REPORT

Update of the toxicological assessment of furanocoumarins in foodstuffs (Update of the SKLM statement of 23/24 September 2004) – Opinion of the Senate Commission on Food Safety (SKLM) of the German Research Foundation (DFG)*

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The DFG Senate Commission on Food Safety (SKLM) has discussed the toxicological assessment of furanocoumarins in foodstuffs and adopted an opinion on 23/24 September 2004 [SKLM, English version: Toxicological assessment of furanocumarins in foodstuffs, 2006; *Mol. Nutr. Food Res.* 2007, *51*, 367–373]. At that time, no analytical data were available on the occurrence and content of furanocoumarins in citrus oils, especially in lime oil and the foodstuffs produced from it. According to the SKLM, the highest levels were likely to be found in products containing lime or bergamot oil. Distilled and cold pressed oils differ in their levels of furanocoumarins; in distilled oils, no furanocoumarins were found. The original estimate of the average daily intake of furanocoumarins in Germany made by the SKLM is based on the assumption that flavoured foods contain cold-pressed citrus oils exclusively (worst case scenario). Recent data, however, indicate that distilled citrus oils are mainly used in flavoured soft drinks. The SKLM has therefore decided to update the assessment of the average intake of furanocoumarins from flavoured food. The following opinion was released in German on 25 January 2010, the English version was agreed on 27/28 September 2010.

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1 Contents in flavoured soft drinks and citrus juices

New analytical data about furanocoumarin contents in flavoured soft drinks and citrus juices show that in 17 out of 18 samples analysed, the furanocoumarins isopimpinellin, 5-methoxypsoralen (5-MOP), and bergamottin were not found [1]. According to the authors, the detection limit was 2.5 μg/100 mL (Eva Gorgus, Dieter Schrenk, personal communication). In one sample (soft drink with lime flavouring), 113 μg/100 mL (Σ of furanocoumarins) were found. This suggests that distilled citrus oils are used for the

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Abbreviation: MOP, methoxypsoralen

*The Senate Commission on Food Safety (SKLM) of the Deutsche Forschungsgemeinschaft (DFG) advises authorities and the government on the safety for health of foodstuffs. Further information on the SKLM activity profile, see Eisenbrand, G., The DFG-Senate Commission on Food Safety (SKLM). *Mol. Nutr. Food Res.* 2005, *49*, 285–288. Further detailed information on the work of the DFG-Senate Commission on Food Safety can be provided by Dr. Gerhard Eisenbrand, Food Chemistry and Toxicology, University of Kaiserslautern or by the Scientific Office of the SKLM: S. Guth, M. Habermeyer and B. Kochte-Clemens, E-mail: sklm@rhrk.uni-kl.de and also by Dr. H. Strelen, DFG-administrative headquarters, E-mail: sklm@dfg.de.

flavouring of soft drinks. The levels in pure lime juice and lime syrup were, on average, 743 or 525 µg/100 mL, respectively. In these studies, grapefruit juice was found to contain a higher level (1650 µg/100 mL) of furanocoumarins than estimated in 2004.

2 Update of the exposure assessment

According to the SKLM, the considerations regarding the maximum acute exposure made in 2004 are still valid. In particular, higher intake values might be reached by consuming microbially infected celery bulbs or parsnips. Consuming 200 g of such parsnips with a furanocoumarin content of 500 mg/kg may result in an intake of 100 mg per person. Consumption of the same amount of commercially available parsnips or celery with an average furanocoumarin content of 20–50 mg/kg leads to an intake estimate of approximately 4–10 mg per person.

In 2004, no published data about the content of furanocoumarins in flavoured foodstuffs were available in the literature. Based on the assumption that only cold-pressed citrus oils are used for flavouring purposes, the SKLM estimated an average intake of furanocoumarins in flavoured foods at around 1.4 mg per person per day. However, based on the new data, flavoured soft drinks do not seem to contribute significantly to the overall exposure to furanocoumarins, even if the number of samples is not yet representative. Assuming a proportion of approximately 5% of positive findings (maximum value 113 µg/100 mL), an average furanocoumarin content of approximately 9 µg/100 mL can be calculated [average content from 17 samples with contents at the detection limit (2.5 µg/100 mL, worst case) and 1 sample at 113 µg/100 mL (maximum value)]. This results in a negligible increase in the daily intake from flavoured food (0.01 mg). Sweets and bakery goods contribute with 0.08 mg per person per day to the exposure from flavoured foods. This latter value is taken from the estimate in 2004, since the data related to these products remained unchanged. The average daily intake from flavoured foods can thus be estimated to be 0.09 mg per person (Table 1).

According to current data, the average daily intake of furanocoumarins from fruits and vegetables has also changed. The estimate from 2004 resulted in a value of 0.04 mg per person per day. Current consumption data from the National Food Consumption Survey II (NVS II) [2, 3] (http://www.was-esse-ich.de/uploads/media/NVS_II_Abschlussbericht_Teil_1.pdf, http://www.was-esse-ich.de/uploads/media/NVSII_Abschlussbericht_Teil_2.pdf) show, however, that the consumption of fruit juices (251 g/day) is significantly higher than those of previously estimated ones. The consumption of soft drinks remained in approximately the same range. According to the NVS II, vegetable juices are consumed in very small quantities and therefore are not relevant for the exposure assessment of furanocoumarins. Based on the assumption that fruit-juice consumption consists of 10% grapefruit juice, 1% lime juice, and 60% orange juice, an estimated average intake from fruit and vegetable juices of around 0.43 mg per person per day can be calculated. As the data from NVS II do not allow for a distinction between individual varieties of fruits and vegetables, the intake from other non-flavoured foods (0.04 mg) was taken from the 2004 assessment. Thus, the estimated daily contribution from non-flavoured foods is about 0.47 mg per person for the average consumer and around 2 mg per person for a high-level consumer (95th percentile).

The average total daily intake of furanocoumarins from non-flavoured foods and flavoured foods is estimated to be approximately 0.56 mg (Table 1), representing only about one-third of the estimated value from the 2004 statement. Flavoured foods contribute to about 10% to the total intake.

3 Summary and conclusion

The toxicological data on furanocoumarins have not changed significantly since the SKLM statement from 2004:

"It is not possible to specify a no observed adverse effect level for the repeated intake of furanocoumarins. Sub-chronic studies in dogs revealed, 48 mg 5-MOP/kg bw/day to still be hepatotoxic. In monkeys, a dose of 6 mg 8-MOP/kg bw/day still led to gastrointestinal toxicity (vomiting). Both, 5-MOP and 8-MOP are genotoxic. In a 2-year study with 8-MOP in rats, even the lowest tested dose of 37.5 mg/kg bw/day was nephrotoxic and carcinogenic. According to Brickl et al. (1984) [4], the lowest furanocoumarin dose in combination with UVA that led to detectable phototoxic effects in adult humans is approximately 14 mg 8-MOP, corresponding to about 0.23 mg/kg bw for a 60 kg bw person. Schlatter et al. (1991) [5] determined 10 mg 8-MOP+10 mg 5-MOP or 15 mg 8-MOP equivalents corresponding to 0.25 mg/kg bw for a 60 kg bw person".

In recent years, the human dietary exposure to furanocoumarins has been estimated for several countries and has produced average figures of 1.3 mg (USA), 1.45 mg (Germany), and maximum values of 1.2 mg (UK) per person per day, corresponding to 0.020–0.023 mg/kg bw/day [6–8] (http://www.archive.official-documents.co.uk/document/doh/toxicity/chap-1c.htm). At that time, no analytical data were available on the occurrence and content of furanocoumarins in citrus oils, especially in lime oil and the foodstuffs produced from it. Lime oil is mostly obtained by distillation, whereby furanocoumarins can be separated. Recent findings suggest that primarily distilled oils are used for soft drink flavouring. Accordingly, these drinks are not likely to contribute significantly to human exposure to furanocoumarins. However, grapefruit juice appears to be a major source of exposure in Western countries. Based on recent data for Germany, a provisional average daily intake of about 0.56 mg per person

Table 1. Estimated average daily intake of furanocoumarins in Germany (modified from [1])

Foodstuff	Average consumption (g/day)[a]	Maximum consumption (g/day)[b]	Average furanocoumarin content (μg/kg)	Average (maximum) furanocoumarin intake (μg per person per day)
Fruit/vegetable juices estimated:	251	1100		
10% Grapefruit juice	25.1	110	16 500	**414** (1815)
1% Lime juice	2.51	11	7 430	**19** (82)
60% Orange juice with	150.6	660		
0.25% Orange oil	**0.38**	**1.65**	**0.5**	**0.0002** (0.0008)
Total				**433** (1897)
Other non-flavoured foods[c]				**39** (91)
(A) Total intake from non-flavoured foods				**472** (1988)
Soft drinks, including those containing caffeine	156	915	90	**14** (82)
Sweets/bakery goods[c]				**76** (248)
(B) Total intake from flavoured foods				**90** (330)
Total (A+B)				**562** (2318)

a) Averaged for men and women.
b) 95th percentile for men and women.
c) According to [6].

per day, corresponding to approximately 0.01 mg/kg bw/day can be assessed. The values might be higher if consumers, due to brand loyalty, prefer to consume products with higher furanocoumarin contents. Considering the limited database, a final exposure estimation is not possible so far and the SKLM emphasizes that there still is a need for further research.

Thus, estimated furanocoumarin intakes for Germany lie in a similar range as for other western countries. These values are approximately two to three orders of magnitude below the lowest doses that are toxic in sub-chronic and chronic animal studies. The margin to the therapeutic dosage (0.5–0.6 mg 8-MOP/kg bw) corresponds to a factor of around 50; and compared with the lowest phototoxic dosage (0.23 mg/kg bw) to a factor of around 20.

The SKLM assessment concerning the maximum acute exposure to furanocoumarins has not been changed.

The updated conclusions on the toxicological assessment of furanocoumarins in foodstuffs confirm the SKLM statement from 2004.

In summary, the SKLM concludes that the consumption of typical quantities of plant-derived foods that potentially contain furanocoumarins does not represent a significant risk for phototoxic effects when appropriately stored or processed. For celery and parsnips in particular, there is a risk for significant increases in furanocoumarin concentrations under inappropriate storage, processing, and production conditions. In such cases, consumption of phototoxic quantities cannot be ruled out.

A conclusive estimation of the *carcinogenic* risk is currently not possible, due to the complexity of the influencing factors, particularly the levels of exposure, the metabolism and its modulation and the influence of light. The typical consumption of foods containing furanocoumarins, including flavoured soft drinks, leads to an exposure that remains well below the phototoxic dose range. As a result, an additional risk of skin cancer is considered to be negligible. High consumption of improperly stored tubers can lead to extreme intakes and should be avoided, particularly by children.

Members of the Senate Commission on Food Safety

Gerhard Eisenbrand (Chair), Manfred Edelhäuser, Karl-Heinz Engel, Johanna Fink-Gremmels, Jan Hengstler, Thomas Hofmann, Hans-Georg Joost, Dietrich Knorr, Ib Knudsen, Sabine Kulling, Alfonso Lampen, Doris Marko, Reinhard Matissek, Gerhard Rechkemmer, Ivonne Rietjens, Josef Schlatter, Peter Schreier, Dieter Schrenk, Christian Steffen, Pablo Steinberg, Stefan Vieths, and Rudi Vogel.

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