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Peter Beckerman, Esq., Deputy Chief Counsel
Program Review for Food and Veterinary Medicine
FDA Office of Chief Counsel
10903 New Hampshire Avenue
Silver Spring, MD 20903

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

RE: Docket No. 2007N-0464 Submitted February 18, 2008

Soy Nutrition Institute's response to comments in regard to Weston A. Price Foundation comments to FDA dated November 9, 2015

The Soy Nutrition Institute (SNI) once again appreciates the opportunity to present the following additional scientific evidence to address the issues regarding the soy protein and risk of coronary heart disease health claim (21 CFR §101.82).

Our additional comments are focused on studies involving humans because animal studies have limited ability to provide insight into the health effects of soyfoods. In addition to the usual limitations of animal models, because rodents and monkeys metabolize isoflavones very differently than humans, they are of little value for understanding soyfoods.[1] The WAPF alleges that because soyfoods are rich sources of isoflavones they exert untoward effects, such as disrupting thyroid function. However, the clinical data suggest otherwise, and in fact, after a comprehensive review of the scientific literature, the European Food Safety Authority (EFSA) recently concluded that isoflavones do not adversely affect the breast, uterus or thyroid.[2]

Of the non-animal studies cited by the WAPF, four are epidemiologic studies[3-6] and seven are clinical studies.[7-13] In addition, seven narrative reviews or meta-analysis were cited.[14-20] For reasons articulated below, the evidence cited by the WAPF is almost entirely irrelevant and provides little insight related to the re-evaluation of the soy protein and coronary heart disease health claim.

Epidemiologic studies

Only one[6] of the four studies[3-5] reported LDL-cholesterol values and none of the four cited by the WAPF are relevant to the soy health claim because daily soy protein intake in all cases was far below the 25 g amount established by the FDA as the daily intake required for cholesterol reduction. More specifically, in the studies by Yu et al.,[3] Talaei et al.[4] Yu et al.[5] and Pan et al.,[6]

the mean (g/d) (SD) fourth quartile or fifth quintile soy protein intake was 16.5 ± 5.7, 11.2 ± 4.2, 17.3 (SD not available) and 16.34 (interquartile range; 14.16–20.95), respectively.

Clinical trials

Of the seven clinical trials cited by the WAPF, participants in two of the studies consumed relatively little soy protein. More specifically, in the studies by Mangano et al.[9] and Liu et al.,[10] mean daily soy protein intake of participants in the soy group was 14.3 and 15 g, respectively.

Two studies of the seven do not provide insight in the cholesterol-lowering effects of soy protein because they did not include a suitable control protein. In the study by Carmignani et al.,[8] the control group consumed maltodextrin and in the study by Sathyapalan et al.,[13] the control group consumed soy protein from which isoflavones were extracted. Having said this, in the study by Carmignani et al.,[8] LDL-cholesterol decreased 1.9% in the soy group but increased 5.5% in the control group (although not the focus of the health claim, triglycerides decreased by 1.1% in the soy group and increased by 21.3% in the control group). The difference in the change in LDL-cholesterol between the two groups, while not statistically significant, is certainly within the range expected for soy protein.

In addition to the lack of suitable control protein, the study by Sathyapalan et al.[13] is irrelevant to the health claim because the participants were subclinical hypothyroid patients (although not the focus of the health claim, isoflavone-rich soy protein significantly lowered blood pressure and C-reactive protein levels and increased insulin sensitivity). One other clinical study cited by the WAPF is irrelevant to the health claim because it did not assess changes in LDL-cholesterol.[11]

Two studies cited by the WAPF did not find soy protein statistically significantly lowered LDL-cholesterol.[7,12] It is notable that in one of these, the dropout rate was 29% and the first cholesterol measurement was taken at the six month time point.[7] In any event, it is not unexpected that in trials involving relatively small numbers of participants statistically significant reductions in outcomes expected to be modestly affected are not always observed. Meta-analyses are often conducted in part to compensate for trials with small numbers. Importantly, both of the aforementioned trials[6,11] were included in a meta-analysis of the clinical data published in 2015 that found soy protein statistically significantly lowered LDL-cholesterol.[21]

Reviews/Meta-analyses

Seven narrative reviews or meta-analysis were cited but the WAPF.[14-20] Three of these concluded that isoflavones don't lower cholesterol which is irrelevant to the soy protein and coronary heart disease health claim.[15,17,20]

The review by Sacks et al.,[19] which is often mistaken for a meta-analysis, was shown by Jenkins et al.[22] to have substantially underestimated the hypocholesterolemic effects of soy protein.

The review by Xiao et al.[18] concluded that "… soy protein appears to consistently lower blood LDL cholesterol in hyperlipidemic subjects."

The paper by Girgih et al.[14] consisted of a narrative review conducted by four Canadian researchers. A response to this review that was also published in the same journal refuted many of the arguments posed in that article.[23] It is notable that while Girgih et al.[14] did call for re-evaluation of the soy protein health claim, one year following the publication of this paper, Health Canada approved a health claim for soy protein similar to the FDA claim.[24]

Finally, the European Natural Soyfoods Association has addressed the decision of the European EFSA.[16] The main objection to the EFSA decision is that they rejected the use of meta-analyses. As already mentioned, conducting meta-analyses is a common statistical approach to evaluating evidence and is especially useful when the individual studies included in the analysis involved relatively small subject numbers.

Final Comments

The results of meta-analyses published since the soy protein health claim was approved in 1999 consistently show that soy protein lowers LDL-cholesterol. In addition, when soyfoods replace common sources of protein in the US diet the polyunsaturated:saturated fatty acid ratio is improved. Soyfoods also have an impressive safety profile. Therefore, the totality of the evidence supports continued approval of the soy protein and coronary heart disease health claim.

Sincerely,

Ratna Mukherjea, PhD
President, Soy Nutrition Institute

Mark Messina, PhD
Executive Director, Soy Nutrition Institute

RM/MM/sv

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