

***DFG – Senate Commission  
on Food Safety***

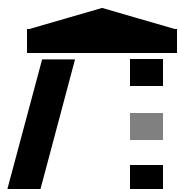
***SKLM***

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**Natural Constituents of Foods:  
Assessing the toxicity of substances administered as pure  
compounds compared to their ingestion as inherent food  
components**

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*The DFG Senate Commission on Food Safety (SKLM) has been asked how to assess substances naturally occurring in food that are ingested together with other food constituents and have shown carcinogenic efficacy when administered alone. The underlying question of whether the food matrix or other food ingredients may potentially influence the effects of a given substance does, however, not solely apply to carcinogens, but basically applies to all substances food. The Commission therefore addressed the question of how the effect of a “natural matrix” needs to be taken into consideration when assessing the toxicity of natural constituents. The SKLM discussed this question in depth and the German opinion was adopted on March 13<sup>th</sup> 2006, the English version was accepted on September 05<sup>th</sup> 2006.*

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This SKLM opinion in general addresses the question of how the effect of the natural combination with other ingredients needs to be taken into consideration when assessing the toxicity of a single compound. These statements can, in principle, be applied as well to natural constituents that are carcinogenic.

**Toxicological assessment of natural constituents in foodstuffs**

Basically toxicological studies with food constituents applied in isolation are needed in order to determine the potential hazard exerted by a particular substance. This is the only way to obtain reliable data on absorption, distribution, metabolism and excretion (toxicokinetics) of a substance and to determine the spectrum of its toxic effects, including acute, subacute/subchronic and chronic, as well as endocrine, embryotoxic and teratogenic, mutagenic and carcinogenic effects (toxicodynamics). Furthermore, the dose-effect relationship up to the MTD (maximum tolerated dose) is only to be obtained in this way.

As isolated compounds, natural food constituents may be administered to laboratory animals orally by gavage, with food or drinking water. Whereas administration by gavage results in a bolus dose, the other methods typically result in a gradual uptake

of the substance. Additionally, when administered in food the substance is taken up together with a large number of other substances present in the food. Administration by gavage permits more accurate body mass-related dosage throughout the experiment and avoids problems due to palatability disturbance if administered in food. Toxicokinetics, however, differ quite significantly from those when administered in food. Nevertheless, the findings obtained using this method provide useful information on the toxicity of the substances under investigation.

Due to similar toxicokinetic conditions, administration in animal feed provides a better model for the uptake of the substance as a natural food constituent. Results from such studies are therefore considered to be particularly relevant, also with respect to potential interactions with other ingredients present in feed or food.

In contrast, studies involving animal experiments in which the substance in question is given as natural constituent in food are less suitable for toxicological risk assessment, since the food usually cannot be applied in adequate quantities without causing undesirable side effects such as nutritional imbalances.

### **The effect of the food matrix and composition**

Since foods usually have a very complex composition, any particular substance under consideration is subject to potential interaction with a large number of other substances. These interactions may include effects on the liberation or absorption characteristics of a given substance, or other interactions with food constituents. In particular, this may significantly alter the bioavailability or efficacy of the substance. There are numerous examples of interactions between substances that result in reduced bioavailability and reduced efficacy. In certain cases, however, it is equally possible that bioavailability is enhanced and efficacy is increased. Furthermore, natural food constituents may also affect the metabolism and excretion of a given compound, thus also influencing its efficacy, for instance by activating or deactivating enzymes of the organism or the intestinal flora. In cases of a similar activity profile, additive or super-additive effects of various constituents may be observed.

Since it is rather difficult to predict such interactions, the effect of the respective food matrix should be investigated case-by-case.

## **Conclusions and recommendations**

Toxicological effects observed in animal experiments with food constituents that are given as isolated compounds, either by gavage or added to the animal diet, do not necessarily occur in the same way or to the same extent when the respective substance is ingested as an inherent constituent of a food. In the absence of data on the influence of the respective constituent and the respective matrix in a foodstuff, they are, nevertheless, be used as a basis for risk assessments. A more detailed evaluation requires further investigations in order to clarify, case-by-case, whether and to what extent the natural matrix in the respective foodstuff influences the effect of the constituent in question.

These additional experiments, required to enable a more detailed risk assessment, include specific studies on the influence of the respective food matrix and composition on the toxicokinetics and effects of the constituent in question administered as isolated compound. The required dosages need to be specified on a case-by-case basis.

It is also possible to administer the constituent with the feed of laboratory animals. Although this method does not actually test the original food matrix, toxicokinetics and influential effects of many substances also present in food are similar to the uptake with food. In certain cases the normal animal food may be replaced by special diets containing the food of interest in a concentrated/enriched form. Such diets need, however, to be nutritionally balanced and need to be acceptable to the animals in terms of taste. In addition, the internal exposure for example by use of appropriate biomarkers, should be determined in such studies. Comparative studies of the internal exposure in humans are suitable to enable well-founded risk assessment.

It is important to know/elucidate the mode of action of the respective substances particularly in humans and in comparison to the animal species used. Such studies can provide useful information for risk assessment.

Such studies have to be performed in accordance with internationally accepted guidelines (OECD).

In conclusion, the Commission noticed that in many cases the current state of knowledge is insufficient for an adequate risk assessment that also takes the effects of the food matrix or other constituents on the toxicity of an individual substance into consideration. A case-by-case assessment is essential.