Risiken erkennen – Gesundheit schützen

High daily intakes of cinnamon: Health risk cannot be ruled out

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Cinnamon capsules are sold as food supplements or as dietetic foods to reduce blood sugar levels in type II *Diabetes mellitus*, a severe chronic disease. The manufacturers recommend a daily long-term dose in the gram range although the safety of a cinnamon dose of this amount has not yet been demonstrated. Furthermore, the claimed ability of cinnamon to reduce blood sugar has not been sufficiently proven up to now. The Federal Institute for Risk Assessment (BfR) was, therefore, asked to assess the daily intake of high amounts of cinnamon from the angle of consumer health protection.

Small amounts of cinnamon have been used for thousands of years as a spice without any reports of side effects. By contrast, no reliable data are available on the effects of the daily continuous administration of amounts in the gram range. When it comes to cinnamon a distinction must be made between Ceylon and cassia cinnamon. Unlike cassia cinnamon Ceylon cinnamon hardly contain any coumarin which – when ingested in large amounts – can cause damage to the liver. The high coumarin levels measured by the control authorities in cinnamon capsules indicate that the manufacturers use cassia cinnamon. Depending on the dose recommendation the taking of capsules with cinnamon powder can lead to an exceeding of the tolerable daily intake of 0.1 milligram coumarin per kilogram body weight that can be ingested daily over a lifetime without posing a risk to health (Tolerable Daily Intake, TDI) established by the European Food Safety Authority (EFSA).

Besides the high coumarin levels, the cinnamaldehyde levels in cinnamon powder capsules may possibly constitute a risk for pregnant women. Animal experiment studies indicate that taking cinnamaldehyde during pregnancy could lead to damage to the unborn offspring. BfR, therefore, recommends that products of this kind should carry warnings, something which has only rarely been the case up to now. No harmful levels of styrene have been identified in the cinnamon powder investigated so far. After harvesting, styrene can form in cinnamon when the transport or storage conditions are unfavourable. It can also migrate from packaging material to the spice.

BfR fundamentally believes that cinnamon products to reduce blood sugar should be classed as medicinal products and not as food supplements. In order to obtain marketing authorisation for their product as a medicinal product, the suppliers would have to provide corresponding proof of efficacy, record side effects and examine interactions with other medicines.

1 Subject matter of the assessment

Cinnamon capsules have been on the market for some time now as food supplements or as dietetic foods to reduce blood sugar in type II *Diabetes mellitus*. The taking of these capsules in line with the indicated amounts leads to exposure (up to several grams cinnamon a day as continuous administration) which is far higher than the amounts of cinnamon normally consumed as a spice. The Federal Institute for Risk Assessment (BfR) has access to measurements from one of the regional food control and animal health laboratories (Chemisches und Veterinäruntersuchungsamt, CVUA, Stuttgart) on coumarin concentrations in cinnamon capsules for diabetics. BfR has taken a stance on the problem of the high coumarin levels in cinnamon and cinnamon-containing biscuits in its Health Assessment No. 043/2006, 16 June 2006. In that expert opinion it classified coumarin as a toxicologically problematic ingredient of cassia cinnamon (BfR 2006). In addition to the coumarin problem BfR was also asked to undertake a toxicological assessment of the daily intake of cinnamon at the doses of the cinnamon products particularly from the angle of the target group "diabetics".

In its assessment BfR also drew on values for coumarin and styrene levels from the Food Institute Braunschweig which were measured in conjunction with food control in 13 samples of ground cinnamon.

2 Findings

While small amounts of cinnamon have been used occasionally as a spice for thousands of years, no reliable data are available on the daily long-term ingestion of amounts in the gram range on the basis of which the risk of high cinnamon exposure of this kind could be assessed.

When it comes to individual ingredients the coumarin concentration in cassia cinnamon is particularly problematic. The values measured in cinnamon capsules (CVUA Stuttgart) confirm the high coumarin levels in cassia cinnamon (between approximately 2100 and approximately 4400 mg/kg cinnamon powder) as had also been previously measured by CVUA (Münster, BfR 2006). By contrast, coumarin can only be found in traces or below the measurement limit in Ceylon cinnamon.

As outlined in the above-mentioned health assessment of the problem of the high coumarin levels in cinnamon and cinnamon-containing biscuits, major consumption of cinnamon as a spice (e.g. frequent helpings of rice pudding with sugar and cinnamon by infants) with a high coumarin level can lead to the exceeding of the TDI of 0.1 mg/kg body weight established by the European Food Safety Authority (EFSA 2004).

The consumption of capsules containing cassia cinnamon powder is also likely to lead to an exceeding of the above-mentioned TDI for coumarin. Solely regarding this coumarin exposure, there are theoretically two steps which could be taken to reduce it:

- the replacement of cassia cinnamon by Ceylon cinnamon (so far we do not know whether it has a similar effect on the blood sugar level of diabetics to that of cassia cinnamon; the recommendation of replacement is subject to the assumption that the effects of cassia cinnamon are confirmed by reliable studies),
- the use of aqueous extracts of cassia cinnamon which, according to the CVUA analyses in Stuttgart, leads to far lower coumarin exposure (exhaustion of the TDI only in the single-digit percentage range). These extracts probably also have a far lower proportion of essential oils (in particular cinnamaldehyde).

All the same these steps only refer to coumarin exposure which, in the opinion of BfR, is not the main problem when it comes to the marketing of cinnamon products as food supplements or dietetic foods to reduce the blood sugar level in type II diabetics. The main problem of the marketed cinnamon products is far more that a daily long-term dose in the gram range (cinnamon powder or extract equivalent) is recommended without there being a solid database indicating the safety of a cinnamon dose of this kind. Furthermore, an impact on blood sugar (in some cases also on blood lipids) is promised which is only backed by one study involving 60 patients who had developed type II *Diabetes mellitus* (Khan *et al*. 2003). In terms of appearance and functionality, the cinnamon products meet the criteria of a medicinal product which is governed by strict marketing authorisation criteria (particularly with regard to proof of efficacy, recording of side-effects, possible interaction with other medicinal products, standardisation regarding active ingredients). In the assessment of the cinnamon capsules it must also be borne in mind that tested and authorised medicines are already available for the treatment of *Diabetes mellitus*.

The Federal Institute for Medicinal Products and Medical Devices (BfArM) also believes that cinnamon products should be classed as medicinal products requiring marketing authorisation is necessary. This would guarantee the recording of side effects when marketing authorisation is granted. At the present time, there are only sporadic reports to public agencies as is customary for food supplements and dietetic foods.

Besides coumarin cinnamon also contains other ingredients which could be problematic from a toxicological point of view when high levels of cinnamon are ingested daily. The main one amongst the natural ingredients is cinnamaldehyde which, in the worst case, may be contained in concentrations in the upper single-digit percentage range. What appears to be particularly problematic in this context is the consumption of high amounts of cinnamon by pregnant women. Data from animal experiments indicate a possible teratogenic potential which could be clarified through further studies. BfR is of the opinion that the packaging of cinnamon capsules should at least carry corresponding warnings.

Other undesirable substances in cinnamon are safrole and styrene. Normally only traces of safrole are found in cinnamon. Higher concentrations are, however, found in oils from cinnamon leaves which may be used for blending purposes with other cinnamon oils. Styrene is formed in cinnamon under unfavourable transport and storage conditions. The concentrations of up to 22 mg/kg cinnamon measured by the Food Institute Braunschweig are safe in toxicological terms. However, in the past far higher levels have been determined. It would, therefore, appear prudent to carry out corresponding controls of the safrole and styrene levels in conjunction with monitoring by the public agencies of the federal states.

3 Reasons

3.1 Cinnamon as a plant product

3.1.1 Cinnamon as a spice

The cinnamon tree is a member of the laurel plant family. Cinnamon is the inner bark of the cinnamon tree which has been used as a spice for thousands of years in dried form as sticks or in ground form as cinnamon powder. In this context a rough distinction should be made between Ceylon cinnamon (also called true cinnamon from the south-east Asian region) which is more expensive than the cassia types (e.g. China cinnamon, Padang cinnamon). Cinnamon has a sweet-spicy taste and gives dishes a slightly hot flavour. Cassia cinnamon is spicier and tarter than Ceylon cinnamon which has a more flowery aroma. Both types of cinnamon can be distinguished on the basis of their different chemical composition: Ceylon cinnamon contains eugenol and benzyl benzoate in comparison to cassia cinnamon but no (at most traces of) coumarin and delta-cadinene (Jayatilaka *et al*. 1995).

Although difficult to harvest, cinnamon is one of the oldest spices in the world. That's why a glance at its history is interesting. The following information comes from the book "Kleine Kulturgeschichte der Gewürze" (Küster 2003). Cassia was already used at the beginning of the third millennium B.C. in its Chinese homeland. In the pre-Christian era this cinnamon was exported along the silk and spice routes of Inner Asia to the Middle East. Chinese cinnamon may already have been known in the middle of the third millennium B.C. in Mesopotamia. At all events Babylon became an important trading centre for this Far East spice. In the Mediterranean the Phoenicians handled the long distance trade in cinnamon. Prior to the year 0, news of Ceylon cinnamon had already reached the Middle East. Ceylon cinnamon and cassia cinnamon are mentioned several times in the Bible. Opinions differ as to whether the Egyptians were also familiar with cinnamon. Everywhere in the Orient cinnamon was a popular incense. The Greeks and Romans were familiar with both types of cinnamon, amongst

other things as a spice for wine. In the Middle Ages the first Europeans saw the cinnamon forests in Ceylon and described the type and nature of cinnamon cultivation. The cinnamon trade fell into the hands of various European seafaring nations, for instance the Dutch. They managed to keep the price for cinnamon artificially high by devising various measures. In central Europe cinnamon was a well known luxury spice which was also coveted as a medicine, for instance to treat liver disease and *angina pectoris*. Already by the Middle Ages cinnamon had found an inseparable partner: sugar. Cinnamon and sugar, sugar and cinnamon – this combination which, as an alliteration, slides easily over the tongue and delights the taste buds if used for alimentation was already mentioned in the 16th century *Zimmersche Chronik* (Chronicle of the German peasant war). Cinnamon and sugar belong together in stewed fruit and milk dishes (for instance rice pudding) and in millet gruel, in biscuits like the renowned star-shaped cinnamon biscuits, cinnamon waffles and cinnamon bread.

For thousands of years small amounts of cinnamon have been occasionally consumed as a spice. Relatively high exposure from single helpings of rice pudding with sugar and cinnamon, which is particularly popular with children, can be expected. In the case of a special liking for cinnamon biscuits during the festive season a higher exposure can be expected over a longer period (recipe for cinnamon biscuits: approx. 1% cinnamon). This is also reflected in the data of the VELS Study (food consumption study to determine the dietary intake by infants and small children in order to estimate the acute toxicity risk from pesticide residues). 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 the data with regard to the alimentation of infants/small children 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). A worst case scenario for these infants (two days peak consumption a week) would lead to a peak exposure over a longer period of 0.063 g cinnamon per kg body weight/day (BfR 2006). There are no corresponding data for adults.

There are no reports of any side effects arising from the occasional consumption of cinnamon as a spice to the extent that this can be said given the lack of scientific studies.

3.1.2 Cinnamon as a medicinal product

As already mentioned above, cinnamon is also used as a medicinal product. Committee E (plant-based medicinal products) of the Drugs Institute of the Federal Health Office (BGA) took a look at cinnamon in 1990. It listed the following effects: antibacterial, fungistatic and motility-promoting. The indications listed both for cassia cinnamon and for Ceylon cinnamon are: "dyspeptic conditions like minor, convulsive disorders in the gastrointestinal area, bloatedness, flatulence". It lists as contraindications over-sensitivity to cinnamon or Peruvian balsam and pregnancy and as side effects "frequent allergic skin and mucosa reactions" (Committee E 1990). It indicates a daily dose of 2 to 4 g. A more comprehensive monograph was drawn up in 1999 by the World Health Organisation (WHO 1999). It describes the above-mentioned indications as the application areas in traditional medicine but also lists loss of appetite and the treatment of abdominal pain in conjunction with diarrhoea and of pain in conjunction with amenorrhoea and dysmenorrhoea. It also lists as contraindications a high temperature of unknown origin and ulcerations of the stomach and duodenum. Furthermore, it points out that not enough data are available to assess the carcinogenic potential and that there are contradictory data about the mutagenic potential of cinnamon. When it comes to dosage the same daily dose of 2 to 4 g is indicated in the WHO monogram with reference to Committee E. Besides the two above-mentioned sources there is an anecdotal information in

Lewin (1992) which refers to a comment which is not described in any more detail from the beginning of the 20th century: "pregnant women who consume large amounts of cinnamon may, as I have observed, develop methaemoglobinuria, haematinuria, albuminuria and cylindruria. Urine of this kind does not decompose. A miscarriage may be triggered by the oil."

The dose recommendation of 2 to 4 g must be viewed as problematic as it is not supported by clinical or epidemiological data. Furthermore, it does not take into account problematic ingredients (first and foremost coumarin and cinnamaldehyde, see below). Concerning the administration of higher daily amounts of cinnamon in the gram range, it must also be borne in mind that the above-mentioned indications only involve short-term administration (not continuous medication). The monograph of Committee E does not reflect the latest scientific findings either (the remit of this Committee was withdrawn in 1994). No reassessment was undertaken as at the present time no product is sold on the market as a medicinal product with Chinese cinnamon as the active substance.

The use of cinnamon with a view to reducing the blood sugar of type II diabetics is new. Cinnamon has only been marketed for a few years as a food supplement or dietetic food after a Pakistani study reported, amongst other things, that it reduced blood sugar and blood lipids in 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 (some with cinnamon powder, others with aqueous cinnamon extract) which diabetics are supposed to take as continuous daily medication. It is not yet known whether the suspected effects of cassia cinnamon can in fact be confirmed by other studies. Two European studies produced contradictory results concerning the effect on blood sugar; the published positive effects on blood lipids could not be confirmed in either of the two studies: Mang *et al*. 2006 (with 122 mg aqueous extract from cassia cinnamon/day), Vanschoonbeek *et al*. 2006 (with 1.5 g cassia cinnamon). The question is also unanswered (if the claimed effect should be confirmed) whether Ceylon cinnamon, which only has traces of coumarin, has the same effect as cassia cinnamon. In animal experiments with rats the extract of cassia cinnamon was shown to have an approximately two times higher effect on the maximum increase in the insulin level than the extract of Ceylon cinnamon. In this study no significant effect on the blood sugar level was shown (Verspohl *et al*. 2005).

From the pharmacological-toxicological angle there are major concerns about the current marketing of cinnamon products for diabetics. This is aside from the questions whether the claimed positive effect of cinnamon on the blood sugar level of type II diabetics actually exists and whether the high coumarin exposure when using cassia cinnamon could be avoided through using Ceylon cinnamon with the same efficacy. These concerns, some of which have also been expressed by the German Diabetes Society (DDG, 2004), can be summed up as follows:

- There is no standardisation regarding active principles. In principle, it is not possible to guarantee a constant composition of plant products (dependencies for instance on species, climate, degradation method, age of tree). The chosen procedure leads to additional variations in the case of the aqueous extracts. The problem of standardisation is even more relevant as the questions about the decisive active substance and the mechanism of action are still being clarified (polyphenols/catechins? Improvement of insulin sensitivity? Anderson *et al*. 2005). At the present time, it is not possible in any case to monitor the concentration of the active substances.
- No toxicological data are available on the long-term daily administration of high levels of cinnamon (see above). More particularly no tests including the conduct of correspondingly designed clinical trials have taken place that would comply with today's criteria for the marketing authorisation of medicinal products (e.g. proof of efficacy,

recording of side-effects like hypoglycaemia, possible interactions with other medicinal products).
- Correspondingly tested and authorised medicinal products are available to treat *Diabetes mellitus*.

It should also be added that *Diabetes mellitus* is a severe chronic disease that requires effectively monitored ongoing treatment in order to avoid or delay irreversible damage. Strictly controlled, disciplined ongoing treatment of this kind is difficult for many people as experience has shown. They often develop unjustified hopes of healing or turn to alternative therapies. This is sometimes where the claims for the above-mentioned cinnamon products for self-medication come in. Based on plant ingredients they promise "natural" treatment and exploit fears and hopes.

BfArM also believes that it is necessary for cinnamon products to be classified as medicinal products requiring marketing authorisation. Classification of this kind would improve the recording of notifications of side effects in conjunction with the corresponding marketing authorisation. At the present time, they are only notified sporadically to the public agencies. If the positive effects of cinnamon on the blood sugar level of type II diabetics were in fact to be proven, then a decision could be taken about marketing authorisation for the medicinal product within the framework of the customary marketing authorisation procedure including a risk-benefit analysis.

3.2 Problematic ingredients of cinnamon

As a plant product, cinnamon contains several substances/substance groups. According to Chaurasia (2003) they encompass more particularly essential oils, diterpenes, catechins, proanthocyanidins, tanning agents, colouring agents, phenolic carboxylic acids, lignans and mucins. Since, as outlined above, only inadequate data are available concerning the safety of larger daily consumed amounts of cinnamon, a risk assessment must also focus on the problematic ingredients of cinnamon. According to the scientific knowledge currently available, this basically means coumarin, cinnamaldehyde, safrol and styrene. Generally speaking when undertaking the health assessment of plants, it must be borne in mind that they constitute a complex mixture of numerous chemical compounds; normally nothing is known about their interaction.

3.2.1 Coumarin (CAS No. 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, etc. 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. A detailed description of coumarin can be found in the BfR expert opinion on coumarin in cinnamon (BfR 2006).

BfR was given eleven coumarin analyses of cinnamon products for the treatment of *Diabetes mellitus* II which were measured by the CVUA Stuttgart (Table 1).

No. 3 and No. 10 are the same product. Out of the total of ten cinnamon products, six were marketed as dietetic foods and four as food supplements.

A cinnamon extract was used to produce four of the products. The information on the packaging describes the extraction procedure in two cases as "aqueous". No information is pro-

vided in the two other cases. In two cases the degree of extraction is given as 1:10; in the other two cases a ratio of a similar order of magnitude results from the description. The coumarin levels were between 274 and 425 mg/kg capsule content for these extract products and are, therefore, far lower than those of the cinnamon powder products considered below. This was to be expected as coumarin is only poorly soluble in water. Hence the values for the exhaustion of the TDI (0.1 mg/kg body weight) for the recommended daily dose for a body weight of 70 kg are between 3 and 7 %. An exhaustion of the TDI on this scale can be considered unproblematic with regard to coumarin exposure.

Table 1: Composition of the coumarin levels in cinnamon capsules measured by CVUA Stuttgart

No.	Classification	Content	Average weight capsule/ tablet/ content (g)	Recommended daily dose (capsules)	Coumarin level (mg/kg)	Coumarin intake at recommended dose (mg/d)	Exhaustion of TDI at 70 kg bw
1	Dietetic food	Natural cinnamon powder, chromium, zinc	0.5932	2	3283	3.89	57 %
2	Dietetic food	150 mg cinnamon extract (1:10)	0.5794	1	312	0.18	3 %
3	Dietetic food	333.3 mg cinnamon powder per 100 g: 57 g cinnamon powder	0.4854	3	3090	4.50	64 %
4	Dietetic food	Momordica fruit paste (50 %), low coumarin cinnamon powder (20 %),	1.2441	4	433	2.15	31 %
5	Dietetic food	Aqueous cinnamon extract (31.6 %, 1 capsule corresponds to approx. 1 g cinnamon)	0.2869	3	317	0.27	4 %
6	Food supplement	500 mg Ceylon cinnamon, vitamins, chromium, zinc	0.5407	3	2300	3.73	53 %
7	Food supplement	Cinnamon powder, vitamin B, chromium, zinc	0.6274	2	3157	3.96	57 %
8	Food supplement	Cinnamon, vitamin B, chromium, zinc	0.6252	2	3171	3.97	57 %
9	Food supplement	200 mg aqueous cinnamon extract (1:10), chromium, zinc	0.5354	2	425	0.46	7 %
10	Dietetic food	333.3 mg cinnamon powder per 100 g: 57 g cinnamon powder	0.5778	3	2533	4.39	57 %
11	Dietetic food	135 mg cinnamon extract powder (corresponds to minimum 1200 mg cinnamon powder) vitamins, trace elements	0.3734	3	274	0.31	4 %

Cinnamon powder was used in the production of the other six products. The coumarin levels were between 2300 mg/kg and 3300 mg/kg capsule content; only 433 mg/kg capsule content were measured solely in sample No. 4 with a particularly low level of cinnamon powder in the preparation (20 %). As not only cinnamon powder but also other additives (in particular chromium, zinc and vitamins) were used in all the products, the coumarin content in the starting substance used, cinnamon powder, can be estimated from the information on composition as between approximately 2100 mg/kg and 4400 mg/kg. The coumarin levels from analyses by CVUA Münster, which examined five samples of cinnamon powder at the beginning of 2006 (BfR, 2006), were also in this range (between 2300 mg/kg and 3300 mg/kg). The levels measured by the Food Institute Braunschweig in the nine samples of ground cinnamon were in the same range (between 2809 and 3722 mg/kg cinnamon).

The consistently high exposure points to the main or exclusive use of cassia cinnamon whereby the relatively low deviation range of test results is surprising. The cinnamon described as "low in coumarin" in analysis No. 4 with an estimated content of approximately 2100 mg/kg, is indeed the cinnamon powder with the lowest coumarin level of the six products examined but this by no means justifies the description "low in coumarin". A description of this kind would certainly be merited in the case of Ceylon cinnamon which does not contain any or only traces of coumarin (e.g. under 15 mg/kg in a sample of stick cinnamon examined by CVUA Münster). In the case of product No. 6 examined, the use of Ceylon cinnamon was indicated; the analysis (measured level in the capsule: 2300 mg/kg), however, clearly points to the use of cassia cinnamon. Through the coumarin levels determined in the six products with cinnamon powder, the recommended daily dose for a body weight of 70 kg leads to an exhaustion of between 31 and 64 % of the TDI. Correspondingly higher exhaustions of the TDI result when the body weight of an adult of 60 kg, as is customary, is taken as the basis. In its risk assessment EFSA (2004) concludes that the established TDI of 0.1 mg/kg body weight/day is largely exhausted by oral and dermal exposure. Since it cannot be assumed that there are different exposure scenarios for diabetics, additional coumarin exposure through capsules with cinnamon with the above-mentioned coumarin levels could lead in isolated cases to an exceeding of the TDI. This applies for an assumed cinnamon dose of approximately 1 g/day which is recommended as the daily dose for the six cinnamon powder products examined by CVUA Stuttgart.

However, there are also products on the market with a far higher recommended daily dose as illustrated by the following examples (in the study by Khan *et al*., 2003, groups were treated with 1, 3, or 6 g daily; the published data did not, however show any dose-related effect in this range). For instance company AAA (name changed as for other companies too) produces 400 mg cinnamon tablets (85 % corresponding to 340 mg cinnamon powder) and 500 mg cinnamon capsules (corresponding to 400 mg cinnamon powder), in each case with a recommended daily dose of 3 times 2 tablets. Hence the daily dose is 2.04 and 2.4 g cinnamon powder. Company BBB also produces 400 mg cinnamon tablets (85 % corresponding to 340 mg cinnamon powder) and recommends a daily dose of 3 times 2-3 tablets leading to a daily dose of up to 3.06 g. Company CCC produces cinnamon capsules with a content of 500 mg cinnamon powder; the daily dose recommended by some internet distributors is 3 times 1 capsule corresponding to 1.5 g cinnamon/day. At least one distributor indicates the daily dose as between 2 and 4 g. With an assumed coumarin content in the cinnamon powder in the medium to upper range of the values established by CVUA Stuttgart, these daily doses would lead to a full exhaustion or even exceeding of the TDI. An amount of 6 g cinnamon daily (highest dose in the study by Khan *et al*. 2003) would definitely lead to the TDI being exceeded.

3.2.2 Cinnamaldehyde (CAS No. 104-55-2) and other essential oils

According to the information in literature cinnamon is composed of between 1 and 8 % of essential oils which determine its flavour. With a share of between 65 and 90 %, cinnamaldehyde is to the fore. Referred to 1 g cinnamon He *et al*. (2005) found levels in cassia cinnamon (raw material) of between 13.1 and 56.9 mg (mean 28.9 mg). The authors quoted the "Chinese Pharmacopoeia" from 2005, which envisages a minimum content of 10 mg as a quality characteristic. In 15 samples of cassia cinnamon, purchased on markets in Hong Kong, these authors found unusually high levels of up to 93.8 mg per gram cinnamon (mean 39.9 mg/g; 4 samples had more than 65 mg/g). In the latter samples the next most important compounds, cinnamic acid and cinnamyl alcohol, showed far lower levels of a maximum 1.9 and 0.7 mg/g cinnamon. Miller *et al*. (1995) found a maximum level of 53.2 mg/g cinnamaldehyde in 24 commercial cinnamon samples from various countries. Only coumarin was significant in terms of quantity in the other 20 compounds examined (maximum 12.2 mg/g, see above). Cinnamyl alcohol was measured at a maximum of 2.6 mg/g, 2-methoxycinnamaldehyde at a maximum of 1.7 mg/g and eugenol at a maximum of 1.7 mg/g cinnamon. The concentrations of the other 16 compounds were lower than 1.2 mg/g cinnamon.

When it comes to essential oils cinnamaldehyde is clearly to the fore in terms of quantity. The risk assessment of essential oils in cinnamon is therefore restricted to this compound which is synthetically produced in large volumes as a flavouring and added in an isolated manner to foods. Cinnamaldehyde heads the field of numerous derivative cinnamon compounds used by the flavour industry. An overview of the American FEMA (Flavour and Extract Manufacturers Association, Adams *et al*. 2004) lists 56 compounds, the main one clearly being cinnamaldehyde in the USA with a production volume of 93 % of a total of approximately 480 tonnes. In Europe only 60 tonnes were produced in total, whereby 30 % are accounted for by cinnamaldehyde (JECFA 2001). Hence the daily per capita consumption ("eaters only") for cinnamaldehyde is indicated as 59 mg in the USA whereas in Europe it is only 2.5 mg.

Cinnamon oils and their individual substances are also used to produce cosmetics, perfumes and toothpaste. Cinnamaldehyde in particular, besides cinnamyl alcohol, cinnamic acid and eugenol, is a problematic compound. These compounds have attracted attention as irritants and allergens and may be responsible for contact eczema, contact urticaria and for phototoxic reactions. The use of cinnamon-containing toothpaste and chewing gum may trigger mucosa inflammation and leucoplacia in the mouth (Hürlimann and Wüthrich, 1995). At least one case report points to carcinoma formation after the consumption of up to five packs of cinnamon chewing gum a day in a 24-year-old non-smoker (Westra *et al*. 1997). Peroral provocation with cinnamon or cinnamon-containing foods is normally negative even in individuals sensitised to cinnamaldehyde. The inadequate epidemiological data do not permit any conclusions about the incidence of corresponding mucosa reactions; it may be that sensitisations are often misinterpreted for instance as inflammation (Hürlimann and Wüthrich, 1995). No findings are available on reactions of the mucosa in the oesophagus or the gastrointestinal tract. In any case it would scarcely be possible to record changes of this kind as a reaction to the consumption of cinnamon and cinnamon-containing foods. The incidence of a possible mucosa reaction of the intestinal tract through the regular consumption of cinnamon in the gram range in individuals with and without sensitisation to cinnamaldehyde cannot, therefore, be estimated at the present time. Should reactions of this kind occur, then patients who already have mucosa damage (e.g. stomach ulcers, intestinal inflammation) must be deemed to be especially at risk.

In particular JECFA (Joint FAO/WHO Expert Committee on Food Additives) has undertaken toxicological assessments of cinnamaldehyde as a food ingredient in recent decades. Fol-

lowing the establishment in 1967 of a conditional ADI (Acceptable Daily Intake) of 1.25 mg/kg body weight/day, a temporary ADI of 0.7 mg/kg body weight/day was published in 1979 which was confirmed at two later meetings (both referred to an NOEL (No Observable Effect Level) of 125 mg/kg body weight in a 16 week feed study in rats (Hagan *et al*. 1967)). At the 35th meeting (1990) no further extension of the value was, however, undertaken because the called for tests were not available. At the 55th JECFA meeting an animal experiment NOEL of 620 mg/kg body weight was established following the assessment of a total of 55 derivative cinnamon flavourings for cinnamaldehyde. The safety margins were also calculated to the above-mentioned exposures in the USA and Europe without establishing an ADI (JECFA 2001). The conclusion regarding current consumption was "no safety concern".

A critical consideration of the JECFA assessment does, however, seem to be appropriate. The animal experiment NOEL of 620 mg/kg body weight stems from a 90-day NTP study in rats from 1995. Hence, it does not take any long-term effects into account, particularly not any concerning carcinogenicity. A 2-year NTP study conducted since then (NTP 2004) in mice and rats did not reveal any signs of neoplasias; the only other noticeable changes were a higher incidence of pigmentation of the olfactory epithelium in the mice. However, the highest dose given to the rats was only 200 mg/kg body weight which could indeed correspond to a NOEL for long-term effects. Furthermore, in conjunction with the preparation of the latter long-term study, a 3-month study in rats (and mice) was also conducted which already showed non-neoplastic changes in the rumen (squamous epithelial hyperplasia) at a dose of approximately 625 mg/kg body weight/day in male and female animals. This meant that the NOEL was the lowest examined dose of approximately 275 mg/kg body weight/day. All the same at this dose (as at higher doses) elevated serum values in bile acid were identified which could be interpreted as the expression of cholestase, hepatocellular damage or an altered liver function (NTP 2004). These two series of tests both produced arguments for a NOEL in the rat of approximately 200 mg/kg body weight/day. Using the customary interspecies and intraspecies factors of 10, this would lead to an ADI above the range of the values originally established by JECFA.

What are also worth noting are data on the reproduction toxicology of cinnamaldehyde which were indeed mentioned in the last JECFA assessment (2001) but not included in the risk assessment. Mantovani *et al.* (1989) treated groups of 14-16 pregnant Sprague Dawley rats between days 7 and 17 of pregnancy with cinnamaldehyde (0, 5, 25 or 250 mg/kg body weight/day). A significantly lower increase in weight coupled with non-impaired feed intake at the higher doses could be interpreted as possible maternal toxicity. The foetal findings showed significant effects particularly in the incidence of skeletal anomalies in the axial skeleton and skull, in ossification and in the incidence of variants and anomalies in the kidneys and excretory urinary tract. However, these findings did not reveal the expected dose dependency. At the lowest tested dose of 5 mg/kg body weight significant increases in the incidence of ossification defects of the cranial bones, kidney changes and dilated ureter were observed. The method used in this study does not, however, comply with the OECD test guidelines valid today concerning more particularly the number of animals used and the treatment duration. Up to now the findings of Mantovani *et al*. (1989) have not been reviewed in any later tests. Concerning other, less reliable test systems Abramovici and Rachmuth-Roizman (1983) observed a teratogenic effect of cinnamaldehyde in chicken embryos (recorded as a percentage of abnormal embryos). Hardin *et al*. (1987) did not observe any changes in the progeny of mice treated during pregnancy (1200 mg/kg body weight/days 6-13) in their study. In the procedure used as a screening test, however, only externally visible, rough morphological changes can be determined (no macroscopic or microscopic examinations of internal organs, no more discrete dysplasia). Overall these results justify the suspicion that cinnamaldehyde may have teratogenic potential; this should be clarified in further tests which comply with today's standards (for instance in a repeat test in a rodent or non-

rodent species, e.g. in rabbits). For the time being it cannot be ruled out that a dose of 5 mg/kg body weight/day could possibly already trigger embryonal changes in rats.

A dose of 5 mg/kg body weight/day would almost be achieved by diabetics (4.7 mg/kg body weight/day, ignoring other sources of cinnamaldehyde consumption) ingesting high levels of cinnamaldehyde in cinnamon (e.g. highest measured concentration of 94 mg/g in He *et al.,* 2003, see above) and the daily consumption of 3 g cinnamon in capsules (mean dose in the study by Khan *et al*. 2003). Exposure of this level is indeed possible given the current marketing of cinnamon capsules and may be particularly problematic for pregnant diabetics (only very few of the labels on cinnamon products carry warnings for pregnant women). In this context, it must also be borne in mind that should the teratogenic effects be confirmed in animal experiments, the dose of 5 mg/kg body weight/day is still not an NOEL. Furthermore, for the establishment of an ADI the customary interspecies and intraspecies factors would have to be used which would lead to a value for pregnant women in the low body weight related microgram range. A value of this kind would probably already be exceeded by the occasional consumption of cinnamon as a spice. These considerations underline yet again the urgent need to clarify the possible teratogenic potential of cinnamaldehyde. For non-pregnant diabetics, too, a dose of 5 mg cinnamaldehyde per kg body weight/day does not seem to be unproblematic since it is far higher than the ADI value of 0.7 mg/kg body weight established by JECFA which was valid up to 1990. As outlined under 3.1.1, a worst case scenario for infants (consumption of rice pudding with sugar and cinnamon) would lead to a peak exposure of 0.063 g cinnamon per kilogram body weight/day which, assuming a high level of cinnamaldehyde (94 mg/g cinnamon, see above), would lead to exposure to this compound of 5.9 mg/kg body weight.

As described above, capsules are sold not only with cinnamon powder but also with aqueous extracts of cinnamon. It is likely that the contents of essential oils in these extracts are far lower than in the cinnamon powder. Some of the manufacturers/distributors of extract products claim that they do not contain any essential oils which may cause health problems.

3.2.3 Safrol (CAS No. 94-59-7)

Only traces of safrol, a genotoxic carcinogen, are contained in the types of bark used to produce cinnamon (Jayatilaka *et al*. 1995). By contrast, foliage oils of cinnamon trees in particular, which may be used to blend cinnamon oils, contain higher levels. Jirovetz *et al*. (2000) found safrol levels (0.8 and 1.2 %) in two essential cinnamon oils declared as cassia oil. It, therefore, seems prudent to measure safrol content within the framework of the official monitoring of cinnamon and cinnamon-containing products.

3.2.4 Styrene (CAS N0. 100-42-5)

Cinnamon may contain relevant concentrations of styrene. This may be for two reasons:

- Styrene is already formed under natural conditions in the tree probably through the degradation of cinnamaldehyde and cinnamic acid. Inside the bark it reaches concentrations of 0.1 mg/kg. As a consequence of the drying, transport and storing of the harvested cinnamon bark, styrene may be formed in far higher concentrations. The formation of styrene is promoted more particularly by high temperatures and a high degree of air humidity (Fragnière *et al*. 2003). Cinnamon should, therefore, be transported in a dry space with the lowest temperatures on board ship (the best solution is ventilated containers). High temperatures also lead to a reduction in value owing to the loss of essential oils.

- Furthermore, styrene may migrate from the packaging material polystyrene to the food. In a British study (MAFF 1999) the styrene exposure through human dietary intake was estimated to be between 0.03 and 0.05 microgram/kg body weight/day. This amount is toxicologically safe (see below). Tang *et al*. (2000) established a similar range after assessing the available literature. Ground cinnamon may possibly have a higher absorptive capacity for styrene because of the relatively large surface of the powder.

When comparing various tested foods (Steele *et al*. 1994) the highest styrene concentrations by far were found in the three different samples of cassia cinnamon (approximately 0.17, 2.5 and 38 mg/kg). The concentrations now measured by the Food Institute Braunschweig within the framework of food control in 13 samples of ground cinnamon were also in this range: between below the detection limit of 2 mg/kg for five samples and values of 14 to 22 mg/kg for the other eight samples. The elevated concentrations are higher than those which are normally caused by migration from the packaging to the food. The formation of styrene at these levels is probably caused by incorrect transport and/or storage.

The consequence of the undesirable styrene formation is an impairment of flavouring caused by a solvent-like foreign odour. This is to be expected in cinnamon from an estimated 20 mg/kg (Cantonal Laboratory Basel City 2001). From the toxicological angle concentrations of this kind are safe even when based on exposure of several grams cinnamon per day which is outside the normal framework (consumed by diabetics in conjunction with the above-mentioned administration): for a person weighing 60 kg consumption of 6 gram cinnamon/day (highest dose in the study by Khan *et al*. 2003) with a styrene concentration of 20 mg/kg cinnamon would lead to a daily styrene intake of 2 micrograms/kg body weight. Other sources of dietary exposure can be ignored (see above: MAFF 1999). Exposure of this kind is below the TDI of 7.7 microgram/kg body weight established by WHO within the framework of the assessment of styrene in drinking water (WHO 1996). It is not known whether diabetics are more sensitive to the neurotoxic effects of styrene because of their higher risk of polyneuropathy.

In conjunction with the daily consumption of cinnamon in the gram range, only a far higher styrene content in cinnamon powder would be problematic regarding the harmful effect of styrene as has already been determined in the past. In 1993 the Chemisches Untersuchungsamt (Chemical Testing Agency) Mainz measured styrene levels in cinnamon sticks of 173 and 203 mg/kg. Correspondingly high levels in cinnamon can clearly lead to harmful concentrations in cinnamon biscuits. The then BgVV expressed an opinion on 17 April 2001 on styrene levels in star-shaped cinnamon biscuits of 25 and 65 mg/kg. As cinnamon biscuits using a customary recipe contain around 1 % cinnamon, far higher concentrations would be expected in the processed cinnamon if the styrene impurities could be traced back to the cinnamon in the biscuits. Hence, some consideration should be given to the possibility that, for instance, cinnamon with a high level of styrene which can no longer be sold as cinnamon powder because of the loss of flavour caused by incorrect storage could then be used to produce cinnamon biscuits or cinnamon capsules. In the course of food control cinnamon capsules should, therefore, also be tested for styrene.

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