for over two thousand years’.
- It is not correct that ‘published epidemiology and feeding studies in both animals and humans indicate no toxic effects at normal dietary levels’ or that ‘soy isoflavones, as part of a soybean based diet, are not associated with reports of adverse health effects’.
- Benefits of dietary intake soy isoflavones have not been proven.

To the consumer, dietary soy isoflavones represent a clear risk whereas the benefits are highly questionable. Rather than accept that soy isoflavones are GRAS, it is my opinion that regulatory agencies such as the FDA should give full attention to consumer protection and deny GRAS status to soy isoflavones.

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