Risiken erkennen – Gesundheit schützen

Consumers, who eat a lot of cinnamon, currently have an overly high exposure to coumarin

BfR Health Assessment No. 043/2006, 16 June 2006

Coumarin is a naturally occurring flavouring substance which is contained in many plants (for example woodruff, sweet clover, tonka beans). Higher concentrations are to be found particularly in some types of cinnamon. Coumarin is used as a fragrance substance in cosmetics and is an active substance in medicinal products. For a few years cinnamon-containing food supplements have also been on sale which are said to reduce the blood sugar level and the blood lipid concentrations of diabetics. Because of the harmful effect of larger amounts – coumarin can cause hepatic damage – coumarin may only be used as an ingredient of flavourings and other food additives with flavouring properties in the food sector. What's more, it has long been known that in animal experiments coumarin can trigger the formation of tumours. More recent scientific findings indicate that there is no genotoxic mechanism of action, something which had been suspected for a long time. The European Commission thereupon submitted a draft amendment to the Flavourings Directive which envisages removing the existing constraints on coumarin. The Federal Institute for Risk Assessment (BfR) took another look at coumarin from the angle of consumer health protection.

In Germany consumers who eat a great deal of cinnamon ingest relatively high amounts of coumarin from food. In its exposure calculations BfR draws on the measurements of an official food monitoring body which recorded the coumarin contents of cinnamon powder and cinnamon biscuits. The tested foods considerably exceeded the maximum levels stipulated in the European Flavourings Directive of 2 milligram per kilogram food. This is an indication that the food industry processes cassia cinnamon which has considerably higher coumarin levels than Ceylon cinnamon. The exposure calculation revealed that in the worst case scenario children who eat a lot of cinnamon clearly exceed the TDI value for coumarin established by EFSA (also taking into account high exposure via the skin). The TDI value indicates the quantity of a substance that can be ingested daily over a lifetime without posing a risk to health.

BfR is of the opinion that dietary coumarin intake should continue to be restricted. In order to avoid high coumarin exposure from direct consumption (e.g. rice pudding with cinnamon and sugar) statutory measures are also desirable.

1 Subject matter of the assessment

The chemical regional and state veterinary monitoring office “Chemisches Landes- und Staatliches Veterinäruntersuchungsamt (CVUA)”, Münster, has measured the coumarin content of cinnamon and cinnamon biscuits. The coumarin levels varied between 22 and 76.8 mg/kg in cinnamon biscuits (13 samples from various manufacturers). Hence they exceeded the currently valid maximum level stipulated in the Flavourings Directive of 2 mg/kg food significantly. Levels between 2.3 and 3.3 g/kg spice were determined in the cinnamon powder analysed as well (5 different samples). Use of cinnamon with these levels (formulation with 1-2% cinnamon in the dough is the one normally used) can roughly explain the coumarin levels measured in the cinnamon biscuits. The high levels indicate that cassia cinnamon and not Ceylon cinnamon was used.

Cassia cinnamon powder (in capsules, with recommended daily intakes in the gram range) has also been used for some time as a food supplement or as a dietetic food to reduce blood

sugar in type II diabetics although these products do in fact meet the various criteria for a medicinal product.

Against this backdrop BfR was asked to undertake the toxicological assessment of the coumarin levels identified in cinnamon and cinnamon biscuits.

2 Results

In its assessment BfR establishes a TDI value taking into account human data on the hepatotoxicity of coumarin which is in the range of the value established by EFSA for daily intake of 0.1 mg per kg body weight. Exposure calculations reveal that a higher intake per kg body weight is to be expected for infants than for adults. Based on the coumarin values measured by CVUA Münster in cinnamon powder this age group has an exposure level – as a worst case scenario - which is almost three times higher than the EFSA TDI value (also taking into account a high intake from cosmetics).

In the EFSA reassessment of coumarin in 2004 a non-genotoxic mechanism of action in conjunction with carcinogenicity was assumed. Because of this, steps were taken on the European level to remove coumarin from Annex II to the Flavourings Directive 88/388/EEC. This would lead to the withdrawal not only of the current constraint for a maximum level of 2 mg/kg through aromatisation of foods with natural raw materials but also to a lifting of the ban on the addition of coumarin as an individual synthetic substance which is regulated in a footnote to the above-mentioned list.

The use of cassia cinnamon with high coumarin contents (like that measured by CVUA Münster) should, in the opinion of BfR, be ruled out at least for the production of foods with a relatively high cinnamon proportion. The same applies to the use of cinnamon extracts with a high coumarin content. Thought should also be given to how coumarin exposure through the direct consumption of cinnamon (e.g. rice pudding with sugar and cinnamon) could be restricted through statutory measures.

3 Reasons

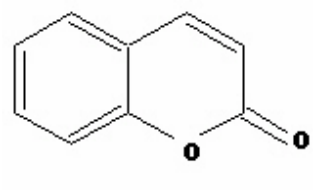
3.1 Risk assessment

In recent decades scientific bodies have repeatedly looked at the health assessment of coumarin. On the European level there are comprehensive opinions of the former Scientific Committee on Food (SCF) of the European Commission from 1994 and 1999 which were revised by the succeeding AFC Panel of EFSA in 2004 on the basis of more recent data on the possible genotoxic mechanism of action in conjunction with carcinogenicity of coumarin. In its review the AFC Panel comes to the conclusion that the data support a non-genotoxic mechanism of action of tumour induction. The previous SCF opinions from 1994 and 1999 had assumed a genotoxic mechanism and had recommended a maximum level of coumarin of 0.5 mg/kg in foods. The Flavourings Directive 88/388/EEC stipulates a general maximum level of 2 mg/kg with deviating provisions for special foods (chewing gum, caramel confectionery, alcoholic beverages). The 2004 EFSA review permitted for the first time the establishment of a TDI value (0.1 mg coumarin per kg body weight).

The main facts from the above-mentioned opinions are summarised below and a closer look is taken at those aspects which, in the opinion of BfR, have not been sufficiently addressed up to now.

3.1.1 Agent

In chemical terms coumarin is 1-benzopyran-2-one (CAS Number: 91-64-5).



The substance is poorly soluble in water but readily soluble in alcohol. It has a pleasant spicy odour of fresh hay, woodruff or vanilla. Besides safrol, menthol, estragol e.g.,cinnamon belongs to the group of ingredients in specific spices and herbs which are described by the Council of Europe as "active principles". In foods they may have a strong flavour but are toxicologically relevant.

Coumarin is widespread in the entire plant kingdom. Besides the blossoms and leaves of many types of grass and clover, higher concentrations of the substance can be measured particularly in certain types of cinnamon. The seeds of tonka beans are another very rich source of coumarin; they are used for perfumery purposes. Woodruff and some types of fruit like strawberries, apricots, cherries, but also garden herbs like sage, dill and camomile as well as a few root vegetables contain this substance.

Coumarin was isolated and purified from tonka beans in 1822. The substance was synthetised for the first time in 1868 and marketed for the first time in 1876. Following findings of a hepatotoxic effect in animal experiments, the addition of synthetic coumarin for the flavouring of foods was initially banned in the USA in 1954. The annual world production for use as a fragrance in cosmetics today amounts to around about 2,000 tonnes (Floc'h *et al.* 2002). Furthermore, coumarin is used as a medicine to treat more particularly the consequences of venous (chronic venous insufficiency) and lymphatic (lymphatic oedemas) drainage disorders.

Coumarin should not be confused with so-called coumarin derivatives (e.g. phenprocoumon, warfarin) which are derived from the basic substance and are widely used as vitamin K antagonists to inhibit blood coagulation by reducing the thromboplastin time (quick value). Coumarin itself does not possess this action.

3.1.2 Hazard potential

Various overview articles and expert opinions of scientific bodies have examined the hazard potential of coumarin (SCF 1994 and 1999, Lake 1999, EFSA 2004). Its carcinogenic and hepatotoxic properties are of importance when it comes to risk assessment and the subject matter of scientific discussion.

3.1.2.1 Carcinogenic properties

The carcinogenic properties of coumarin in animal experiments have been known since the 1970s and have led since then to ongoing discussions about the importance of these findings for humans and the underlying mechanism of action. In the SCF expert opinions from 1994 and 1999 it was assumed that a genotoxic mechanism cannot be ruled out. Hence, strict

maximum levels in foods were recommended (0.5 mg/kg) and there was a call for further elucidation studies. The EFSA AFC Panel came to the conclusion in its expert opinion dated 6 October 2004 that new data on the DNA adduct formation of coumarin in the liver and kidneys of rats supported the assumption of a non-genotoxic mechanism of action of tumour induction. BfR has access to the published study findings of Api (2001) and Edwards (2000), but not to the study findings of Swenberg (2003). Hence, at the present time, BfR cannot undertake a definitive assessment of coumarin regarding a possible genotoxic mechanism of action in conjunction with carcinogenicity. A possible re-evaluation of coumarin does not seem to be urgent concerning its mechanism of action in conjunction with carcinogenicity and should not be undertaken until all study findings have been published.

3.1.2.2. Hepatotoxic properties

The hepatotoxic properties of coumarin identified in the middle of the last century in animal experiments led to a ban on the addition of synthetic coumarin during food production. However, the substance was approved from the 1980s onwards in various countries as a medicinal product to treat for example oedemas caused by venous (chronic venous insufficiency) and lymphatic (lymphatic oedemas) drainage disorders. There were also symptoms of hepatotoxicity in the patients treated which ranged from elevated serum transaminases down to liver failure (e.g. WHO 1995, Andrejak *et al.* 1998). This effect could be observed for the first time within weeks up to a maximum of six months after commencement of treatment. In the 1990s these findings led to these products being withdrawn from the market in several countries (Australia, Belgium, France and Canada). In Germany a national pharmacovigilance procedure was introduced that led at the end of 2005 to the refusal of post-marketing authorisation which was mainly based on the hepatotoxic risks.

What is worth mentioning when it comes to the hepatotoxic effect in humans is that at higher doses the severity of the liver function disorders increased but no clear dose-response relationship was observed concerning the percentage of people affected. It was far more the case that only a relatively small proportion of the population seemed to be sensitive to this effect. The details on the level of this proportion varied. Whereas some authors assumed that this was a rare side effect, others identified numbers in the one-digit percentage range. Loprinzi *et al.* (1999) reported on the results of a placebo-controlled study in which 6 % of female patients manifested unusual serologically transaminases ($p<0.006$ compared with the placebo phase). In a more recent German study (Burian *et al.* 2003, Schmeck-Lindenau *et al.* 2003, Vanscheidt *et al.* 2002) nine out of the 114 patients treated (7.9 %) manifested elevated transaminases in serum which were only partly interpreted by the authors as being causally linked to the medicinal product. Treatment was given over 16 weeks with 5 blood tests during that time. When it comes to the recordability of transaminase elevations it should be borne in mind that in clinical studies this depends on the frequency of the blood samples taken. When coumarin is administered as medication it is possible that in a few patients, despite unchanged intake, the serum values could normalise again at a later date. A continuation of treatment of this kind with control of the laboratory parameters is possible under clinical conditions; a similar situation is not acceptable for the food sector.

The published clinical studies did not succeed in identifying the risk factors for the hepatotoxic effect. Frequently the individual reaction capacity is described as "idiosyncratic". There was also extensive discussion of possible metabolic anomalies, in particular a restricted 7-hydroxylation capacity because of a polymorphism in the CYP2A6 system. However, the more recent German study mentioned above did not determine an association of this kind (Burian *et al.* 2003). The findings of this study indicate that possible previous liver disorders

like hepatitis could increase the risk of a hepatotoxic reaction to coumarin (Schmeck-Lindenau *et al.* 2003).

The findings concerning the NOAEL (No Observed Adverse Effect Level) for hepatotoxic effects in humans are discussed in Chapter 3.1.4 and used for quantitative risk assessment.

3.1.3 Exposure

3.1.3.1 Oral exposure

An important component in risk assessment, particularly when establishing maximum levels for foods, is the exposure consideration for coumarin.

There are no systematic measurements of coumarin in foods. As mentioned above, the substance is contained in various plants (e.g. woodruff, sweet clover, tonka beans, lavender). Given the general eating habits in Germany they are probably not important for exposure. At the present time it must, therefore, be assumed that most coumarin exposure is to cinnamon-containing foods or cinnamon as a spice. This does not just encompass the direct addition of cinnamon to foods but also the use of cinnamon oils and other cinnamon extracts by the food industry.

3.1.3.1.1 Coumarin levels in cinnamon and cinnamon products

The cinnamon levels in various parts of the cinnamon tree (bark, leaves, roots) and the essential oils made from it vary considerably. When it comes to use as a spice the internal bark of the tree is important. It has been used for centuries in dried form as sticks and in ground form as cinnamon powder. Here a rough distinction should be made between Ceylon cinnamon (also called true cinnamon) which is finer and more expensive and the cassia species (e.g. China cinnamon, Padang cinnamon). The chemical composition of the two types of cinnamon is different. In contrast to cassia cinnamon, Ceylon cinnamon contains eugenol and benzyl-benzoate but no (at most traces) coumarin or delta cadinine (Jayatilaka *et al.* 1995). The coumarin levels in the bark of cassia cinnamon vary considerably. They depend for instance on the respective sub-species or climatic conditions. In their examination of a total of 44 cassia samples from various Asian countries He *et al.* (2005) identified levels of more than 1 g/kg in ten samples; the maximum level measured was 12.2 g/kg. Miller *et al.* (1995) identified coumarin levels from below the detection level to 0.19 g/kg in Ceylon cinnamon (n=12) and between 0.7 and 12.2 g/kg in cassia cinnamon (n=12). The CVUA Münster analyses of stick cinnamon identified relatively low values of under 0.015 g/kg for Ceylon cinnamon (only one sample) and of 0.09, 0.29 and 0.53 g/kg for three samples of cassia cinnamon. In contrast, surprisingly high levels were identified in five samples of cinnamon powder of between 2.3 and 3.3 g/kg (obviously cassia cinnamon) which correspond in the customary formulation to the levels measured in cinnamon biscuits. These relatively constantly high coumarin levels in cinnamon powder have since been confirmed in further analyses. The Food Institute Braunschweig analysed 9 samples of cinnamon powder with levels between 2.8 and 3.7 g/kg. CVUA Stuttgart identified levels between approximately 2.1 and 4.4 g/kg in cinnamon powder from capsules for diabetics (analyses of six products, calculated from manufacturer's details on composition and analytical findings of the capsule content). More details on this can be found in the Health Assessment No. 044/2006 on high cinnamon intakes of 18 August 2006 (BfR 2006).

In studies on coumarin levels from commercial cinnamon oils Ehlers *et al.* (1995) identified levels between 16 and 25 g/kg in various cassia oils. No coumarin could be detected in the bark and leaf oils of Ceylon cinnamon. In the commercial cinnamon CO_2 high pressure extracts examined as well, coumarin levels were observed from below the detection limit up to 2 g/kg in Ceylon cinnamon products and between 2 and 46 g/kg in cassia cinnamon products. Jirovetz *et al.* (2000) found coumarin levels of 8.4 and 4.7 % in two cassia oil samples from China. BfR is not aware of the scale on which these essential oils are used for aromatisation by the food industry and to what extent possibly high concentrations are linked to coumarin.

3.1.3.1.2 Estimate of oral coumarin exposure

An exposure estimate for coumarin brings with it major uncertainties because of the lack of systematic measurements of its levels in food. It is assumed that the main oral exposure to cinnamon and cinnamon products is via their use in food production; however no quantitative data are available. Furthermore, cinnamon, as described above, may be found to have very different concentrations of coumarin. The exposure estimate for foods that are clearly identifiable as containing cinnamon is hampered by inadequate epidemiological data on their consumption.

In its opinion of 6 October 2004 EFSA calculated a TAMDI (Theoretical Added Maximum Daily Intake) of 1.5 mg coumarin for adults; this corresponds to a value of 0.025 mg/kg body weight for a weight of 60 kg. In this context consumption was assumed of 324 g general beverages, 133.4 g general solid food, 27 g sweets, 2 g chewing gum and 20 g alcoholic beverages - each with the maximum permitted level of coumarin in accordance with the Flavourings Directive 88/388/EEC. Lake (1999) also calculated a TAMDI of 4.1 mg coumarin from general consumption data which he described as unrealistically high. A value of 1.2 mg coumarin (0.02 mg/kg body weight for 60 kg weight) seemed to him to be more realistic (assumption: maximum 5 % of solid food flavoured with cinnamon). In this case the maximum permitted levels were also taken as the basis in accordance with the Flavourings Directive 88/388/EEC.

None of the above-mentioned exposure estimates took children into account as a possible group of high consumers (referred to body weight or concentrations in the body). As cinnamon must also be seen as a main source of oral coumarin intake by children, exposure data from the VELS study (food consumption study to determine the dietary intake of infants and toddler in order to estimate the acute toxicity risk from pesticide residues) can be used. In this study parents kept an exact three-day food log on two occasions with an interval of several months which permitted the later breakdown of individual components of food including spices (Banasiak *et al.* 2005). The evaluation of toddlers aged between 2 and 5 for a total number of 475 children in this age group showed that 140 children ate cinnamon or cinnamon-containing products at least on one of the six days recorded. For these consumers the 97.5 percentile showed consumption of 0.22 g per kg body weight (peak exposures normally through rice pudding with cinnamon and sugar). Based on a coumarin level of 3 g/kg cinnamon (measurements by CVUA Münster) this would mean coumarin exposure of 0.66 mg/kg body weight as the worst case for oral exposure. This does, however, constitute peak exposure on individual days.

Exposure over a longer period (days to weeks), which would be deemed relevant for possible hepatotoxicity, cannot be calculated from the available data because of the study design of the VELS study (maximum three-day logs) and, therefore, has to be estimated. In this case it must be borne in mind that in the run up to Christmas there is an accumulation due to the

consumption of corresponding biscuits (according to the data from the VELS study 47.3% of the consumption days were in the months September to December). It is, therefore, assumed that in the worst case there were two peak exposures of this kind in one week and that the other days can be ignored. Based on these assumptions this means exposure of 1.32 mg/kg body weight/week (0.19 mg/kg body weight/day) for the 2 to 5 year-olds. The estimated exposures from the consumption of the star-shaped cinnamon biscuits analysed by CVUA Münster were on a similar scale (in the worst case of 76.4 mg coumarin per kg biscuits, 20 g biscuits already contain 1.5 mg coumarin which, for a child weighing 15 kg, already corresponds to exposure of 0.1 mg/kg body weight; a toddler can definitely consume a multiple of this amount within a short period of time without this being problematic).

The values for toddlers are the result of a worst case scenario for oral exposure and, as such, the basis for further risk assessment of the hepatotoxicity of coumarin. Greater relevance is attributed to them than to the estimates for adults described above (EFSA 2004, Lake 1999). This is because toddlers must be regarded as a risk group with higher exposure because of their higher energy requirements and their special eating habits. Furthermore, the estimate is based on reliable epidemiological data on cinnamon consumption and on the coumarin levels actually measured in cinnamon (as outlined above, it cannot simply be assumed that the admissible maximum levels are complied with). In the case of the calculations for toddlers undertaken above, other possible coumarin sources than cinnamon as well as possibly concealed sources through the addition of cinnamon to foods were not taken into account.

3.1.3.1.3 Special consideration: coumarin as a medicinal product/"food supplement"

Given the above comments there is a special exposure situation for diabetics who take cinnamon capsules to reduce their blood sugar. For some years now cinnamon-containing food supplements or dietetic foods have been sold following reports in a Pakistani study that they had a blood sugar and blood lipid reducing effect on type II diabetics (Khan *et al.* 2003). The patients were given up to 6 g cassia cinnamon daily. There are numerous products on the German market, partly as encapsulated cinnamon powder and partly as aqueous cinnamon extracts. No measurements are available up to now of the coumarin content of extracts of this kind. The taking of 6 g cassia cinnamon daily in capsule form, assuming a content of 3 mg coumarin pro g (as measured by CVUA Münster), would mean additional exposure of 18 mg coumarin/day. This would correspond to 0.3 mg/kg body weight for an adult weighing 60 kg. This value is 12 times higher than the value for oral intake of 0.025 mg coumarin per kg body weight/day estimated by EFSA as the worst case exposure scenario for adults. This consideration does not take account of possible parallel dietary coumarin intake and possible dermal exposure (see below). What should also be borne in mind here is that diabetics have to take cinnamon capsules on a continuous basis and that this is not short-term peak exposure.

At the present time it is unknown whether the suspected effect of cassia cinnamon has actually been confirmed by other studies (two European studies produced contradictory results about the impact on blood sugar; the published positive effects on blood lipids could not be confirmed: Mang *et al.* 2006; Vanschoonbeek *et al.* 2006). Another question that is unanswered (if the claimed effect does exist) is whether Ceylon cinnamon, that only has traces of coumarin, is efficacious in the same way.

Besides the administration of coumarin as a prescription-only medicine to treat the consequences of venous and lymphatic drainage disorders described in Chapter 3.1.2.2, sweet clover (*Meliloti herba*) is also listed with a similar indication as a herbal medicinal product. A

dose of two to three cups infused tea is the daily recommendation for treating varicose veins; this corresponds to between 3 and 30 mg coumarin (Bundesanzeiger, 13 March 1986).

3.1.3.2 Dermal exposure

Besides oral exposure dermal exposure must also be taken into account. In contrast to use in food production, synthetic coumarin may be used without constraints as a fragrance in cosmetics. According to EU Regulation 76/768/EEC on cosmetic products (Official Journal of the EU, 11 March 2003) coumarin must only be declared when its concentration exceeds 0.001 % in "leave-on" products and 0.01 % in "rinse-off" products.

It already becomes clear from a brief look at the production volume of synthetic coumarin, converted to a per capita proportion in the population, that dermal exposure is by no means insignificant. Yourick and Bronaugh (1997) calculated an average daily coumarin amount of 1.2 mg per US American from an annual production of 250,000 lbs (113.4 t) in the USA for a population of 250 million.

As the formulations of cosmetics are not normally publicly accessible, only insufficient data are available on coumarin levels. Harris and Wisneski (2001) found the compound in 71 % of the US American products examined at concentrations between 0.002 and 0.61 %. Lake (1999) referred to a compilation of the International Fragrance Association in Geneva, which indicates a coumarin level of 6.4 % in a few thousand fragrance mixtures as the 97.5 percentile. Based on this value he indicated a daily intake of 9.8 mg coumarin for adults (0.16 mg/kg body weight for a person weighing 60 kg). However this amount seemed to him to be unrealistically high and he estimated a daily intake of 2.3 mg coumarin (0.04 mg/kg body weight for an adult weighing 60 kg) as realistic for a worst case scenario. This calculation reflected the fact that coumarin is taken in relatively quickly and to a high degree via the skin (absorption rate approximately 60 %: Huntington Life Sciences quoted in Lake, 1999; Yourick and Bronaugh, 1997). The daily dermal intake estimated by Lake (1999) is, therefore, twice as high as the daily oral intake for adults of 0.02 mg/kg body weight for an adult weighing 60 kg (see above) estimated in the same publication.

Given the unfavourable ratio of body surface to body weight, a value that is roughly twice as high as the value for adults must be taken to estimate the dermal intake of toddler referred to body weight. This would lead to a value of 0.08 mg coumarin per kg body weight for toddlers. This estimate results from the assumption that the reflections by Lake (1999) also apply to cosmetics (cream, soap, shower gel, hair shampoo) which are used for children.

3.1.3.3 Total exposure

A total daily exposure of 0.19 mg + 0.08 mg = 0.27 mg per kg body weight for 2 to under 5 year-olds, the group with the highest exposure, results from the worst case considerations of oral and dermal coumarin intake outlined above.

3.1.4 Risk characterisation

In its expert opinion from October 2004 following the evaluation of new studies on adduct formation, EFSA comes to the conclusion that *in vivo* coumarin does not bind in a covalent manner to the DNA of target organs and that it does not, therefore, possess any genotoxic mechanism of action in conjunction with carcinogenicity. A threshold value based assessment is, thus, assumed with the establishment of a NOAEL or TDI value. After evaluation of the available oral animal experiment studies for sub-acute and chronic toxicity, hepatotoxicity in dogs (Hagan *et al.* 1967) has been identified as the most sensitive effect. These results were used to establish a NOAEL value of 10 mg/kg body weight/day. By using an interspecies factor of 10 and an intraspecies factor of 10 as well, a TDI value of 0.1 mg/kg body weight/day is calculated. EFSA concludes that the exposure scenarios calculated by it or others are below this value.

The establishment of a TDI value by EFSA does not seem to be particularly conservative in the opinion of BfR: the results reported by Hagan *et al.* (1967) for Beagle dogs are only based on the observation of two to four animals per dose group: the two animals given 100 mg/kg body weight/day died after nine and 16 days; of the three animals given 50 mg/kg body weight daily, one perished after 35 days; in the case of the three animals given 25 mg/kg body weight/day one suffered moderate emaciation and jaundice; the autopsies conducted between day 133 and day 330, identified, amongst other things, clear macroscopic and microscopic changes to the liver. In the case of the four animals given 10 mg/kg body weight/day no definite effect was observed during autopsy (examinations between day 297 and day 350). There was no control group. The descriptions of the examinations in this study are extremely brief. As there were clear changes in the 25 mg/kg group, it is unlikely that no changes at all could be observed in the 10 mg/kg group. This is possibly due to the less sophisticated techniques used in the 1960s. Furthermore, it must be borne in mind that possible habituation effects were not taken into account. For instance a regular examination of liver enzymes in serum would possibly have identified an interim increase in the values.

Furthermore, EFSA does not take into account the available findings on hepatotoxicity in humans obtained from the use of coumarin as a medicinal product. This is probably inadvertent as, in earlier SCF expert opinions from 1994 and 1999, these results were briefly presented but not discussed in any detail because of the genotoxic action assumed at that time and the non-existent necessity to establish a TDI. As the following considerations show, closer examination of these human data on hepatotoxicity can be very helpful when it comes to establishing a TDI. In this respect the EFSA expert opinion only refers to a more recent study (Schmeck-Lindenau *et al.*, 2003; Burian *et al.*, 2003) from the angle of the polymorphism of CYP2A6.

As indicated under 3.1.2.2, experience with the use of coumarin as a medicinal product revealed hepatotoxic symptoms in a one-digit percentage range of the population. They begin with elevated transaminases in serum and may proceed via clinical symptoms of hepatitis at higher doses to liver failure. In 1999 the Federal Institute for Medicinal Products and Medical Devices (BfArM) prepared a non-published expert opinion "on the assessment of coumarin in medicinal products with regard to a human hepatotoxic effect". It evaluated the case reports available to the Institute at that time. There were reports of a total of 82 cases of possible coumarin-associated liver damage based on international notifications with seven cases of liver failure (survival of the patients) and seven fatalities. A dose classification could be undertaken for 51 cases of the notified liver damage linked to the taking of coumarin-containing medicinal products. The most frequent dose corresponded to the daily dose of 90 mg coumarin prescribed for the main indication "lymphatic disorders and varicose veins”. 10 % of

the cases occurred at the lowest doses (25 and 30 mg daily, which is probably prescribed less frequently than the standard dose). As in the other studies no clear dose-toxicity relationship could be identified. This is probably because only a small percentage of the population is sensitive to this effect. What has been discussed is, for example, a restricted 7-hydroxylation capacity because of a polymorphism in the CYP2A6 system.

According to the expert report liver damage for part of the population cannot be ruled out at a daily dose of 25 mg coumarin. Hence for this dose no human NOAEL can be assumed. What has still not been taken into account here is that coumarin is mainly administered as co-medication with troxerutin which may have a hepatoprotective effect. When coumarin is administered in isolation, this hepatoprotective effect might be lost, which means that a comparatively stronger hepatotoxic effect would have to be expected. Corresponding study findings from the isolated perfused rat liver were published recently (Adam *et al.* 2005).

In order to comply with the strict yardsticks for the risk assessment of food, a factor of 5 is deemed to be adequate by means of which a dose of 5 mg coumarin can be established which will very probably no longer have a hepatotoxic effect. When choosing this factor it was borne in mind that more exact findings on the mechanism of action in sensitive individuals are not available. As this group of persons must already be viewed as the most sensitive sub-group in the population with regard to the considered effect, no additional intraspecies factor was used. From the established safe daily dose of 5 mg coumarin, a TDI value can be calculated which is slightly below the EFSA value of 0.1 mg/kg body weight if this is based on an adult weighing 60 kg. This is, however, a negligible difference given the existing uncertainties. Overall the TDI value of EFSA is reinforced here through the reflections about the available human data and used to interpret the various exposure scenarios.

The above presentation of the possible worst case exposure of infants of 0.27 mg/kg body weight is almost three times higher than the EFSA TDI value. As outlined in Chapter 3.1.3.1.2, the EFSA TDI value is already reached by infants who consume 20 g of star-shaped cinnamon biscuits if the highest measured amount (76.4 mg coumarin per kg biscuit) is taken into account. In the worst case scenario for diabetics (6 g cassia cinnamon daily in capsule form, coumarin content of 3 mg per g) outlined above (Chapter 3.1.3.1.3), this additional coumarin exposure (0.3 mg/kg body weight for an adult weighing 60 kg) would already exceed by a factor of 3 the TDI value of 0.1 mg/kg body weight/day without including dietary or dermal exposure.

4 Discussion and action framework/measures

One result of the 2004 EFSA review of coumarin concerning a genotoxic mechanism of action in conjunction with carcinogenicity is that coumarin is to be removed on the European level from Annex II to the Flavourings Directive 88/388/EEC. This would lead not only to the removal of the current constraints of a maximum level of 2 mg/kg through flavouring of foods with natural raw materials but would also lead to a lifting of the ban on the addition of coumarin as an individual substance which is mentioned in a footnote in the above list. An initiative of this kind is already questionable because EFSA has used the maximum level of 2 mg/kg in its risk assessment to calculate the TAMDI and estimated an exposure value (0.025 mg coumarin per kg body weight/day) which already exhausts one quarter of the TDI value (0.1 mg coumarin per kg body weight/day) for adults established on the basis of hepatoxicity. The EFSA expert opinion also points out that, in integrated risk assessment, dermal exposure through cosmetics must also be taken into account. According to Lake (1999) this is two times higher than the oral route for adults. This means that, assuming that the foods already

contain the maximum level of 2 mg/kg which are relevant for the calculation, the EFSA TDI value has already been largely exhausted.

It should be examined whether, perhaps through statutory measures, coumarin exposure through the direct consumption of cinnamon (e.g. rice pudding with sugar and cinnamon) can be restricted.

One particular problem in this context is the consumption of large amounts of cinnamon powder from capsules by type II diabetics. The described use of cinnamon capsules fulfils several criteria of a medicinal product. This means that there are grounds for regulation. If this product were classified as a medicine, the manufacturer would also have to supply the corresponding evidence more particularly of efficacy, purity, constant composition and safety. In this case adverse effects would be recorded and notified far more reliably.

5 References

Adam BS, Pentz R, Siegers CP, Strubelt O, Tegtmeier M. Troxerutin protects the isolated perfused rat liver from a possible lipid peroxidation by coumarin. Phytomedicine. 2005 Jan;12(1-2):52-61.

Andrejak M, Gersberg M, Sgro C, Decocq G, Hamel JD, Morin M, Gras V. French pharmacovigilance survey evaluating the hepatic toxicity of coumarin. Pharmacoepidemiol Drug Saf. 1998 Aug;7 Suppl 1:S45-50.

Api AM. Lack of effect of coumarin on the formation of micronuclei in an in vivo mouse micronucleus assay. Food Chem Toxicol 2001; 39: 837-841.

Banasiak U, Heseker H, Sieke C, Sommerfeld C, Vohmann C. Abschätzung der Aufnahme von Pflanzenschutzmittel-Rückständen in der Nahrung mit neuen Verzehrsmengen für Kinder. Bundesgesundheitsbl Gesundheitsforsch Gesundheitsschutz 2005; 1:84-98.

BfR. High daily intakes of cinnamon: A health risk cannot be ruled out. Health Assessment No. 044/2006, 18 August 2006, http://www.bfr.bund.de/cm/208/hohe_taegliche_aufnahmemengen_von_zimt_gesundheitsrisiko_kann_nicht_ausgeschlossen_werden.pdf

Burian M, Freudenstein J, Tegtmeier M, Naser-Hijazi B, Henneicke-von Zepelin HH, Legrum W. Single copy of variant CYP2A6 alleles does not confer susceptibility to liver dysfunction in patients treated with coumarin. Int J Clin Pharmacol Ther. 2003 Apr;41(4):141-7.

Edwards AJ, Price RJ, Renwick AB, Lake BG. Lack of effect of coumarin on unscheduled DNA synthesis in the in vivo rat hepatocyte DNA Repair Assay. Food Chem Toxicol 2000; 38:403-409.

EFSA 2004, Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contacts with Food (AFC) on a request from the Commission related to Coumarin; Adopted on 6 October 2004. The EFSA Journal (2004) 104, 1-36. Includes in the Appendix also the previous opinions of the Scientific Committee on Food (SCF) of 1994 and 1999.

Ehlers D, Hilmer S, Bartholomae S. Hochdruckflüssigchromatographische Untersuchung von Zimt-CO2-Hochdruckextrakten im Vergleich zu Zimtölen. Z Lebensm Unters Forsch 1995; 200: 282-288.

Floc'h F, Mauger F, Desmus JR, Gard A, Bagneris F, Cariton B. Coumarin in plants and fruits: implication in perfumery. Perfumer Flavorist 2002, 27: 332-36.

Hagan EC, Hansen WH, Fitzhugh OG, Jenner PM, Jones WI, Taylor JM, Long EL, Nelson AA, Brouwer JB. Food flavourings and compounds of related structure. II. Subacute and chronic toxicity. Food Cosmet Toxicol. 1967 Apr;5(2):141-57.

Harris H, Wisneski HH. Determination of Coumarin in Fragrance Products by Capillary Gas Chromatography with Electron Capture Detection. J AOAC Internat. 2001, 84: 689-692.

He ZD, Qiao CF, Han QB, Cheng CL, Xu HX, Jiang RW, But PPH, Shaw PC. Authentication and quantitative analysis on the chemical profile of cassia bark (cortex cinnamoni) by high pressure liquid chromatography. J Agric Food Chem. 2005; 53:2424-2428.

Jayatilaka A, Poole SK, Poole CF, Chichila TMP. Simultaneous micro steam distillation/solvent extraction for the isolation of semivolatile flavor compounds from cinnamon and their separation by series coupled-column gas chromatography. Analyt Chim Acta. 1995. 302:147-162.

Jirovetz L, Buchbauer G, Eberhardt R (2000) Analyse und Qualitätskontrolle von ätherischen Zimtölen (Rinden- und Blattöle) verschiedenen Ursprungs mittels GC, GC-MS und Olfaktometrie – Bestimmung des Coumarin- und Safrol-Gehaltes. Ernährung/Nutrition 2000; 24:366-369.

Khan A, Safdar M, Ali Khan MM, Khattak KN, Anderson RA. Cinnamon improves glucose and lipids of people with type 2 diabetes. Diabetes Care. 2003 Dec;26(12):3215-8.

Lake BG. Coumarin metabolism, toxicity and carcinogenicity: relevance for human risk assessment. Food Chem Toxicol. 1999 Apr;37(4):423-5.

Loprinzi CL, Kugler JW, Sloan JA, Rooke TW, Quella SK, Novotny P, Mowat RB, Michalak JC, Stella PJ, Levitt R, Tschetter LK, Windschitl H. Lack of effect of coumarin in women with lymphedema after treatment for breast cancer. N Engl J Med. 1999 Feb 4;340(5):346-50.

Mang B, Wolters M, Schmitt B, Kelb K, Lichtinghagen R, Stichtenoth DO, Hahn A. Effects of a cinnamon extract on plasma glucose, HbA, and serum lipids in diabetes mellitus type 2. Eur J Clin Invest. 2006 May;36(5):340-4.

Miller KG, Poole CF, Chichila TMP. Solvent-assisted supercritical fluid extraction for the isolation of semivolatile flavor compounds from cinnamons of commerce and their separation by series-coupled column gas chromatography. J High Resol Chromatogr 1995. 18:461-471.

Schmeck-Lindenau HJ, Naser-Hijazi B, Becker EW, Henneicke-von Zepelin HH, Schnitker J. Safety aspects of a coumarin-troxerutin combination regarding liver function in a double-blind placebo-controlled study. Int J Clin Pharmacol Ther. 2003 May;41(5):193-9.

Swenberg JA. Covalent binding index study on coumarin, Report of Laboratory of Molecular Carcinogenesis and Mutagenesis, University of North Carolina, Chapel Hull, NC 27599,

USA. April 2003, Submitted by European Flavour and Flagrance Association (EFFA), Square Marie-Louise, 49, B-1000, Brussels.

Vanscheidt W, Rabe E, Naser-Hijazi B, Ramelet AA, Partsch H, Diehm C, Schultz-Ehrenburg U, Spengel F, Wirsching M, Gotz V, Schnitker J, Henneicke-von Zepelin HH. The efficacy and safety of a coumarin-/troxerutin-combination (SB-LOT) in patients with chronic venous insufficiency: a double blind placebo-controlled randomised study. Vasa. 2002 Aug;31(3):185-90.

Vanschoonbeek K, Thomassen BJ, Senden JM, Wodzig WK, van Loon LJ. Cinnamon supplementation does not improve glycemic control in postmenopausal type 2 diabetes patients. J Nutr. 2006 Apr;136(4):977-80.

WHO. Coumarin: a strong association with hepatotoxicity. WHO Drug Information 1995; 9:159.

Yourick JJ, Bronaugh RL. Percutaneous absorption and metabolism of Coumarin in human and rat skin. J Appl Toxicol. 1997 May-Jun;17(3):153-8.