Letter to the Editor

Answer to Dr. Messina's Letter to the Editor

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The Senate Commission on Food Safety of the Deutsche Forschungsgemeinschaft (SKLM) disagrees with the letter to the Editor by Dr. Mark Messina *"Conclusion that isoflavones exert estrogenic effects on breast tissue and may raise breast cancer risk unfounded".* In his letter [1], Dr. Messina criticizes that one of the two primary conclusions of the opinion of the SKLM [2] is not supported by the literature. Furthermore, the last sentence of his letter says: *"…the evidence clearly does not warrant the conclusion reached by the SKLM that isoflavones exert estrogenic effects on breast tissue in women, and especially not in a way that increases breast cancer risk"* [1]. However, this is not what was said. The context explains that a conclusive assessment of the effects of isoflavones on the breast tissue of women with an increased risk of breast cancer at present is not possible. To quote the exact wording (chapter 4.1, last paragraph):

"[…] In view of the difficulties associated with transferring data from animal experiments to humans and because of the very limited number of clinical studies available, it is not possible at present to make a conclusive assessment of the effect of isoflavones on the female breast, particularly regarding the risk of breast cancer in women at elevated risk or the survival time of breast cancer patients (Messina et al., 2006). Available data from prospective studies on the increased intake of isoflavone-containing foods did not indicate a lowering of breast cancer incidence. However, a conclusion that can be drawn from the available data is that isoflavones, particularly at high dosage, can exert an estrogenic stimulus on the mammary gland tissue in women." [2]. Importantly, the SKLM opinion [2] also expressed that *"biological effects connected with the intake of isoflavones in an isolated, highly dosed or enriched form are not comparable to those associated with the intake of isoflavones in complex foods, as is the case for the consumption of soy-based foods in Asian countries. The safety of isoflavone preparations based on soy and red clover as food supplements or as dietary foods for special medical purposes cannot be derived from the traditional use of soy-based foods*" [2].

Furthermore, Messina's main critique addresses the pilot/preliminary character of the clinical studies cited by the SKLM. However, his objection mainly refers to evidence from clinical pilot studies [3–5], studies with short intervention periods [3, 4] or with small numbers of test persons [5]. He also considers clinical studies (including one in postmenopausal women) that have not shown a correlation between isoflavone intake and breast tissue density [6–9]. However, in a review on a workshop held in 2005, Messina himself (*et al.*) made the point *"… that if an intervention alters breast density, it does not necessarily follow that the intervention will alter breast cancer risk; conversely, interventions may alter risk of breast cancer without changing density"* [9]. This highlights the need, as expressed in the SKLM opinion, to develop better and reliable biomarkers related to breast cancer risk.

Messina further refers to an epidemiological study in Chinese breast cancer patients reporting that soy food intake prior to diagnosis was found to be unrelated to disease-free breast cancer survival [10]. However, this study had several limitations (partially alluded to already by the authors). These include isoflavone intake assessment by food frequency questionnaire at the baseline only (with a separate subgroup reporting "no recent change in soy food intake"), lack of detailed information on tamoxifen use and the fact that the major part of the cohort represented premenopausal women.

In the final conclusions, the SKLM stated that *"the currently available data do not allow a conclusive assessment of the effects of isoflavones on the breast tissue of women with an increased risk of breast cancer"*. Furthermore, *"particular problems might be associated with the intake of isoflavones by postmenopausal women, since they represent the main target group for these preparations, but also are considered at particular risk with regard to undesirable side-effects"*.

In summary, the SKLM opinion represents a precautionary note reflecting the state of knowledge at the time the opinion was written. The SKLM continues to carefully monitor upcoming scientific evidence in order to appropriately take

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into consideration further developments concerning safety evaluation of isoflavones.

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