

Appendix V:

Independent report of “The Potential Estrogenicity
of SDG Flax Lignan Extract”

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The Potential Estrogenicity of SDG Flax Lignan Extract

SDG flax lignan extract "is a water/alcohol extract of defatted flax flour which produces a 35-40% concentrate of secoisolariciresinol glucoside or SDG for short. This compound is a weak phytoestrogen (1000 X lower than E2) of the lignan (dibenzyl butane) class." (Empie, 2005) Anticipated daily doses of SDG for adult humans will be 500-600 mg although doses up to 700 mg/day are being considered. Will these doses of SDG result in estrogenic effects in humans?

Lignans are found in highest concentration in the defatted portion of flax seeds. In the gastrointestinal tract of mammals (including humans), they are converted to mammalian lignans, mainly enterolactone and enterodiol. Lignans are structurally similar to estrogens and have a low binding affinity to estrogen receptors; that is, they are very weak estrogens. Weak estrogens may compete with potent estrogens for estrogen receptors. It has been reported that lignans inhibit estrogen sensitive breast cancer cell proliferation probably by affecting estrogen metabolism resulting in an increase in urinary C-2 hydroxyestrone, which beneficially alters the C-2 C-16 ratio.

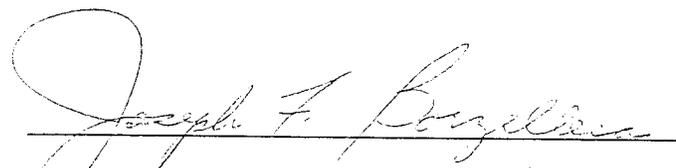
The safety of SDG flax lignan extract (complex) was evaluated in male and female Sprague-Dawley rats. The study was consistent with USFDA Redbook Guidelines and with USFDA GLP regulations. The rats were gavaged daily for 13 weeks with corn oil (control group), or 2.5, 12.5, 62.5, or 250 mg of IRR SDG flax lignan complex. There were no deaths. There were no treatment-related adverse effects on any of the parameters evaluated. Significant treatment-related toxicological effects should be dose-dependent, seen in both sexes (unless target organ is sex-related gonadal tissue) and consistent; functional changes should be accompanied by morphological changes (but lack of morphological findings does not negate functional changes). There were no indications in this study of significant estrogenic effects; that is, there were no changes in estrogenically sensitive tissues including mammary glands, ovaries, uterus, vagina, testes, and prostate. The uterus is especially sensitive to the influence of estrogens and is the basis for the rat uterotrophic method for assaying estrogenic potency. The No-Observed-Adverse-Effect-Level (NOAEL) was 250 mg SDG flax lignan extract/kg bw/day, the highest dose tested.

In a clinical study designed to assess the safety of SDG flax lignan extract, 56 male adults, ages 28-79 years, received either a placebo, 300 or 600 mg doses of SDG flax lignan extract per day. The following were reported and were generally dose-dependent: lowering of blood glucose, total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides. There were no reported effects on creatinine, BUN, ALT, and GGT. There were no reported adverse effects. These findings suggest that these doses did not elicit any signs of toxicity and are considered safe. Estrogenic effects were not assessed since this was not the purpose of the study.



While the data reviewed are supportive of the safety of SDG flax seed lignans, the sum total of the flax literature was not evaluated. Therefore, a conclusive determination of the GRAS status of SDG flax seed lignans was not made. However, the history of safe use of flax products provides additional support for the safety of this product.

With regard to the estrogenic potential of the SDG flax seed lignan product, it is important to note the rat is an appropriate species for studying estrogenic responses. The subchronic study conducted in rats did not identify adverse effects in estrogenically sensitive tissues. These findings can be extrapolated to humans due to the appropriateness of the rat model. One can conclude from these data that it is unlikely that adverse estrogenic activity will be observed in adults consuming the SDG product at the proposed levels of 500- 700 mg/person/day.


Joseph F. Borzelleca 13 September 2005

Appendix VI:

Selected key articles cited in the literature

1. Mazza, G. and Oomah, B.D., 1995 Flaxseed, dietary fiber, and cyanogens. Chapter 4. In "*Flaxseed in Human Nutrition.*" Editors: Cunnane, S. and Thompson, L.U. Published by AOCS Press.
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5. Wang, L.Q. 2002. Mammalian phytoestrogens: enterodiol and enterolactone. *J. of Chromatography B*, 777, 289-309.
6. Kuijsten, A., Arts, I.C.W., Vree, T.B. and Hollman, P.C.H. 2005. Pharmacokinetics of enterolignans in healthy men and women consuming a single dose of secoisolariciresinol diglucoside. *J. Nutr.* 135: 795-801.