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Association of the European Self-Medication Industry
Europäischer Verband der Arzneimittel-Hersteller

AESGP Position Paper on the HMPC draft reflection paper on the risks associated with furocoumarins contained in preparations of Angelica archangelica L.

AESGP represents the manufacturers of non-prescription medicines in Europe.

AESGP appreciates the opportunity to provide comments on the draft reflection paper (EMEA/HMPC/317913/2006) released for consultation on 11 January 2007.
This draft reflection paper proposes to limit the daily intake of total furocoumarins from preparations containing *Angelica archangelica* at a dose of 15 µg.

After detailed discussion with member companies and based on the four enclosed reports of toxicologists, AESGP has the following detailed comments.

SUMMARY

- The HMPC extrapolated the carcinogenic potential of 8-methoxypsoralen (8-MOP) combined with UV radiation to furocoumarins-containing plants in general, and particularly to *Angelica* preparations. Based on this extrapolation, the HMPC concludes that 'a daily intake for total furocoumarins in a herbal preparation that is equal or below 15µg would not be considered to pose an unacceptable risk to consumers'.
The proposed model of dose limitation is only based on a theoretical extrapolation from data referring to the properties of isolated and highly dosed compounds to Angelica preparations rather than on specific scientific data or case reports of suspected adverse events.
Such a procedure stands in clear contrast to the contents of a concept paper of the HMPC[1], where an extrapolation for preparations with no known risk potential is considered wrong.

- Important risk assessments from scientific bodies, e.g. from the British COT (1996) and a supra-national scientific board, the SKLM of the DFG (2006) have not been taken into consideration. These reports estimated the average daily intake of furocoumarins via food of being in the range of 1,2 mg per person for Great Britain (COT, 1996) and 1,45mg per person for Germany (SKLM 2006). They came to the conclusion that the additional risk of skin cancer arising from the

[1] HMPC draft concept paper on the development of a guideline on the assessment of genotoxic constituents in herbal substances/preparations (EMEA/HMPC/413271/2006) which states under item 3, lines 76 to 79 that the authorities should not ban the use of herbal medicinal preparations "on the basis of extrapolated suspicions, but their remit is to develop sound risk-benefit approaches for HMPCs, with which to protect consumers".

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consumption of typical quantities of furocoumarin-containing foods, which remain appreciably below the range of phototoxic doses – circa 14 mg per day- is regarded as insignificant. Intake of furocoumarins with Angelica archangelica preparations are estimated to be in the order of magnitude of average dietary intake and even combined with dietary furocoumarins, doses required for phototoxicity are not attainable.

- The assessment and the conclusions drawn up in the draft reflection paper on Angelica came from the extrapolation of the data from highly dosed isolated substances, e.g. 8-MOP (used to treat psoriasis) to Archangelica preparations. The latter contains a broad range of different substances which is in no way comparable to the isolated chemical substance used in psoriasis treatment. Plant extracts contain low level of psoralens, the only furocoumarin with definitive carcinogenic potential. Carcinogenic tests for other furocoumarins did not show increase in skins tumours or have resulted in ambiguous results due to contamination with psoralens.

- The reflection paper mixes two different and independent approaches, both of them not applicable to herbal medicinal products. The TTC approach and the limits defined therein where explicitly recommended for genotoxic and carcinogenic impurities. Furocoumarins in herbal medicinal products should not be compared to impurities because they are part of the therapeutic principle of herbal medicinal products. As for any other medicine, a therapeutic risk benefit analysis should be used. Recognised strategies at international level for hazard identification and risk estimation for photogenotoxins are available and can be used for herbal medicinal products.

- The conclusion to limit the daily dose of furocoumarins to 15 μg would not lead to a 'risk reduction' as the risk is already insignificant. However, such a restriction may lead to an unjustified ban of such medicinal products ignoring the well-established benefits for patients and the potential economic consequences for the European pharmaceutical sector. This would be a clear example of 'overregulation'.

- We call on the HMPC to revise the reflection paper taking into account the opinion of the toxicologists and studies presented in our comments. AESGP is willing to participate to any further discussion on the revision of this reflection paper.

DETAILED COMMENTS

1. Introduction (Background)

The first paragraph states that the assessment may be used when evaluating the safety of herbal medicinal products containing preparations not only from Angelica archangelica L., but also of other herbal preparations containing furocoumarins with a phototoxic potential. From our point of view this is not appropriate because this would represent an unjustified double extrapolation of an already extrapolated theoretical toxicological risk.

To evaluate the furocoumarin intake from herbal medicinal preparations, it is essential to look at the overall furocoumarin intake by consumers. Estimates of the average daily dietary intake of furocoumarins were published by various authors, being in the range of 1.3 mg per person for the

USA, 1.2 mg per person for Great Britain (COT, 1996), and 1.45 mg per person for Germany (SKLM, 2006, Schrenk 2007).

The third paragraph of this chapter states that characterization of systemic exposure needs detailed knowledge of the constituents of a preparation, by a transformation of constituents upon administration and pharmacokinetics. In this context, we would like to mention that a lot of data on kinetics and (bio) transformation of furocoumarins are available. They have been extensively reviewed and summarized in the report of the SKLM (senate commission on food safety of the German Research Community DFG, SKLM 2006). In fact, a threshold for systemic absorption exists, below which a pronounced first-pass effect can be observed (Schrenk 2007). Data on the overall absorption, bioavailability and kinetics are available. They should either be reflected in this paper or the statement made in the third paragraph should be deleted.

2. Safety evaluation of furocoumarins

As Schrenk (2007) states, data from the kinetics, phototoxicity and photocarcinogenicity of the main furocoumarins found e.g. in *Angelica archangelica*, does not allow to consider them as equipotent to 8-methoxypsoralen (8-MOP) and 5-methoxypsoralen (5-MOP), the most potent furocoumarins. There is also evidence indicating a lower oral bioavailability of furocoumarins in complex biological matrices when compared to 8-MOP in its isolated form (Schrenk 2007). Furthermore, sufficient toxicological data on consumers' exposure to furocoumarins exist to conduct a thorough assessment on a potential toxicological or genotoxic/ carcinogenic risk (SKLM 2006).

For the reasons outlined above, extrapolation of the findings obtained with 8-MOP and 5-MOP to Angelica preparations is not appropriate and not scientifically sound. The statement (line 29-30) that the present model provides acceptance criteria for the assessment of relevant herbal medicinal products, does not apply.

2.1. Phototoxicity of furocoumarins

This paragraph states that the toxicity of 5-MOP and 8-MOP is enhanced in the presence of ultraviolet A radiation and can cause acute skin reactions. From our point of view a generalising extrapolation of this statement to preparations with *Angelica archangelica* is misleading.

The occurrence of phototoxicity after intake of furocoumarins-containing *Angelica archangelica* herbal preparations has never been observed during decades of long-term medicinal use (Schrenk 2007, Schmidt 2007) nor during normal uptake of herbal food potentially containing furocoumarins (SKLM 2006).

It should also be clarified that isolated furocoumarins are used in high enough doses to provoke purposely a phototoxic reaction aimed at treating skin disorders such as psoriasis and eczema (SKLM 2006)

2.2. Carcinogenic potential of furocoumarins

The first paragraph of the HMPC reflection paper describes conclusions drawn by the IARC working group on the carcinogenicity of 5-MOP and 8-MOP in the 1980ies (IARC 1986, 1987). The HMPC extrapolates these conclusions to medicinal plant preparations containing various furocoumarins and in particular to preparations of Angelica, although recent clinical results on the carcinogenic potential of PUVA are contradictory (Schulze 2007, Schmidt 2007). From our point of view the evidence resulting from these assessments is pointing, if at all, to a strictly dose-dependent relation. Carcinogenic effects occur only at doses above that of furocoumarins having a phototoxic effect and highly above doses potentially resulting from normal intake of food or herbal medicinal products (Schrenk 2007).

Data obtained from the treatment of psoriasis have shown no increase of skin cancer in patients exposed to daily doses as high as 30 mg for at least 100 treatment cycles. An increased incidence was only described in treatment groups which received significantly higher dose. However, even this assumption has been questioned in a more recent study showing that at least a major number of skin tumours observed in PUVA therapy had been induced by the UV B exposure during UV A irradiation with non-selective sources of UV light rather than by psoralens plus UV A (Schulze 2007). The evaluation of these data is further complicated by the fact that psoriatic patients were shown to have a higher risk of skin cancer (Schmidt 2007).

Erythema occurs at the same or even lower doses than that of genotoxic effects, as the genotoxic effects provoked by UV A radiation of furocoumarins are identical or related to those causing cell damage. Thus, doses lower than a phototoxic 'threshold dose' are likely to represent a negligible additional cancer risk (Schrenk 2007). From this, it can be assumed that an enhanced genotoxic or carcinogenic risks due to furocoumarin are preceded by the occurrence of erythema. Therefore, it seems rather improbable that genotoxic effects would have been overlooked and not reported.

2.3. Mechanism of action

From the data available, it can be assumed that the genotoxicity/ carcinogenicity of furocoumarins is activated by UV A light. Upon UV A radiation, both the angular and the linear furocoumarins can form covalent bonds with DNA bases. The genotoxicity of furocoumarins is based on the same mechanisms as the one causing their phototoxicity. It can be assumed that the genotoxic components formed by UV A radiation of furocoumarins in cells are identical or related to those causing cell damage. Under these assumptions, doses lower than a phototoxic 'threshold dose' are unlikely to represent any relevant additional cancer risk (Schrenk 2007).

2.4. Human toxicity

A potential relationship between PUVA treatment and skin cancer has been discussed in literature. Besides the fact that psoriatic patients are not representative of the general population (as they may have a favourable disposition for skin cancer), more recent data, as already mentioned above, have shown no increase of skin cancer in patients exposed to daily doses as high as 30 mg for at least 100 treatment cycles. An increased incidence was only described in treatment groups with significantly

higher exposure, which effect was partly due to the concomitant UV B exposure rather than to psoralens plus UV A (skin cancer formation was much higher in those areas normally not exposed to the sun, whereas the occurrence of skin cancers in head and neck was much lower) (Schulze 2007). PUVA requires doses of psoralens exceeding the metabolic first-pass capacities of the organism. A threshold of 30ng/ml of 8-MOP in the bloodstream was considered the most appropriate estimate for photoreactions triggered by 8-MOP. This threshold can be reached through the typical doses applied in PUVA therapy, but not with intake of furocoumarins in Angelica preparations (Schmidt 2007). The rough assumption made does not take into account the dose dependency of the discussed carcinogenic effects. Thus it is of no relevance for the evaluation of putative toxic effects of preparations containing *Angelica archangelica.*

2.5. Various considerations for risk assessment purposes

Even the initial statement in the first paragraph - stating that photogenotoxicity and photocarcinogenicity are the most important toxic outcomes of furocoumarins from the risk assessment point of view - may be questioned under some circumstances, as e.g. furocoumarins from grapefruit may be more relevant as inducers of interactions than as phototoxins (SKLM 2006). The following two sentences only take into account the physicochemical nature of the potential phototoxic reactions of furocoumarins, but not the involvement of toxicokinetics and metabolism as preconditions of such reactions.
Moreover the concluding last sentence of the paragraph neglects the fact that even those furocoumarins, which have a genotoxic and carcinogenic potential, do pose this hazard to humans only under specific conditions which are not those of normal exposure of furocoumarins via food intake (SKLM 2006) or via phytomedicinal preparations *Angelica archangelica* (Schrenk 2007).

In the context of potential mutagenic and carcinogenic risks, Speit (2007) refers to the statement by Müller et al. (1998) : "with respect to the environmental and lifestyle related risk of UV B exposure, it has to be questioned whether there is any additional risk to humans from the exposure to photochemical genotoxins as pharmaceuticals or cosmetic ingredients".

The HMPC draft itself states that a detailed scheme of risk assessment for genotoxicity and/or carcinogenicity of herbal medicinal products is not available. However, approaches used to assess the risk are not appropriate for herbal medicinal products due to the inappropriate extrapolations.

First, the content of furocoumarins in cosmetic products as mentioned in the Scientific Committee on Consumer Products (SCCP) opinion cannot be linked to the oral intake of plant preparations. Cosmetic products are used topically and have a complete different profile of penetration and absorption. The limit of 1 ppm is therefore not considered relevant for the oral intake of plant preparations containing furocoumarins (Schmidt 2007).

Second, the EFSA Scientific Committee recommends a calculated margin of exposure of 10.000 or higher. This limit, however, relates to food products which, for their safe use, have to undergo a "pure risk assessment" whereas medicinal products need to undergo a benefit risk assessment (Schmidt 2007).

Speit (2007) states that furocoumarins in herbal medicinal products should not be compared to impurities which they are not; they are part of the active principle. Therefore, a comprehensive risk benefit analysis should be undertaken. The application of the threshold for toxicological concern (TTC) concept might lead to an unjustified restriction of such medicinal products. In conclusion, the use of the TTC concept for herbal medicinal products is inappropriate as it leads to an unjustified over-estimation of potential risks and potential far-reaching negative consequences for patients and pharmaceutical companies (Speit 2007).

The last paragraph of part 2.5 mentions that the standard uncertainty factor approach cannot be used without any added value from a public health point of view since the two assumptions given are not fulfilled: the HMPC draft clearly states that there is uncertainty with regard to the evidence for a carcinogenicity threshold and there is no study available providing information on a NOAEL. Instead of the approach followed, a risk-benefit evaluation should be applied for pharmaceuticals (Speit 2007, Schmidt 2007).

The following calculation (line 112, "as an exercise") is based on formal assumptions which are not fulfilled in case of herbal medicinal preparations. As stated above, from our point of view a theoretical extrapolation is not suitable and thus such an exercise is not considered useful to predict the risk reduction in consumer/patient (SKLM 2006). The PUVA therapy using isolated chemical substances in extremely high doses is not a suitable basis for the application of uncertainty factors like 1.000 for herbal medicinal preparations. It cannot be extrapolated to the lower doses and to the different toxicological profile of furocoumarins present in herbal preparations.

Finally, the application of safety factors like 1.000 is derived from environmental toxicology or risk toxicology and again it does not apply to the risk benefit evaluation (Schrenk 2007).

2.6. Problems in risk assessment of other derivatives

There is a number of data available which could be used to rate the phototoxic potential of other furocoumarin derivatives (Schulze 2007). They account for the majority of furocoumarins contained in many plants and also in *Angelica archangelica*. The database for the kinetics, phototoxicity and photocarcinogenicity of the major furocoumarins found, e.g., in *Angelica archangelica* tincture does not allow to consider them as equipotent to 8-MOP (Schrenk 2007).

3. Conclusions

The statement that the furocoumarins of *Angelica archangelica* L. are posing health risks in humans is merely based on theoretical extrapolations from contradictory data obtained during the therapeutic use of 5-MOP and 8-MOP.

With reference to Speit (2007), the average daily consumption of psoralens in the order of 1300 µg has to be considered. Although, from a theoretical point of view, it is unclear to what extent the correlation between psoralens in food and natural UV irradiation may contribute to the background levels / prevalence of skin cancer. From a practical point of view, it has to be critically assessed whether any (additional) risk from the intake of preparations of *Angelica archangelica* L. can be

expected. Speit (2007) concludes that, under the real exposure conditions of a therapy with herbal medicinal preparations of *Angelica archangelica* L. such a risk should be negligible.

The conclusion reached in the second sentence ("furocoumarins pose a clear hazard") is wrong because it is based on data obtained during the use of isolated 8-MOP and 5-MOP in high doses in PUVA therapy. This is not applicable to herbal medicinal preparations containing furocoumarins, for which a risk assessment is possible, as demonstrated by the SKLM (SKLM 2007).

The third paragraph, which relates to the suggested TTCs, leads to a wrong conclusion because the TTCs relate to impurities. Even in case a TTC dose is calculated, the conclusion to restrict the daily intake for total furocoumarins to 15 μg (instead of 120 μg according to the highest TTC dose of Muller et al. 2006) is arbitrary and not justified by scientific data. Furthermore there is no reason to equate all detectable furocoumarins to 8-MOP because other furocoumarins have a completely different toxicologic and molecular profile. Calculation on a molar basis is not possible because in several of the cases the molecular weights are not known.

RISK ASSESSMENT AND CALCULATION OF DOSE

Furocoumarins are a regular part of the human diet. An average daily intake of 1.45 mg of dietary furocoumarins was estimated by a senate commission of the German DFG in a recent toxicological assessment (SKLM 2006) and the UK COT (2007). The DFG report concludes that with food such as celery or parsnips the intake can reach peak values of up to 14 mg which apparently do not pose a special risk.

A limitation of 15 µg/day based on theoretical assumptions clearly contradicts the amounts coming from nutrition (alone). Neither the UK Committees on Mutagenicity and Carcinogenicity (COT 1996) nor the SKLM of the German DFG (SKLM 2006) found a risk arising from food containing furocoumarins. These reports also came to the conclusion that, based on the ability of the human organism to degrade a certain amount of potentially toxic compounds, a quantity of 14-15 milligrams of furocoumarins (e.g. from celery, parsnip or orange juice) would pose no special risk.

This dose is 1000 times higher than that proposed by the HMPC for Angelica preparations based on theoretical extrapolations (Schmidt 2007).

Schrenk (2007) gives a similar statement. Related to the well-documented occurrence of furocoumarins in food, the COT (1996) and the SKLM (2006) concluded that the carcinogenic and photocarcinogenic risk caused by average dietary intake of furocoumarins in these countries was very small or insignificant. It has to be kept in mind that the intake of furocoumarins from a typical tincture from *Angelica archangelica* would be in the same range.

Raquet et al. in a recent paper (Raquet et al. 2007) come to the same conclusion. Based on an assumed level of total furocoumarins in Angelica tincture of 1 mg/ml and a daily dose of 1,5 g tincture (according to the German Commission E monograph), the authors estimate a total daily intake of about 1,5 mg furocoumarins corresponding to a daily intake of 25 μg (microgram) per kg

body weight, which is comparable to the average intake via food. With respect to the phototoxic "threshold dose" (circa 14 mg/day), the intake via a phytomedicine would be in the range of 10 %. This proportion is in reality even very much lower due to the lower phototoxic potency of the herbal furocoumarins. The author concludes that the intake of herbal medicinal products containing Angelica root extract does not contribute in a relevant way to phototoxicity and it within the range of average intake via food.

In a further recent paper, Schulze (2007) concludes that no carcinogenesis warning can be based on the furocoumarin content of herbal extracts.

Speit (2007) also points out that modern approaches for the evaluation of genotoxicity takes into account the biological relevance of positive in vitro tests for the in vivo situation, the validity of in vivo findings in the context of toxicokinetics and the mode of (genotoxic) action of the test compound. This thus prevents an overestimation of the risks shown by using the TTC or the safety factor approach in cases where a risk-benefit evaluation should be used. Such an inappropriate use of the TTC or safety factor approach is also underlined in another recent paper by Schmidt (2007).

CONCLUSIONS

The conclusion of the HMPC draft reflection paper to limit furocoumarins in Angelica extracts is improper. This is neither based on case reports of suspected adverse events nor on a sound benefit/risk assessment of a medicinal herbal preparation. They are only based on theoretical extrapolations coming from isolated substances to the whole group of Angelica preparations. The conclusion to limit the daily dose of furocoumarins to 15 μg would not lead to a 'risk reduction' as the risk is already insignificant. **However, such a restriction may lead to an unjustified ban of such medicinal products ignoring the well-established benefits for patients and the potential economic consequences for the European pharmaceutical sector.**

We call on the HMPC to revise the reflection paper taking into account the opinion of the toxicologists and studies presented in our comments. AESGP is willing to participate to any further discussion on the revision of this reflection paper.

Brussels, 16 May 2007

Expert statement (enclosed)

Is there a Phototoxic/Photocarcinogenic Risk from Angelica archangelica L. in Phytomedicines? Toxicological evaluation. Expert Statement by Prof. Dr. med. Dr. rer. nat. Dieter Schrenk, Department of Toxicology & Food Chemistry, University of Kaiserslautern, Germany

Comment on the HMPC's "Reflection Paper on the Risk Associated with Furocoumarins Contained in Preparations of Angelica archangelica L.. Expert Statement by Prof, Dr. G. Speit, Institute for Human Genetics, University of Ulm, Germany

Comments on the HMPC draft reflection paper on the risks associated with furocoumarins contained in preparations of Angelica archangelica L.. Expert statement by Prof. Dr. med. Johannes Schulze, University of Frankfurt, Germany.

Risk assessment: Carcinogenic potential of Angelica archangelica L.. Expert Statement by Dr. M. Schmidt, Herbresearch Germany, Tussenhausen, Germany

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Schmidt M. (2007) Recent Developments in Risk Assessments of Herbal Medicinal Products: Unlimited limitation? Abstract (submitted to the 55th Annual Meeting and International Congress

of the Society for Medicinal Plant Research, Sept 2 - 6, 2007, Graz, Austria)

Speit G. (2007) Modern strategies for the assessment of genotoxicity of herbal medicinal products. Abstract (submitted to the 55th Annual Meeting and International Congress of the Society for Medicinal Plant Research, Sept 2 - 6, 2007, Graz, Austria)

*SKLM (2006) Toxicological Assessment of Furocoumarins in Foodstuffs. DFG – Senate Commission on Food Safety, Kaiserslautern, Germany (http://www.dfg.de/ aktuelles_presse/reden_stellungnahmen/2006/download/sklm_furocoumarine_en_2006.pdf)

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Dose limitation of furanocoumarins in Angelica preparations

Introduction

The roots of *Angelica archangelica* contain furanocoumarins, some of which may be phototoxic and carcinogenic when applied in isolated form and in high therapeutical doses for PUVA-treatment. The Herbal Medicinal Products Committee of the EMEA has recently proposed to drastically limit the quantities of furanocoumarins in preparations from the roots of *Angelica archangelica* [1].

Even though the HMPC did not provide evidence for an inherent risk by herbal extracts prepared from plant material containing, among other constituents, various furanocoumarins, the committee still discussed various approaches for risk minimization (to be more exact: for the minimization of risks of a herbal extract for which no carcinogenic risk is known, based on data with isolated chemicals in high doses that may or may not exist in the herbal matrix in low concentrations) such as the Margin of Exposure-approach or the Threshold for Toxicological Concern approach. The HMPC also discussed safety factors to reach furanocoumarin contents which would not pose a risk on long-term intake – all approaches used for the limitation of toxic impurities for which human contact is to be avoided. As a result of the application of such methods (obviously unsuitable for food and medicinal plants), the HMPC suggests the limitation of furanocoumarins to a daily dose of less than 15 micrograms of total furanocoumarins, calculated as the compound with the highest known toxic potential (at doses of approximately 30 mg), 8-methoxypsoralen [1].

The EFCAM is an association representing, among other methods of alternative and complementary medicine, Chinese traditional medicine. Within this system, preparations from *Angelica sinensis* are very popular, with a wide-spread use not only in China, but also in most Western countries including the EU member states. Like *Angelica archangelica*, *Angelica sinensis* also contains furanocoumarins. A decision to limit the contents of corresponding preparations of *Angelica archangelica* below 15 µg/day would immediately affect the use of *Angelica sinensis* – hence the interest of the EFCAM to voice its opinion in this toxicological assessment.

Conclusions

The action proposed by the HMPC is unacceptable. Its application would impact the use of herbal medicinal preparations known to have a history of safe and toxicologically uneventful use. Because of its importance as a medicinal plant, *Angelica sinensis* (Dong quai) was even positively monographed by the WHO [2]. The proposed dose limitation would lead to a ban of Dong quai, a measure not justified by the overall perfect record of tolerability.

Pharmacovigilance is an important tool for consumer protection. However, its goal should be to protect the consumer from real risks, not from theroretical hazards extrapolated from data not corresponding to the use of *Angelica* preparations in real life. In fact, a ban of *Angelica*

based on furanocoumarin contents would also be inappropriate in view of the regular consumption of furanocoumarins with food, which by far surpasses the contribution of medicinal *Angelica* preparations – again without any known and apparent risk.

In addition, furanocoumarins such as they exist in Angelica preparations are a regular part of our diet. An average daily intake of 1.45 mg of dietary furanocoumarins was estimated by the German DFG in a recent toxicological assessment [3], with similar estimates made by the US and UK health authorities [4;5]. It was even estimated that with food such as celery or parsnips the intake can reach peak values of up to 14 mg, which apparently does not pose a special risk [3], although the quantity would seem very close to the threshold where according to the Swiss authorities and the German DFG phototoxic reactions may be expected in combination with UV irradiation (>14-15 mg) [3;6]. The contribution of medicinal *Angelica* preparations to the overall dietary intake of furanocoumarins – which is usually well-tolerated – is thus negligible.

A limitation of 15 µg/day based on theoretical assumptions clearly – and obviously deliberately – ignores the facts from real life and especially from nutrition. The conclusion of a deliberate omission is made on the grounds that a risk assessment of dietary furanocoumarins has already been made by different authorities from Switzerland [6], the US (where Angelica has GRAS status) [5], the UK Committees on Mutagenicity and Carcinogenicity [4], and the German DFG [3]. In none of these evaluations a risk of food materials containing furanocoumarins was found. These evaluations also came to the conclusion that (based on the ability of our organism to cope with a certain amount compounds that may be toxic when the bodies metabolic capacities are exceeded) a quantity of 14-15 milligrams of furanocoumarins (e,g, from celery, parsnips or orange juice) would pose no special risk. This dose is 1000 times higher than that proposed by the HMPC for *Angelica* preparations, based on a theoretical extrapolation.

Summarizing, the proposal of the HMPC to limit furanocoumarins in *Angelica* extracts is unrealistic. It is not even based on case reports of suspected adverse events, as it should be expected, but merely on a theoretical extrapolation. Whereas the work of the HMPC is clearly valuable when it comes to managing emerging or known risks, it cannot be the task of this committee to protect the consumers from unknown, theoretical and most probably even non-existing risks. This conclusion is in line with a recent EMEA concept paper of the HMPC, stating (verbatim):

Last, but not least, consumers and patients have used, currently use, and probably continue to use, herbal medicinal preparations to treat themselves. The authorities should not ban this use on the basis of extrapolated suspicions, but their remit is to develop sound risk-benefit approaches for HMPs, with which to protect consumers. [7].

The limitation of furanocoumarins in Angelica roots would correspond to a de facto ban, despite the fact that a carcinogenic risk of *Angelica* preparations is not known. Such an action would therefore clearly contradict the own declared policy of the HMPC, and is neither acceptable nor appropriate.

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1 HMPC-assessment of photo/genotoxic risk of Angelica preparations as herbal medicinal products

The Herbal Medicinal Product Committee (HMPC) recently called for comments in the discussion of potential photo-cancerogenic effects of furocoumarins as constituents of Anglica preparations. According to the committee, furocoumarins "*have to be regarded as posing genotoxic and carcinogenic hazard to humans, and exposure to furanocoumarins from herbal preparations may pose a significant health risk to humans*" [1].

For the assessment of the risk involved in the intake of Angelica preparations, the committee used various approaches:

- The "Margin of Exposure" approach (MOE), which is usually applied to genotoxic impurities in the manufacturing process, and for which the application would lead to a dose limitation for safe use by far below the values usually encountered in Angelica preparations.
- The "Threshold for Toxicological Concern" approach (TTC), defining a limit of 120 µg per day for short-term application, and of 1.5 µg daily for life-time exposure. According to the HMPC, herbal remedies containing furocoumarins can be expected to be taken for a considerable portion of adult life. Thus, the threshold of 120 µg/day is not acceptable for the committee, however, the lower limit of 1.5 µg/day would not reflect the current use of herbal medicinal products. The HMPC assumes that a daily intake of ≤ 15 µg of total furocoumarins, calculated as 8-methoxypsoralen, would not be considered an unacceptable risk to consumers.
- The definition of safety factors as a consequence of the lack of adequate evidence of carcinogenicity of Angelica preparations. These safety factors were derived from the use of 8-methoxypsoralen as a chemical entity in PUVA therapy. With the lowest dose considered as safe on long-term application and the use of a safety factor of 1000, a safe daily dose of 30 µg of furocoumarins was suggested [1].

2 Comments to the assessment

The propositions of the HMPC cannot be discussed in the context of the use of Angelica preparations alone, but must be seen in the more general context of nutrition. A dose limitation of furocoumarins in Angelica extracts used as herbal medicinal products would necessarily have an impact on the question of furocoumarins from food sources and the risks involved with such food products.

In this context it must be pointed out that this discussion is not new, and has already been presented for plants from the food sector several times in the recent past:

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- In 1991 the Swiss Federal Office of Public Health defined a threshold dose for photo/genotoxicity of 15 mg (not microgram!) of 8-methoxypsoralen – a dose which is not reached with dietary sources of furocoumarins [2].
- In 1996 the same topic was discussed by the UK Department of Health Committees on Mutagenicity and Cancerogenicity. These standing committees concluded that there is no risk involved with usual doses of furocoumarins from food sources [3].
- The same result was obtained by the German Research Community DFG in 2005. Again, a threshold dose for concern of 14 mg (not microgram!) was calculated [4].

In addition, Angelica specifically has GRAS status in the United States, which implies that the FDA has also made a risk assessment.

Nutritional intake of furocoumarins can easily lead to ingested quantities of 4-14 mg per meal [4]. This figure would, however, not represent the average long term daily consumption, which was rather uniformly calculated to be between 1.2 and 1.45 mg per day in the United States, the UK and Germany [3-5]. The contribution of furocoumarins in Angelica extracts would be expected to be in the range of 1.5 mg/day maximum with the application of 3-4 g of Angelica roots as recommended by the monographs for clinical application. In addition, no 8-methoxypsoralen has been found in Angelica preparations – thus the reflection is based on the theoretical toxicity of a constituent not even present in the plant.

No adverse effect pointing to genotoxicity are known for food use of furocoumarin-containing plants including Angelica, und much less so for Angelica extract preparations. With furocoumarin containing plants having been under close examination by bodies specialized on questions of genotoxicity and cancerogenicity for at least three times, and with a clear conclusion of no harm involved from food source furocoumarin quantities in every single assessment, the very strict limitations proposed by the HMPC would only seem appropriate if case reports of suspected adverse effects pointed to an existing risk.

As it seems, the HMPC's assessment, which clearly contradicts the outcome of all previous assessments, is not only far from any practical applicability, but is also entirely based on a theoretical extrapolation of a hitherto unseen risk. Even according to the EMEA, such extrapolations are unacceptable when the toxicological concern is not based on facts [6].

In conclusion, the proposed limitation of furocoumarins in Angelica extract preparations is unacceptable for the following reasons:

- Neither concept of risk management (TTC, MOE and safety factors) is applicable or appropriate, since these methods were proposed for the limitation of toxic impurities, not of compounds naturally occurring in a food or medicinal plant matrix.
- The assessment of the HMPC wrongly attributes the toxicological characteristics of one single exemplary component not even present in Angelica roots to all structures of furocoumarins, whereas it is well known that not all furocoumarins are in fact photo/genotoxic. This leads to a gross overestimation of the risk.

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Such an approach would only be acceptable if the compound in question were an avoidable impurity, but not when food matrices without any known risk are discussed.

- When potential hazards of furocoumarins are discussed, the metabolic fate of furocoumarin concentrations typically found in food would have to be taken into account. The proposal of the HMPC treats Angelica extract (and thus also celery, parsnips or orange juice, just to name a few) like psoralen or 8-methoxypsoralen as an isolated single chemical entity, which they are not. The proposal of the HMPC completely skips questions of metabolic protective mechanisms such as the first pass effect, which is indeed a major reason why the human body tolerates furocoumarins from food sources without any known or apparent problems.
- Angelica extracts in medicinal products were used as a specific example. Angelica archangelica is, however, not only used in pharmaceutical products, but is also a regularly consumed food in the EU (e.g., Angelica candies), with ingested quantities easily surpassing the intake recommendation of the monographs for medicinal plant use. No toxicological concern has ever been presented for Angelica in food.
- The definition of the limit is arbitrarily chosen for the species Angelica. However, furocoumarins are common components in many regularly consumed foods, for which – as for Angelica – no carcinogenic risk has ever been observed. A limitation of furocoumarins in Angelica based on a theoretical extrapolation would automatically trigger a discussion of furocoumarins in vegetables and fruit juices, and have a major negative impact on eating habits long recognized as healthy and recommendable.

Extrapolations of hitherto unknown risks are unacceptable, especially when the consequences of the proposed action would cause more problems than they might theoretically solve.

3 References

[1] Draft: Reflection Paper on the risks associated with furanocoumarins contained in preparations of Angelica archangelica L. (2007) EMEA/HMPC/317913/2006

[2] Schlatter J, Zimmerli B, Dick R, Panizzon R, Schlatter C (1991) Dietary intake and risk assessment of phototoxic furocoumarins in humans. Food Chem Toxicol 29: 523-530

[3] Report of the Committees on toxicity, mutagenicity, carcinogenicity of chemicals in food, consumer products and the environment (1996) UK Dept Health

[4] Toxikologische Beurteilung von Furocumarinen in Lebensmitteln (2005) In: Eisenbrand G (ed). Lebensmittel und Gesundheit II. Sammlung der Beschlüsse und Stellungnahmen/Opinions (1997-2004), Wiley-VCH, Weinheim, pp 55-87

[5] Wagstaff DJ (1991) Dietary exposure to furocoumarins. Regul Toxicol Pharmacol 14: 261-272

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[6] Concept paper on the development of a guideline on the assessment of genotoxic constituents in herbal substances/preparations (2006) EMEA/HMPC/413271/2006: 1-4

Munich, 08.05.2007

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COMMENTS FROM: BPI - German Pharmaceutical Industries Association (Bundesverband der pharmazeutischen Industrie)

Bundesverband der Pharmazeutischen Industrie e.V.
BPI
Leben ist Vielfalt

On the reflection Paper on the risks associated with furocoumarins contained in preparations of Angelica archangelica L., EMEA/HMPC/317913/2006

GENERAL COMMENTS

The conclusions of the reflection paper summarize, that a daily intake for total furocoumarins in an herbal medicinal preparation that is equal or below 15 µg would not be considered as an unacceptable risk to consumers, while higher doses could not be considered as acceptable.

The scientific data which are the basis of these conclusions did not include the assessments of the toxicological relevance of plant furocoumarins by various national bodies from the UK[1], the US[2], Switzerland[3], and – most recently and exhaustively – from Germany[4]. In these the conclusion was drawn that the usual daily intake of furocoumarins in the range of 1.4 mg, mainly from dietary sources, is below levels for toxicological concern, which is likewise true for the furocoumarin intake from herbal preparations from Angelica archangelica L., so that, due to the lack of a toxicological risk to consumers, the proposed dose limitations would not improve consumer safety, while resulting in a factual ban of herbal medicinal preparations from Angelica archangelica L..

The conclusions of HMPC are merely based on extrapolations of data from the therapeutic use of highly dosed 8-methoxypsoralen (8-MOP) and 5-methoxypsoralen (5-MOP) in combination with UV A radiation in psoriasis (PUVA). PUVA is an established therapy of this disease, which has been associated with an enhanced risk of skin cancer. This risk is questioned by more recent data, which allow the conclusion that a potential carcinogenic risk, if any, is limited to doses above the threshold of phototoxicity. Phototoxicity has never been reported for oral uptake of herbal preparations from Angelica and even not for usual dietary uptake of plant furocoumarins, so that there is no indication for a potential hazard to human health.

Extrapolations from potential risks associated with the use of isolated highly dosed 8-MOP and 5-MOP to preparations of Angelica containing a different spectrum of furocoumarins with a low phototoxic potential and in low amounts are not appropriate and have to be rejected. The same is true for the use of the threshold of toxicological concern (TTC) and the safety factor approach in the assessment of active substances from herbal medicinal preparations, as these were developed and are suitable for the assessment of environmental toxins or impurities.

The draft reflection paper is not in accordance with the HMPC draft concept paper on the development of a guideline on the assessment of genotoxic constituents in herbal substances/preparations (EMEA/HMPC/413271/2006), where it is stated that the authorities should not ban the use of herbal medicinal preparations on the basis of extrapolated suspicions, but their remit is to develop sound risk-benefit-approaches for HMPs, with which to protect consumers. Therefore the content and conclusions are considered not acceptable, so that the proposition of changes is not applicable, whereas comments are made in the following.

[1] UK Department of Health: Report of the Committees on toxicity, mutagenicity, carcinogenicity of chemicals in food, consumer products and the environment (1996)
[2] Wagsteaff, D.J.: Dietary exposure to furocoumarins. Regul. Toxicol. Pharmacol. 14: 261-272 (1991)
[3] Schlatter, J. et al.: Dietary intake and risk assessment of phototoxic furocoumarins in humans. Food Chem. Toxicol. 29: 523-530 (1991)
[4] Eisenbrand, G.: Toxicological assessment of furocoumarins in foodstuff. Assessment of the DFG Senate Commission (2006). Available online at http://www.dfg.de/aktuelles_presse/reden_stellungnahmen/2006/download/sklm_furocoumarine_en_2006.pdf

SPECIFIC COMMENTS ON TEXT, page 2 of 7		
GUIDELINE SECTION TITLE		
Line no. + paragraph no.	**Comment and Rationale**	**Proposed change (if applicable)**
Page 3: Paragraph 1: Lines 1-11	The reflexion paper claims to present an assessment of the *risks associated with the use of herbal preparations containing Angelica archangelica L.*, while in fact it focuses on the toxicological properties of isolated and highly dosed 8-MOP and 5-MOP, not on the fraction of furocoumarins as can be detected in Angelica preparations. Furtheron it recommends the use when evaluating the safety of other herbal preparations than those from Angelica, containing furocoumarins with a toxic risk, without including any data from these herbs. These extrapolations seem not appropriate for a sound and reasonable risk-benefit-assessment.	Not applicable.
Page 3: Paragraph 1: Lines 12-17	While stating that *it may be worth of stressing that the composition of preparations containing Angelica archangelica L does not directly reflect the systemic exposure of an individual, because many glycosides may be immediately hydrolyzed before absorption and aglycones are furthermore extensively metabolized before entering the systemic circulation,* the scientific data supporting the relevance of such effects[4] for a toxicological evaluation are not included into the further assessment and not reflected in the conclusions of the paper regarding a carcinogenic risk, which are therefore not appropriate.	Not applicable.
Page 3: Paragraph 1: Lines 25-28	The statement *that the present model provides acceptance criteria for the assessment of safety of relevant herbal medicinal products that may be used in absence of any specific* tests is not conclusive, as significant parts of the scientific data available were not included, regarding the proposed model substances 8-MOP and 5-MOP as well as regarding furocoumarins from natural sources. These data have been evaluated in the toxicological assessments mentioned above, which all came to completely different conclusions than the actual reflection paper. So even the actual evaluation lacks a sound scientific basis and results in misleading conclusions, which would presumably be the case also for the application of this model to other groups of herbal medicinal	Not applicable.

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	products.	
Page 3: Paragraph 2.1: Lines 33-39	While the phrase, that *linear furocoumarins such as 8-methoxypsoralen (8-MOP) and 5-methoxypsoralen (5-MOP) are phototoxic - their toxicity is enhanced in the presence of ultraviolet A radiation and they cause acute skin reaction* suggests a relevant toxicity of these substances even without radiation, their toxicity without radiation is known to be low[4], and very high oral doses of more than 14 mg 8-MOP, in combination with intensive UV A radiation, as they are applied in PUVA therapy, are needed to induce phototoxicity.	Not applicable.
Page 4: Paragraph 2.2: Lines 41-51	The paper refers to monographs from *the IARC Working group (IARC 1986),* which *has concluded, on the basis of sufficient evidence from both human and animal data, that 8-MOP plus ultraviolet radiation is carcinogenic to humans (Group 1).* It has to be added, that since 1986 the volume of scientific data on the risks of PUVA therapy has significantly increased, and that several studies[5,6,7,8,9] have questioned this generalizing statement and allow, on the one hand, the conclusion that a strong link between phototoxicity and carcinogenicity exists, and on the other hand the conclusion that carcinogenicity, if linked to PUVA, is limited to the highest dose ranges applied. These doses are in the order of magnitude highly above doses applicable by the intake of herbal preparations from Angelica archangelica L., so that direct conclusions to these are not admissible.	Not applicable.
Page 4: Paragraph 2.2: Lines 53-58	It is relevant, that the in vitro studies presented give information about putative mechanisms of action of the tested compounds, but do not allow the conclusion that they are carcinogenic after oral application in vivo..	Not applicable.
Page 4: Paragraph 2.3: Lines 60-62	Regarding to the mechanisms of action is stated that *binding of photo-activated furocoumarins to DNA has been extensively characterized (Loveday 1996). They have also been shown to interact with proteins, lipids in membranes, and ribosomes (Bordin 1999).* But it should be added that, due to this fact,	Not applicable.

[5] Fitzsimons, C.P. et al.: Synergistic carcinogenic potential of methotrexate and PUVA in psoriasis. Lancet 8318: 235-236 (1983)
[6] Harrist, T.J. et al. Chronic cutaneous effects of long-term psoralen and ultraviolet radiation therapy in patients with vitiligo. Natl. Cancer Inst. Monogr. 66: 191-196 (1984)
[7] Henseler, T.: Skin tumors in the European PUVA Study. Eight-year follow-up of 1,643 patients treated with PUVA for psoriasis. J. Am. Acad. Dermatol. 16: 108-116 (1987)
[8] Lassus, A. et al.: PUVA treatment and skin cancer: A follow-up study. Acta Derm. Venerol. 61: 141-145 (1981)
[9] Lim JL, Stern RS. High levels of ultraviolet B exposure increase the risk of non-melanoma skin cancer in psoralen and ultraviolet A-treated patients. J Invest Dermatol. 124: 505-13 (2005)

SPECIFIC COMMENTS ON TEXT, page 4 of 7		
	carcinogenic effects are linked to phototoxic effects[4]. Phototoxic effects have never been reported over the long time herbal preparations from Angelica have been used, which leads to the conclusion that also carcinogenic effects do not occur.	
Page 4: Paragraph 2.4: Lines 64-66	*The PUVA treatment of humans is known to be associated with acute or delayed skin reactions and also skin cancer as a late sequela (IARC 1986).* Whereas PUVA treatment is of course associated with acute or delayed skin reactions, which are the aim of therapy, the question, under which conditions PUVA induces skin cancer, is under debate, according to newer data[4], which should be stated here. This applies also to the question of slight immunotoxicity triggered by highly dosed PUVA. In both cases, such effects have never been observed with herbal preparations from Angelica, which contain significantly less active furocumarins in very much lower amounts.	Not applicable.
Page 4: Paragraph 2.4: Lines 67-83	The statement that *there is a clear consensus on the basis of several large cohort and case-control studies that PUVA treatment causes squamous cell skin cancer in a dose- and time-dependent fashion* does not take into account several studies questioning a correlation between PUVA and squamous skin cell cancer[5,6,7,8,9], and at least point to a lack of such an effect after application of low doses[10], so that the "rule of thumb" has to be questioned and is obviously irrelevant for risk estimation of low doses of the structurally different furocoumarins from herbal preparations, which can be compared to the doses from dietary sources, which have been rated as representing no additional cancer risk[4]. So, the assumption of a significant health risk of furocoumarins from herbal medicinal products is a mere allegation and lacks a relevant scientific background.	Not applicable.
Page 4-5: Paragraph 2.5: Lines 84-92	The SCCP opinion refers to external use of furocoumarins, not the oral intake of Angelica extract preparations. Since topical application would circumvent first-pass metabolism, the situations are not comparable. The corresponding lines should therefore be omitted.	Not applicable.
Page 5: Paragraph 2.5: Lines 93-102	With regard to the margin of exposure (MOE) approach of the European Food Safety Authority Scientific Committee (EFSA SC) is stated, that *the MOE approach would lead to a very low acceptable exposure to furocoumarins.*	Not applicable.

[10] Müller, L. et al.: Photochemical genotoxicity and photochemical carcinogenesis - two sides of a coin? Toxicol. Lett. 102-103: 383-387 (1998)

SPECIFIC COMMENTS ON TEXT, page 5 of 7		
	The recommendation of the MOE approach by the scientific committee of the EFSA relates to toxic impurities where there is no threshold condition, and not for active components from medicines, which can not be rated as impurities. In case of the furocoumarins from Angelica archangelica, also the lack of a risk resulting from the usual dietary sources and medicinal plants should be taken into account. *Recently a framework of thresholds for toxicological concern (TTC) has been suggested for potentially genotoxic and carcinogenic impurities of pharmaceuticals (...). Although constituents of herbal medicinal products are not 'impurities', this approach may offer an approach to deal with the present case.*	
Page 5: Paragraph 2.5: Lines 103-107	The TTC approach refers to impurities for which any contact is to be avoided as far as possible. Furocoumarins from medicinal plants do not qualify as impurities, as they are part of the extract as the active ingredient of preparations, so that a risk/benefit evaluation is necessary. This is underlined by the conclusions from the above mentioned risk evaluations[1,2,3,4] which lead to the conclusion that limiting the exposure to furocoumarins from Angelica extracts cannot be expected to have any positive effect on the consumers' health.	Not applicable.
Page 5: Paragraph 2.5: Lines 108-117	As another approach for risk assessment, the standard uncertainty (safety) factor approach is mentioned, and even, as an exercise, a calculation is conducted with the intention to serve *as an illustration for potential exposures.* A reply to this is, that the standard safety factor approach is only rated to be standard for environmental toxins without pharmacological benefit, and for which contact is to be avoided as far as possible. In addition, this method would require the detection of a signal for a potential risk with the dose and application form of the corresponding preparation. A dose reduction calculated from the effects of pure and isolated compounds applied to herbal extracts would lead to ineffective doses. As long as there is no known toxicity implied in the use of an extract matrix, the safety factor approach cannot be applied to single constituents in medicinal plant preparations. The statement of uncertainty with respect to the threshold of carcinogenicity is misleading, since, contrary to the previous assessments, it implies phototoxicity/photocarcinogenicity at any dose of furocoumarins, which is	Not applicable.

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	clearly contradicting scientific data[4].	
Page 5: Paragraph 3: Lines 123-128	The conclusion begins with the statement, that *Angelica archangelica L. contains a number of constituents including furocoumarins, which are implicated as posing health risks in humans. Furocoumarins are photogenotoxic and photocarcinogenic and pose a clear hazard to human health in this respect.* This conclusion refers to the use of 8-MOP in high doses in PUVA therapy, exceeding 30 mg/day in combination with UV irradiation, but not to quantities of furocoumarins, as taken up from herbal preparations, which are non comparable with regard to their phototoxic potency. Potential health risks are implicated with PUVA, but not with the use of Angelica preparations. If for a typical Angelica tincture a furocoumarin concentration not above 1 mg/ml and a daily dose of 1.5 ml is assumed, this results in a daily intake of furocoumarins of maximally 1.5 mg. This is well in the range of dietary furocoumarin intake, and far below potentially phototoxic doses known from the application of 8-MOP. The difference is even more significant due to the much lower phototoxic potential of Angelica furocoumarins, compared with 8-MOP.	Not applicable.
Page 5: Paragraph 3: Lines 130-133	As already stated, the TTC approach is a tool for the avoidance of toxic impurities and not suitable for application to herbal medicinal preparations. Its use in risk assessment of herbal medicinal preparations has never been demonstrated or even scientifically discussed. The paragraph does not add anything substantial to the risk assessment of Angelica preparations and should therefore be deleted.	Not applicable.
Page 5-6: Paragraph 3: Lines 134-140	*The highest TTC dose of 120 µg cannot be considered acceptable, because it is applicable for treatments of less than one month and is thus too high for expected intermittent exposures with different herbal preparations that contain furocoumarin derivatives lasting a significant portion of adult life. On the other hand, life-time exposure, for which a maximum daily TTC dose of 1.5 µg might be considered, is not likely to reflect the current use of herbal medicinal products. Therefore, an daily intake for total furocoumarins in a herbal medicinal preparation that is equal or below 15 µg would not be considered to pose an unacceptable risk to consumers.* The dose limits of 120 and of 1.5 µg, as proposed, are both completely unrelated to the pharmacological properties of the compound under discussion. In addition, the increase by the factor of 10 to a limit of 15 µg proposed by the HMPC is	Not applicable.

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	arbitrary. Before the background of an average daily intake of furocoumarins in a range of 1.4 mg, and a phototoxic threshold dose of 8-MOP not below 14 mg, a dose limit for the structurally different and, according to scientific data[4], less potent furocoumarins from Angelica preparations cannot be expected to make a relevant contribution to consumer and patient safety and seems not appropriate. The recommendation of a calculation of all detectable furocoumarins on a molar basis as 8-methoxypsoralen does not take into account, that the molecular weights of several of the compounds involved are not yet known, therefore the practical applicability of this approach is not given. Taken together, the conclusions are based on extrapolations instead of a thorough analysis of the existing scientific data. They would result in a ban of herbal preparations from Angelica archangelica L. used by patients, without any reduction of health risks, and should therefore replaced by a sound risk/benefit evaluation, based on all available scientific data.	
Page 6: Paragraph 4: Lines 144-172	In the reference list important actual references are lacking, which would have permitted a more sound and reliable scientific evaluation.	

KOOPERATION PHYTOPHARMAKA GbR

Comments on the DRAFT EMEA Reflection Paper on the risks associated with furocoumarins contained in preparations of *Angelica archangelica* L.

The paper is intended to be used by the national competent authorities for the assessment of the safety of herbal preparations containing *Angelica archangelica* and of other herbal products containing furocoumarins with a phototoxic potential.

The paper focuses on coumarin derivatives, as these compounds are most relevant for possible phototoxic reactions, especially on psoralen, 8-methoxypsoralen and 5-methoxypsoralen as well as on the less important angular furocoumarins as angelicin (isopsoralen) and its derivatives.

As model substances for risk assessment 8-methoxypsoralen (8-MOP) and 5-methoxypsoralen (5-MOP) are taken instead of the constituents of *Angelica archangelica,* as these substances are comparatively well studied.

8-MOP is used in combination with UV A radiation for PUVA treatment of psoriasis. Under these conditions erythema occurred at apparent threshold blood concentrations of 30-50 ng/ml (corresponding to an intake of 120μg-200μg/men). This threshold is probably connected with the first-pass metabolism in the liver, which is saturated at higher doses and only under these conditions furocoumarins reach the general circulation in an amount sufficient to induce phototoxicity.

Both furocoumarins (8-methoxypsoralen (8-MOP) and 5-methoxypsoralen (5-MOP)) are regarded as human carcinogens on the basis of phototoxic reactions, though the level of evidence is more pronounced for 8-MOP. For angelicin and its derivatives there is only limited evidence for a cancer risk.

Two risks have to be discussed for furocoumarins:

1.) The risk of a direct carcinogenicity as it was described in the report of the National Toxicology Program of the National Institute of Health of The American Government (1989) on the toxicology and carcinogenesis studies of 8-methoxypsoralen. In a DFG Report on the toxicology of furocoumarins a nephrotoxic and cancerogenic activity of 8-MOP in male F344/N rats was mentioned based on this investigation which was observed even in a dose of 37.5 mg/kg b.w./d.

Comparable results of carcinogenic effects in the kidneys of male F344/N rats were obtained e.g. with limonene and eugenol, effects which could not be confirmed in

other rat strains. The nephrotoxicity of limonene as that of 8-MOP or eugenol proved to be a consequence of an increased formation of $\alpha_{2\mu}$-globuline in the liver which accumulates in the kidneys. The protein is formed under androgenic control, its production is maximum at an age of 60-80 days. As a result of the cytotoxicity of the $\alpha_{2\mu}$-globuline accumulation in the kidneys, an increased turnover in the epithelium of the kidney takes place first, as a long-term effect carcinogenicity results. Thus hints on carcinogenicity obtained in male rats of this specific strain could not be confirmed in other rat strains. This is a strain, sex and age-specific process which has also been observed for a considerable number of further substances (Dill et al, 2003, Doi et al 2004, Turner et al, 2001).

The carcinogenicity of 8-MOP was studied in Cynomolgus monkeys (*Macaca fascicularis*). The monkeys were treated orally for 26 weeks on three days a week with 2, 6, or 18 mg/kg bw. Emesis was observed at doses above 3 times/6 mg/kg/week not at lower doses. The only histopathological finding was a proliferation of Kupffer cells. No hints on carcinogenic effects were obtained, which confirms the data from clinical application in man.

The pharmakokinetics of 8-methoxypsoralen proved to be non linear with a saturation at higher doses (above 3x2 mg/kg/week). At a dose of 3x2 mg/kg/week an increased clearance was obvious, which was explained as the consequence of a saturable first pass effect and of a supposed enzyme induction (Rozman et al, 1989).

To summarize: A direct carcinogenic effect of furocoumarins was not shown.

2.) Anyway the main risk adressed in the paper of the EMEA is the phototoxicity of furocoumarins. In the presence of ultraviolet radiation the toxicity of these substances is clearly enhanced.

Moreover in vitro 5- and 8-MOP are only weakly mutagenic in the absence of UV-light, in combination with UVA radiation in different test systems genotoxic and mutagenic effects were shown (SKLM 2006). This might be due to differences in the type of reaction with the DNA: In the dark 5- MOP and 8-MOP form noncovalent complexes with DNA, whereas in the presence of light covalent binding to DNA was observed.

A direct mutagenic effect in vivo - formation of mikronuclei - was shown for 8-MOP after oral application of 300 and 600 mg/kg b.w without UV radiation.

The in vitro data cited showing mutagenic effects of 5-MOP and 8-MOP are irrelevant as contradictory in vivo data were obtained.

For doses below these very high doses of furanocoumarins phototoxic reactions seem to be a prerequisite for DNA damage. Erythema occur at the same or even lower doses than genotoxic effects. Thus doses lower than a phototoxic 'threshold dose' are likely to represent a negligible additional cancer risk. This does also mean that an enhanced genotoxic or carcinogenic risk due to furocoumarin intake can be assumed to be always indicated by the previous occurrence of erythema, so that overlooking of genotoxic effects of preparations from *Angelica archangelica*, if there were any, does not seem to be a realistic risk.

As threshold doses above which phototoxic effects in humans occur, 14 mg/adult 8-MOP, for a combination of 5-MOP and 8-MOP 10 mg of each/adult were determined. This can be explained by the clear dose-dependent first pass metabolism: The pharmakokinetics of 8-methoxypsoralen proved to be nonlinear with a saturation at higher doses (above 3x2 mg/kg/week). That means at lower doses only very small amounts of the furanocoumarins will reach the general circulation.

Obviously the bioavailibility after intake of plant material is much worse than that of the pure compounds. Following the intake of even 500 g celery by each volunteer neither psoralens could be identified at any time in plasma nor phototoxic reactions could be detected following using the minimal phototoxic doses method (Gral et al (1993).

A further wrong assumption from the HMPC draft is that the spectrum of all furocoumarins in Angelica can be considered to be equipotent to 8-MOP. This is in contrast to both reviews dealing with possible risks of furocoumarins in food (COT, 1996, SKLM 2006).

The conclusions of the draft are not regarded to be justified: the calculation of a theoretical risk never seen is not justified from the data. From our point of view a theoretical extrapolation does not take into account the occurrence of furocoumarins in food and the fact that they do not pose a relevant risk to the consumer (SKLM 2006).

Furthermore the evaluation of furocoumarins in cosmetic products cannot be used for a risk assessment following systemic exposure. As mentioned above, lower doses of psoralens are metabolised to a large amount already by first pass metabolism and thus do not reach the systemic circulation and the skin in amounts comparable to an exposition by an external use. The limit of 15 µg furocoumarins per daily dose is therefore not considered relevant for the oral intake of plant preparations containing furocoumarins.

As a conclusion, it seems unnecessary and scientifically not justified to define such a limitation for the furocumarin content of herbal medicinal products.

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COMMENTS FROM

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COMMENTS TO THE DRAFT

Reflection Paper on the risks associated with furocoumarins contained in preparation of Angelica archangelica L. Doc. Ref. EMEA/HMPC/317913/2006

Aims

With the "Reflection paper on the risks associated with furocoumarins contained in preparation of Angelica archangelica L." (EMEA/HMPC/317913/2006) the Herbal Medicinal Products Committee called for comments in the consultation process. On closer examination of the topic, the proposed action would not seem appropriate, since various recent official statements have not attributed any toxicological relevance regarding quantities of furocoumarins as regularly taken in. This intake derives mainly from the diet. Furocoumarins from Angelica archangelica cannot be expected to make a significant contribution to that overall daily intake. Thus, the proposal of reducing the furocoumarin content of Angelica archangelica preparations to 15 µg in the daily dose on the on hand would not imply an improvement of patient safety with regard to furocoumarins exposure. On the other hand, the HMPC's conclusion of furocoumarins from Angelica archangelica posing a health risk is not endorsed by relevant scientific data. It is based on a theoretically assumed hazard, which does not exist according to existing scientific data, so that the use of methods of calculation based on typical approaches for toxic impurities is not adequate and gaining entirely arbitrary and thus unacceptable results.

The following comments will follow the line of arguments presented in the HMPC's reflection paper. They are based on the results of official statements regarding the toxicological relevance of furocoumarins from various national authorities such as the FDA, the UK Department of Health, the Swiss Federal Office of Public Health (Division of Food Science), and, most recently, the Senate Commission of the German Research Community (DFG) (Anon 1996; Eisenbrand 2006; Schlatter et al. 1991; Wagstaff 1991), and have in all cases led to the conclusion that typical dietary quantities of furocoumarins, to which the uptake with herbal medicines does not contribute in a relevant way, do not impose a relevant health risk. As these statements – the most recent and rather exhaustive treatment of the topic was published by the Senate Commission of the DFG in 2006 (Eisenbrand 2006) - include all relevant literature, it is thus not necessary to repeat in details all references. The following conclusions are based on the actual literature in that field, which has been used for this risk assessment.

HMPC Reflection Paper:

1. Introduction (Background)

"The reflection paper focuses on coumarin-derivatives present in Angelica archangelica L., as these substances are the most relevant constituents for phototoxicity."

A major misunderstanding of the reflection paper refers to this point. Whereas Angelica archangelica indeed contains furocoumarins, the paper essentially refers to the phototoxicity of 8-methoxy-psoralen (8-MOP), which, however, even if contained in Angelica preparations at all, is only one minor component of them. It also refers to doses of the pure compound 8- MOP used in psoralen plus UVA radiation (PUVA) therapy, whereas Angelica archangelica preparations, even in combination with dietary sources of furocoumarins and on gross overdosing, can not be expected to lead to any critical doses of furocoumarins that may represent a relevant potential for phototoxicity – and much less so for mutagenicity and carcinogenicity.

Thus, the reflection paper is a priori based on a conclusion not in accordance with scientific data.

The analyses of the reflection paper lead to incorrect conclusions since they did not even include the comprehensive scientific knowledge about dietary furocoumarins from sources like parsnip, celery and citrus fruits, and which has been extensively discussed also regarding the point of metabolic detoxification. In fact, it is known that the human body has efficient means to cope with quantities of furocoumarins in a range at least 10,000 times higher than the limit proposed by the HMPC for Angelica archangelica, in view of regular daily intakes of approximately 1.5 milligrams of furocoumarins per day, and peak values of 14-15 mg per day. These are figures proposed by the above mentioned official assessments of the potential hazards of dietary furocoumarins.

In addition, the high doses of psoralens needed for oral PUVA therapy are known to be required because of the capacity of the human organism to metabolize amounts in the range of the typical dietary intake. The minimum quantity of 8-methoxypsoralen to induce skin effects in combination with UV light is a minimum of 0.6 mg/kg body weight. The HMPC itself points to the fact that the metabolic fate of furocoumarins has to be taken into consideration. Generally, this topic is not new for furocoumarins. With the fact of metabolic transformation known since long and with various official assessments stating that no danger is to be expected from typical dietary quantities of furocoumarins, it can be concluded that the natural content of furocoumarins in Angelica archangelica does not pose a relevant risk at all for its application in phytomedicine.

2. Safety evaluation of furocoumarins

The approach used by the HMPC would only be understandable if there would be any hint for a toxicological or carcinogenic hazard implied by the use of Angelica archangelica preparations. Due to the molecular mechanisms involved in the mechanisms of action of furocoumarins and according to epidemiologic data (Eisenbrand 2006), the potential photogenotoxic and carcinogenic effects of furocoumarins are linked to phototoxic effects (erythema). So, if there were any relevant mutagenic or carcinogenic effects of Angelica, they would be connected to phototoxic effects and so be easily observed. But there are no descriptions of or hints on phototoxic effects of phytomedicines containing Angelica extracts in the medicinal and scientific literature. So, the HPMC's proposed rating of the furocoumarins in phytomedicines containing Angelica archangelica as hazardous has two major shortcomings:

a) Since there is no hint on any mutagenic or carcinogenic effect of the quantities and types of furocoumarins in Angelica archangelica preparations, a rating of the toxicity of the furocoumarins in Angelica on the base of the level of the compound with the highest known toxicological potential, 5-MOP (Eisenbrand 2006) would automatically lead to an overestimation of the toxic potential of the majority of the Angelica furocoumarins.

b) Potential hazardous effects of furocoumarins are connected to phototoxicity (erythema) and would so easily have been recognized, if they would ever have occurred.

2.1 Phototoxicity of furocoumarins

The following statement in the concept paper does not support conclusions on a potential hazard arising from oral intake of furocoumarins from natural sources as Angelica preparations: "*Long term PUVA treatment with 8-MOP can cause persistent pigmentation and other skin changes. Erythema occurred at apparent threshold blood concentrations of 30 - 50 ng/ml. It is possible that this threshold may be connected with the first-pass metabolism of 8-MOP in the liver before reaching the general circulation. Saturation of this metabolism probably occurs at clinically used PUVA doses.*"

The role of first pass metabolization for the availability of furocoumarins in the peripheral blood circulation was already addressed above. Scientific data allow the conclusion, that phototoxic furocoumarins reach the peripheral circulation only in doses as high as those used in PUVA therapy, which by far surpass the usual dietary or medicinal plant related intake of furocoumarins (for an average adult of 60 kg a dose of 60 x 0.6 = 36 mg psoralen is required in PUVA therapy, which is 2.400 times more than the dose limit of 15 µg of total furocoumarins suggested by the HMPC for Angelica archangelica), there is no scientific base for the discussion of theoretical harms arising from quantities of furocoumarins the human organism is well adapted to.

In fact, the logic of the discussion is based on a potential carcinogenic effect of furocoumarins when used in dose ranges exceeding the human metabolic capacities. Only then furocoumarins may have phototoxic effects (which is the mechanism of PUVA therapy), and only then mutagenicity or carcinogenicity may become a potential problem – the human genetic repair mechanisms not withstanding. This has the consequence, that the approaches of risk assessment discussed hereafter

(Margin Of Exposure/MOE and Threshold of Toxicological Concern/TTC) are not applicable to quantities by far below the threshold of metabolic capacities.

2.2 Carcinogenic potential of furocoumarins

The HMPC cites the conclusions of the IARC from 1986 stating that 8-methoxypsoralen and probably (at a lesser degree) also 5-methoxypsoralen are potential carcinogens. This property as well as the mechanism outlined in section 2.3 is undisputed; however, the HMPC's statement dose not take into account the dose dependency of the effect. As already mentioned, the phototoxic and (as a consequence of the phototoxic mechanism) mutagenic effects only become apparent on exceeding the metabolic capacities of the human organism, which is not to be expected with the usual dietary intake of furocoumarins, and even less so with phytomedicinal preparations from Angelica archangelica.

2.4 Human toxicity

The following assumption in the HMPC consensus paper is not correct: *"There is a clear consensus on the basis of several large cohort and case-control studies that PUVA treatment cause squamous cell skin cancer in a dose- and time-dependent fashion, relative risks being about roughly from 6- to 12-fold after about 8-10 years follow-up."*

In deed, there is no consensus that PUVA treatment is correlated with an increased risk of squamous skin cell cancer. Data from European sources do not show this correlation (Fitzsimons et al. 1983; Harrist et al. 1984; Henseler et al. 1987; Lassus et al. 1981), and point to potential confounders in life style and deliberate exposition to sunlight between the United States and Europe. Whereas it still appears prudent to be vigilant when it comes to PUVA treatment, it has again to be stressed that the intake of Angelica archangelica preparations cannot be equalized with PUVA treatment. The data stated by the HMPC does explicitly **not** refer to dietary or herbal medicinal sources and quantities of furocoumarins. E.g., a publication by the German BfArM from 1998 used by the HMPC to stress the point of a potential danger inherent in the intake of Angelica preparations in fact pointed to potential cancer risk from 8-methoxypsoralen only in long term highly dosed intake combined with UV irradiation (Müller et al. 1998). Consequently, this publication can not be the basis of the assumption that low quantities of structurally mostly different furocoumarins may have a carcinogenic effect because high quantities of 8-methoxyopsoralen and long exposures to this compound combined with UV light may have such an effect.

2.5 Various considerations for risk assessment purposes

The conclusion regarding herbal medicines in the following statement in the concept paper is clearly not in accordance with scientific data and published evaluations of regulatory bodies: *"Photogenotoxicity and photocarcinogenicity are the most important toxic outcomes of furocoumarins from the risk assessment point of view (Muller et al 1998). These phenomena can be best described as co-carcinogenic conditions and it is not known for sure whether they should be interpreted as threshold or non-threshold conditions. Because the formation of phototoxic agents is an essentially physicochemical phenomenon, it is prudent to assume that it occurs equally in humans and experimental animals. Consequently, at least some furocoumarins have to be regarded as posing genotoxic and carcinogenic hazard to humans and exposure to furocoumarins from herbal preparations may pose a significant health risk to humans."*

The line of arguments on which the assumption of a potential carcinogenicity of furocoumarins from Angelica archangelica is based on is not consistent with the bibliographic sources (Anon 1996; Eisenbrand 2006; Schlatter et al. 1991; Wagstaff 1991). Whereas it is correct that co-carcinogenic conditions are indeed not necessarily threshold conditions, this general statement is not applicable to the specific situation with furocoumarins – neither for 8-methoxypsoralen in PUVA therapy nor for dietary furocoumarins. Both are clearly threshold conditions, with the consequence that the dietary intake of furocoumarins from vegetables and fruits does not implicate a relevant risk of phototoxicity and carcinogenicity.

It is undenied that mutagenicity can be experimentally triggered by some furocoumarins when combined with UV irradiation, and since PUVA therapy is based on phototoxicity of 8-methoxypsoralen, no assumption needs to me made that furocoumarins in sufficiently high doses and combined with UV irradiation do in fact cause photoreactions. However, there is no similarity between the known dose-related phototoxicity of 8-methoxypsoralen in PUVA therapy and the ingestion of

dietary/phytotherapeutic quantities of furocoumarins in doses not surpassing the metabolic capacities and without additional UV irradiation. Thus, the first part of the consequence drawn by the HMPC is common knowledge: Some furocoumarins must be indeed regarded as genotoxic and potentially carcinogenic compounds – if taken in sufficiently high quantities and if combined with therapeutic UV irradiation. The second part of the conclusion is, however, unrelated to the first, and not in accordance with actual scientific knowledge.

SCCP recommendation for furocoumarin-containing cosmetics

The recommendation of the SCCP of limiting the furocoumarin content in cosmetics to 1 ppm is irrelevant for the discussion of the potential health risk of Angelica archangelica preparations. The products covered by this SCCP recommendation are for topical use only, and in addition are meant for an application not aimed at a therapeutic benefit. Topical application is not comparable with oral intake, leading to high local concentrations not achievable by oral intake, and especially since oral intake leads to a first pass effect, which explains the quick and potent metabolization of dietary of phytotherapeutic furocoumarins.

The MOE approach, as suggested by the scientific committee of the EFSA for genotoxic and carcinogenic compounds was proposed for toxic impurities, especially for compounds where there is no threshold condition. This approach is not applicable to the properties and quantities of furocoumarins from Angelica archangelica:

- The quantities of furocoumarins ingested with preparations from Angelica archangelica do not surpass or even relevantly contribute to the quantities regularly ingested with the diet.
- Furocoumarins from dietary sources, as well as from herbal extracts as active constituents of phytomedicines, cannot be treated as avoidable impurities. Likewise, they are part of the herbal matrix in the case of Angelica archangelica. Any extraction method aimed on a reduction of furocoumarin contents may influence the therapeutic efficacy of the total extract. As there are no scientific data pointing to a risk arising from Angelica extracts as commonly used in therapy, this would have a negative impact on the risk-benefit ratio of these extracts.

The TTC approach also suggested by the HPMC is likewise not applicable, since it exclusively refers to impurities for which any contact is to be avoided as far as possible. The HMPC itself grants that "*constituents of herbal medicinal products are not 'impurities'*", but nevertheless applied this approach to Angelica archangelica.

Again, it is to be stressed that furocoumarins from medicinal plants or dietary sources are not avoidable impurities. In medicinal use, they are part of the total extract and may even contribute to the overall effect. In the diet, they are likewise unavoidable and potentially could even be beneficial for of the body's defence mechanism, in analogy to the polyphenols. Beneath these assumptions two things are clear:

- Whereas the concept paper points to hypothetical risks arising from trace amounts of furocoumarins from herbal medicinal products, nothing is known about the effect of a complete avoidance of dietary furocoumarins on the human health.
- If the furocoumarins from Angelica archangelica were really reduced to the proposed daily dose of 15 µg (or even 1.5 µg according to the TTC approach), the dietary contribution fro regular foodstuff such as celery, fennel, parsnips, oranges, grapefruit or lemons (just to mention a few) would still be present. A regulatory action against the amounts present in Angelica extracts would thus have not the slightest effect on assumed patient safety.

In addition, the exemplary TTC calculation of a low level of cancer risk with 30 µg of 8-methoxy-psoralen in PUVA therapy simply neglects the fact that such a concentration might be safe, but not efficacious, and that the regular daily intake of furocoumarins is approximately 50 to 500 times higher and – according to actual assessments - without any toxicological relevance.

3. CONCLUSIONS of the concept paper

"Angelica archangelica L. contains a number of constituents including furocoumarins, which are implicated as posing health risks in humans."

This conclusion refers to the use of 8-methoxypsoralen in high doses in PUVA therapy. But it is not true to the furocoumarin doses regularly ingested from dietary sources or medicinal plants.

"Furocoumarins are photogenotoxic and photocarcinogenic and pose a clear hazard to human health in this respect. A significant exposure via herbal preparations would occur to furocoumarins and consequently a risk to human health should be assessed."

Whereas the first part of this statement again refers to pure 8-methoxypsoralen in doses exceeding 30 mg/day in combination with UV irradiation, it is unrelated and incorrect in the second part. A risk of dietary furocoumarins has been excluded by several actual scientific assessments on the base of the complete scientific knowledge regarding this class of compounds, and the quantities applied with herbal medicinal products do not make relevant contributions that might exceed doses for which any relevant impact on cancer risk can be excluded.

"The risk assessment for preparations of Angelica archangelica L. that contain furocoumarin derivatives may be based on the assumptions that recently suggested thresholds for toxicological concern (TTC) for potentially genotoxic and carcinogenic impurities can be applied in this case also for herbal medicinal products."

The applicability of the method of risk assessment developed specifically for toxic impurities or environmental toxins on extract matrices from herbal medicinal products has never been demonstrated or even scientifically discussed. The assumption that such an approach may be applied to herbal medicinal products is in contrast to generally accepted scientific practice in toxicology.

"The highest TTC dose of 120 µg cannot be considered acceptable, because it is applicable for treatments of less than one month and is thus too high for expected intermittent exposures with different herbal preparations that contain furocoumarin derivatives lasting a significant portion of adult life. On the other hand, life-time exposure, for which a maximum daily TTC dose of 1.5 µg might be considered, is not likely to reflect the current use of herbal medicinal products. Therefore, a daily intake for total furocoumarins in a herbal medicinal preparation that is equal or below 15 µg would not be considered to pose an unacceptable risk to consumers."

The proposed upper dose limit of 120 µg and the lower limit of 1.5 µg are both related to toxic impurities and completely unrelated to the pharmacological properties of the compound under discussion, and not suitable for the risk assessment of natural compounds in an herbal extract matrix. In addition, the increase by a factor of 10 to a limit of 15 µg proposed by the HMPC is arbitrary. If a safe level of a given impurity could only be reached with 1.5 µg/day, there would be no reason to raise this limit to 15 µg. If, however, the limit of 1.5 µg does not reflect the current use of herbal medicinal products or other sources of furocoumarin intake – the same argument would apply to the chosen limit of 15 µg. In fact, the average daily dietary intake of furocoumarins has been rated as 1.5 milligram (not microgram), and found to be safe up to 15 milligram. Thus, if for the current use of herbal medicinal products, it should also allow for dietary realities. Accordingly, there is no reason for concern with quantities in the range of 1.5 mg – a dose which herbal medicinal products cannot be expected to relevantly exceed or even to reach.

This should be ascertained on the basis of the analysis of the contents of the actual herbal medicinal preparation, calculating all detectable furocoumarins as 8-methoxypsoralen on a molar basis.

Even the assessment of all furocoumarins from Angelica archangelica as 8-methoxypsoralen, which would lead to a clear overestimation of the risk potential for Angelica archangelica, would not justify the proposed dose limits, since the quantities of furocoumarins applied with Angelica products are not in ranges above the dietary total intake and so, according to actual state of scientific knowledge, without toxicological relevance. A calculation of furocoumarins as 8-methoxypsoralen on a molar basis would not increase consumer safety, but lead to unnecessary confusion.

Overall conclusions and summary

The reflection paper of the HMPC is entirely based on the assumption that the known risk potential of pure and highly dosed 8-methoxypsoralen in PUVA therapy may be extrapolated to the content of furocoumarins as a fraction of the constituents in herbal medicinal products. However, the reflection paper does not take into account the actual state of scientific knowledge regarding the toxicological relevance of oral furocoumarins intake and does not give any evidence that such an approach is rational, or that any risk potential other than a theoretical extrapolation is involved in the use of Angelica archangelica preparations. Such an extrapolation should, however, be avoided according to

the recent "Concept paper on the development of a guideline on the assessment of genotoxic constituents in herbal substances/preparations" in cases where there is only a theoretically possible risk (HMPC 2006).

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Additional commentary

It is so relevant to comment this concept paper not merely with respect to Angelica archangelica, but as the new approach, which was applied by the HMPC in this case, can hit almost any other herb used in phytomedicine, with the consequence of a ban of its therapeutic use. The approach is:

1. Defining a phytochemical component out from that herb, for which chemically related substances with known toxicity/mutagenicity/genotoxicity in (even extremely) high doses is known.
2. Defining a maximum limit, which is a factor of e.g. 10,000 lower than these doses, for the intake of that herb, so making its therapeutic use impossible.

So for virtually any, otherwise untoxic herb, a ban due to toxicological reasons can result.

Poznań 15th May 2007

European Medicines Agency

SUBMISSION OF COMMENTS ON Reflection paper on the risks associated with furocoumarins contained in preparation of Angelica archangelica L. (EMEA/HMPC/317913/2006)

COMMENTS FROM

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GENERAL COMMENTS

Aims

With the "Reflection paper on the risks associated with furocoumarins contained in preparation of Angelica archangelica L." (EMEA/HMPC/317913/2006) the Herbal Medicinal Products Committee called for comments in the consultation process. On closer examination of the topic, the proposed action would not seem appropriate, since various recent official statements have not attributed any toxicological relevance regarding quantities of furocoumarins as regularly taken in. This intake derives mainly from the diet. Furocoumarins from Angelica archangelica cannot be expected to make a significant contribution to that overall daily intake. Thus, the proposal of reducing the furocoumarin content of Angelica archangelica preparations to 15 µg in the daily dose on the on hand would not imply an improvement of patient safety with regard to furocoumarins exposure. On the other hand, the HMPC's conclusion of furocoumarins from Angelica archangelica posing a health risk is not endorsed by relevant scientific data. It is based on a theoretically assumed hazard, which does not exist according to existing scientific data, so that the use of methods of calculation based on typical approaches for toxic impurities is not adequate and gaining entirely arbitrary and thus unacceptable results.

The following comments will follow the line of arguments presented in the HMPC's reflection paper. They are based on the results of official statements regarding the toxicological relevance of furocoumarins from various national authorities such as the FDA, the UK Department of Health, the Swiss Federal Office of Public Health (Division of Food Science), and, most recently, the Senate Commission of the German Research Community (DFG) (Anon 1996; Eisenbrand 2006; Schlatter et al. 1991; Wagstaff 1991), and have in all cases led to the conclusion that typical dietary quantities of furocoumarins, to which the uptake with herbal medicines does not contribute in a relevant way, do not impose a relevant health risk. As these statements – the most recent and rather exhaustive treatment of the topic was published by the Senate Commission of the DFG in 2006 (Eisenbrand 2006) - include all relevant literature, it is thus not necessary to repeat in details all references. The following conclusions are based on the actual literature in that field, which has been used for this risk assessment.

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HMPC Reflection Paper:

1. Introduction (Background)

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A major misunderstanding of the reflection paper refers to this point. Whereas Angelica archangelica indeed contains furocoumarins, the paper essentially refers to the phototoxicity of 8-methoxy-psoralen (8-MOP), which, however, even if contained in Angelica preparations at all, is only one minor component of them. It also refers to doses of the pure compound 8- MOP used in psoralen plus UVA radiation (PUVA) therapy, whereas Angelica archangelica preparations, even in combination with dietary sources of furocoumarins and on gross overdosing, can not be expected to lead to any critical doses of furocoumarins that may represent a relevant potential for phototoxicity – and much less so for mutagenicity and carcinogenicity.

Thus, the reflection paper is a priori based on a conclusion not in accordance with scientific data.

The analyses of the reflection paper lead to incorrect conclusions since they did not even include the comprehensive scientific knowledge about dietary furocoumarins from sources like parsnip, celery and citrus fruits, and which has been extensively discussed also regarding the point of metabolic detoxification. In fact, it is known that the human body has efficient means to cope with quantities of furocoumarins in a range at least 10,000 times higher than the limit proposed by the HMPC for Angelica archangelica, in view of regular daily intakes of approximately 1.5 milligrams of furocoumarins per day, and peak values of 14-15 mg per day. These are figures proposed by the above mentioned official assessments of the potential hazards of dietary furocoumarins.

In addition, the high doses of psoralens needed for oral PUVA therapy are known to be required because of the capacity of the human organism to metabolize amounts in the range of the typical dietary intake. The minimum quantity of 8-methoxypsoralen to induce skin effects in combination with UV light is a minimum of 0.6 mg/kg body weight. The HMPC itself points to the fact that the metabolic fate of furocoumarins has to be taken into consideration. Generally, this topic is not new for furocoumarins. With the fact of metabolic transformation known since long and with various official assessments stating that no danger is to be expected from typical dietary quantities of furocoumarins, it can be concluded that the natural content of furocoumarins in Angelica archangelica does not pose a relevant risk at all for its application in phytomedicine.

2. Safety evaluation of furocoumarins

The approach used by the HMPC would only be understandable if there would be any hint for a toxicological or carcinogenic hazard implied by the use of Angelica archangelica preparations. Due to the molecular mechanisms involved in the mechanisms of action of furocoumarins and according to epidemiologic data (Eisenbrand 2006), the potential photogenotoxic and carcinogenic effects of furocoumarins are linked to phototoxic effects (erythema). So, if there were any relevant mutagenic or carcinogenic effects of Angelica, they would be connected to phototoxic effects and so be easily observed. But there are no descriptions of or hints on phototoxic effects of phytomedicines containing Angelica extracts in the medicinal and scientific literature. So, the HPMC's proposed rating of the furocoumarins in phytomedicines containing Angelica archangelica as hazardous has two major shortcomings:

a) Since there is no hint on any mutagenic or carcinogenic effect of the quantities and types of furocoumarins in Angelica archangelica preparations, a rating of the toxicity of the furocoumarins in Angelica on the base of the level of the compound with the highest known toxicological potential, 5-MOP (Eisenbrand 2006) would automatically lead to an overestimation of the toxic potential of the majority of the Angelica furocoumarins.

b) Potential hazardous effects of furocoumarins are connected to phototoxicity (erythema) and would so easily have been recognized, if they would ever have occurred.

2.1 Phototoxicity of furocoumarins

The following statement in the concept paper does not support conclusions on a potential hazard arising from oral intake of furocoumarins from natural sources as Angelica preparations: "*Long term PUVA treatment with 8-MOP can cause persistent pigmentation and other skin changes. Erythema occurred at apparent threshold blood concentrations of 30 - 50 ng/ml. It is possible that this threshold may be connected with the first-pass metabolism of 8-MOP in the liver before reaching the general circulation. Saturation of this metabolism probably occurs at clinically used PUVA doses.*"

The role of first pass metabolization for the availability of furocoumarins in the peripheral blood circulation was already addressed above. Scientific data allow the conclusion, that phototoxic furocoumarins reach the peripheral circulation only in doses as high as those used in PUVA therapy, which by far surpass the usual dietary or medicinal plant related intake of furocoumarins (for an average adult of 60 kg a dose of 60 x 0.6 = 36 mg psoralen is required in PUVA therapy, which is 2.400 times more than the dose limit of 15 µg of total furocoumarins suggested by the HMPC for Angelica archangelica), there is no scientific base for the discussion of theoretical harms arising from quantities of furocoumarins the human organism is well adapted to.

In fact, the logic of the discussion is based on a potential carcinogenic effect of furocoumarins when used in dose ranges exceeding the human metabolic capacities. Only then furocoumarins may have phototoxic effects (which is the mechanism of PUVA therapy), and only then mutagenicity or carcinogenicity may become a potential problem – the human genetic repair mechanisms not withstanding. This has the consequence, that the approaches of risk assessment discussed hereafter (Margin Of Exposure/MOE and Threshold of Toxicological Concern/TTC) are not applicable to quantities by far below the threshold of metabolic capacities.

2.2 Carcinogenic potential of furocoumarins

The HMPC cites the conclusions of the IARC from 1986 stating that 8-methoxypsoralen and probably (at a lesser degree) also 5-methoxypsoralen are potential carcinogens. This property as well as the mechanism outlined in section 2.3 is undisputed; however, the HMPC's statement dose not take into account the dose dependency of the effect. As already mentioned, the phototoxic and (as a consequence of the phototoxic mechanism) mutagenic effects only become apparent on exceeding the metabolic capacities of the human organism, which is not to be expected with the usual dietary intake of furocoumarins, and even less so with phytomedicinal preparations from Angelica archangelica.

2.4 Human toxicity

The following assumption in the HMPC consensus paper is not correct: *"There is a clear consensus on the basis of several large cohort and case-control studies that PUVA treatment cause squamous cell skin cancer in a dose- and time-dependent fashion, relative risks being about roughly from 6- to 12-fold after about 8-10 years follow-up."*

In deed, there is no consensus that PUVA treatment is correlated with an increased risk of squamous skin cell cancer. Data from European sources do not show this correlation (Fitzsimons et al. 1983; Harrist et al. 1984; Henseler et al. 1987; Lassus et al. 1981), and point to potential confounders in life style and deliberate exposition to sunlight between the United States and Europe. Whereas it still appears prudent to be vigilant when it comes to PUVA treatment, it has again to be stressed that the intake of Angelica archangelica preparations cannot be equalized with PUVA treatment. The data stated by the HMPC does explicitly **not** refer to dietary or herbal medicinal sources and quantities of furocoumarins. E.g., a publication by the German BfArM from 1998 used by the HMPC to stress the point of a potential danger inherent in the intake of Angelica preparations in fact pointed to potential cancer risk from 8-methoxypsoralen only in long term highly dosed intake combined with UV irradiation (Müller et al. 1998). Consequently, this publication can not be the basis of the assumption that low quantities of structurally mostly different furocoumarins may have a carcinogenic effect because high quantities of 8-methoxyopsoralen and long exposures to this compound combined with UV light may have such an effect.

2.5 Various considerations for risk assessment purposes

2.5 Various considerations for risk assessment purposes

The conclusion regarding herbal medicines in the following statement in the concept paper is clearly not in accordance with scientific data and published evaluations of regulatory bodies: *"Photogenotoxicity and photocarcinogenicity are the most important toxic outcomes of furocoumarins from the risk assessment point of view (Muller et al 1998). These phenomena can be best described as co-carcinogenic conditions and it is not known for sure whether they should be interpreted as threshold or non-threshold conditions. Because the formation of phototoxic agents is an essentially physicochemical phenomenon, it is prudent to assume that it occurs equally in humans and experimental animals. Consequently, at least some furocoumarins have to be regarded as posing genotoxic and carcinogenic hazard to humans and exposure to furocoumarins from herbal preparations may pose a significant health risk to humans."*

The line of arguments on which the assumption of a potential carcinogenicity of furocoumarins from Angelica archangelica is based on is not consistent with the bibliographic sources (Anon 1996; Eisenbrand 2006; Schlatter et al. 1991; Wagstaff 1991). Whereas it is correct that co-carcinogenic conditions are indeed not necessarily threshold conditions, this general statement is not applicable to the specific situation with furocoumarins – neither for 8-methoxypsoralen in PUVA therapy nor for dietary furocoumarins. Both are clearly threshold conditions, with the consequence that the dietary intake of furocoumarins from vegetables and fruits does not implicate a relevant risk of phototoxicity and carcinogenicity.

It is undenied that mutagenicity can be experimentally triggered by some furocoumarins when combined with UV irradiation, and since PUVA therapy is based on phototoxicity of 8-methoxypsoralen, no assumption needs to me made that furocoumarins in sufficiently high doses and combined with UV irradiation do in fact cause photoreactions. However, there is no similarity between the known dose-related phototoxicity of 8-methoxypsoralen in PUVA therapy and the ingestion of dietary/phytotherapeutic quantities of furocoumarins in doses not surpassing the metabolic capacities and without additional UV irradiation. Thus, the first part of the consequence drawn by the HMPC is common knowledge: Some furocoumarins must be indeed regarded as genotoxic and potentially carcinogenic compounds – if taken in sufficiently high quantities and if combined with therapeutic UV irradiation. The second part of the conclusion is, however, unrelated to the first, and not in accordance with actual scientific knowledge.

SCCP recommendation for furocoumarin-containing cosmetics

The recommendation of the SCCP of limiting the furocoumarin content in cosmetics to 1 ppm is irrelevant for the discussion of the potential health risk of Angelica archangelica preparations. The products covered by this SCCP recommendation are for topical use only, and in addition are meant for an application not aimed at a therapeutic benefit. Topical application is not comparable with oral intake, leading to high local concentrations not achievable by oral intake, and especially since oral intake leads to a first pass effect, which explains the quick and potent metabolization of dietary of phytotherapeutic furocoumarins.

The MOE approach, as suggested by the scientific committee of the EFSA for genotoxic and carcinogenic compounds was proposed for toxic impurities, especially for compounds where there is no threshold condition. This approach is not applicable to the properties and quantities of furocoumarins from Angelica archangelica:

- The quantities of furocoumarins ingested with preparations from Angelica archangelica do not surpass or even relevantly contribute to the quantities regularly ingested with the diet.
- Furocoumarins from dietary sources, as well as from herbal extracts as active constituents of phytomedicines, cannot be treated as avoidable impurities. Likewise, they are part of the herbal matrix in the case of Angelica archangelica. Any extraction method aimed on a reduction of furocoumarin contents may influence the therapeutic efficacy of the total extract. As there are no scientific data pointing to a risk arising from Angelica extracts as commonly used in therapy, this would have a negative impact on the risk-benefit ratio of these extracts.

The TTC approach also suggested by the HPMC is likewise not applicable, since it exclusively refers to impurities for which any contact is to be avoided as far as possible. The HMPC itself grants that *"constituents of herbal medicinal products are not 'impurities"*, but nevertheless applied this approach to Angelica archangelica.

Again, it is to be stressed that furocoumarins from medicinal plants or dietary sources are not avoidable impurities. In medicinal use, they are part of the total extract and may even contribute to the overall effect. In the diet, they are likewise unavoidable and potentially could even be beneficial for of the body's defence mechanism, in analogy to the polyphenols. Beneath these assumptions two things are clear:

- Whereas the concept paper points to hypothetical risks arising from trace amounts of furocoumarins from herbal medicinal products, nothing is known about the effect of a complete avoidance of dietary furocoumarins on the human health.
- If the furocoumarins from Angelica archangelica were really reduced to the proposed daily dose of 15 µg (or even 1.5 µg according to the TTC approach), the dietary contribution fro regular foodstuff such as celery, fennel, parsnips, oranges, grapefruit or lemons (just to mention a few) would still be present. A regulatory action against the amounts present in Angelica extracts would thus have not the slightest effect on assumed patient safety.

In addition, the exemplary TTC calculation of a low level of cancer risk with 30 µg of 8-methoxy-psoralen in PUVA therapy simply neglects the fact that such a concentration might be safe, but not efficacious, and that the regular daily intake of furocoumarins is approximately 50 to 500 times higher and – according to actual assessments - without any toxicological relevance.

3. CONCLUSIONS of the concept paper

"Angelica archangelica L. contains a number of constituents including furocoumarins, which are implicated as posing health risks in humans."

This conclusion refers to the use of 8-methoxypsoralen in high doses in PUVA therapy. But it is not true to the furocoumarin doses regularly ingested from dietary sources or medicinal plants.

"Furocoumarins are photogenotoxic and photocarcinogenic and pose a clear hazard to human health in this respect. A significant exposure via herbal preparations would occur to furocoumarins and consequently a risk to human health should be assessed."

Whereas the first part of this statement again refers to pure 8-methoxypsoralen in doses exceeding 30 mg/day in combination with UV irradiation, it is unrelated and incorrect in the second part. A risk of dietary furocoumarins has been excluded by several actual scientific assessments on the base of the complete scientific knowledge regarding this class of compounds, and the quantities applied with herbal medicinal products do not make relevant contributions that might exceed doses for which any relevant impact on cancer risk can be excluded.

"The risk assessment for preparations of Angelica archangelica L. that contain furocoumarin derivatives may be based on the assumptions that recently suggested thresholds for toxicological concern (TTC) for potentially genotoxic and carcinogenic impurities can be applied in this case also for herbal medicinal products."

The applicability of the method of risk assessment developed specifically for toxic impurities or environmental toxins on extract matrices from herbal medicinal products has never been demonstrated or even scientifically discussed. The assumption that such an approach may be applied to herbal medicinal products is in contrast to generally accepted scientific practice in toxicology.

"The highest TTC dose of 120 µg cannot be considered acceptable, because it is applicable for treatments of less than one month and is thus too high for expected intermittent exposures with different herbal preparations that contain furocoumarin derivatives lasting a significant portion of adult life. On the other hand, life-time exposure, for which a maximum daily TTC dose of 1.5 µg might be considered, is not likely to reflect the current use of herbal medicinal products. Therefore, a daily intake for total furocoumarins in a herbal medicinal preparation that is equal or below 15 µg would not be considered to pose an unacceptable risk to consumers."

The proposed upper dose limit of 120 µg and the lower limit of 1.5 µg are both related to toxic impurities and completely unrelated to the pharmacological properties of the compound under discussion, and not suitable for the risk assessment of natural compounds in an herbal extract matrix. In addition, the increase by a factor of 10 to a limit of 15 µg proposed by the HMPC is arbitrary. If a safe level of a given impurity could only be reached with 1.5 µg/day, there would be no reason to raise this limit to 15 µg. If, however, the limit of 1.5 µg does not reflect the current use of herbal medicinal products or other sources of furocoumarin intake – the same argument would apply to the chosen limit of 15 µg. In fact, the average daily dietary intake of furocoumarins has been rated as 1.5 milligram (not microgram), and found to be safe up to 15 milligram. Thus, if for the current use of herbal medicinal products, it should also allow for dietary realities. Accordingly, there is no reason for concern with quantities in the range of 1.5 mg – a dose which herbal medicinal products cannot be expected to relevantly exceed or even to reach.

This should be ascertained on the basis of the analysis of the contents of the actual herbal medicinal preparation, calculating all detectable furocoumarins as 8-methoxypsoralen on a molar basis.

Even the assessment of all furocoumarins from Angelica archangelica as 8-methoxypsoralen, which would lead to a clear overestimation of the risk potential for Angelica archangelica, would not justify the proposed dose limits, since the quantities of furocoumarins applied with Angelica products are not in ranges above the dietary total intake and so, according to actual state of scientific knowledge, without toxicological relevance. A calculation of furocoumarins as 8-methoxypsoralen on a molar basis would not increase consumer safety, but lead to unnecessary confusion.

Overall conclusions and summary

The reflection paper of the HMPC is entirely based on the assumption that the known risk potential of pure and highly dosed 8-methoxypsoralen in PUVA therapy may be extrapolated to the content of furocoumarins as a fraction of the constituents in herbal medicinal products. However, the reflection paper does not take into account the actual state of scientific knowledge regarding the toxicological relevance of oral furocoumarins intake and does not give any evidence that such an approach is rational, or that any risk potential other than a theoretical extrapolation is involved in the use of Angelica archangelica preparations. Such an extrapolation should, however, be avoided according to the recent "Concept paper on the development of a guideline on the assessment of genotoxic constituents in herbal substances/preparations" in cases where there is only a theoretically possible risk (HMPC 2006).

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Additional commentary

It is so relevant to comment this concept paper not merely with respect to Angelica archangelica, but as the new approach, which was applied by the HMPC in this case, can hit almost any other herb used in phytomedicine, with the consequence of a ban of its therapeutic use. The approach is:

1. Defining a phytochemical component out from that herb, for which chemically related substances with known toxicity/mutagenicity/genotoxicity in (even extremely) high doses is known.

2. Defining a maximum limit, which is a factor of e.g. 10,000 lower than these doses, for the intake of that herb, so making its therapeutic use impossible.

So for virtually any, otherwise untoxic herb, a ban due to toxicological reasons can result.

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Comment from the UK Herbal Forum on the HMPC Reflection Paper on the risks associated with furocoumarins contained in preparation of Angelica archangelica L.

We note that *"The reflection paper focuses on coumarin-derivatives present in Angelica archangelica L., as these substances are the most relevant constituents for phototoxicity."*

It is true that Angelica archangelica contains furocoumarins, but the HMPC paper essentially refers to the phototoxicity of 8-methoxy-psoralen (8-MOP), which if found in Angelica preparations at all, is only one minor component. The paper also refers to doses of the pure compound 8-MOP used in Psoralen plus UVA radiation (PUVA) therapy, whereas Angelica archangelica preparations, even in combination with dietary sources of furocoumarins and in gross overdose would not deliver doses of furocumarins that could have the potential for phototoxicity – and even less so for mutagenicity and carcinogenicity.

Therefore, in our view, the reflection paper is based on an incorrect assumption that the risk potential for pure, high dose 8 MOP in PUVA can be extrapolated to the content of furocoumarins in herbal medicines. Further, we note that the recent 'Concept Paper on the Development of a Guideline on the Assessment of Genotoxic Constituents in herbal substances/preparations, specifically advised against such an approach where the potential for risk was only theoretical.

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Comments of the IGEPHA (The Austrian Self-Medication Industry) on Reflection Paper on the risks associated with furocoumarins contained in preparations of Angelica archangelica L., EMEA/HMPC/317913/2006

General Comments

In the reflection paper it is concluded that a daily intake for total furocoumarins in an herbal medicinal preparation, that is equal or below 15 µg, would not be considered to pose an unacceptable risk to consumers, while higher dose cannot be considered acceptable.

Basis of this conclusion is the statement, that furocoumarins are photogenotoxic and photocarcinogenic and pose a clear hazard to human health in this respect, and that therefore recently suggested thresholds for toxicological concern (TTC) for potentially genotoxic and carcinogenic impurities can be applied in this case also for herbal medicinal products.

From our point of view, neither this assumption nor the conclusion drawn from it can be considered reliable and acceptable:

- The generalizing statement that furocoumarins pose a clear hazard to human health is based on an incomplete analysis of scientific data. E.g. none of the published toxicological risk assessments on the average daily intake of furocoumarins in consumers has been included. The most recent and detailed of these is the assessment of the Senate Commission of the German DFG (SKLM 2006. Other assessments, with a similar outcome, are the assessments of the UK Department of Health Committees on Toxicity, Mutagenicity and Carcinogenicity (COT 1996), and of J. Schlatter et al. (1991) from the Swiss Federal Office of Public Health. The safety of Angelica archangelica L. is further supported by fact that it has GRAS status based on a safety assessment of the FDA (see EMEA/MRL/412/98).

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- Based on the very conservative assumption that the total furocoumarins in plants a phototoxic potency equal to 8-methoxypsoralen (8-MOP), the SKLM and COT conclude, that the threshold of concern for daily furocoumarin uptake is not below 14 mg/day (SKLM 2006, COT 1996). This does is clearly above furocoumarin doses potentially taken up with Angelica extracts, which can be assumed to have a content of not above 1 mg/ml of Angelica furocoumarins, which have a phototoxic potential far below that of 8-MOP (Schimmer 1983).

- The application of thresholds of toxicological concern (TTC) and safety factor concepts, which were originally developed for impurities of pharmaceuticals, is not indicated for application on active components from medicines.

  This is especially the case for Angelicae radix, as there have never been reported any data which could point to any phototoxic or carcinogenic effects connected to the therapeutic use of this drug.

  Instead of taking this into account, the risk assessment in the reflection paper has been based on IARC-monographs dating from 1986 resp. 1987, which concluded that the use of isolated 8-MOP and 5 MOP in the therapy of psoriasis in doses of above 30-50 mg per day, in combination with highly intensive UV A-radiation (PUVA-therapy), is connected with an increased risk of skin cancer. But it has to be taken into account, that since the appearance of these monographs, the published data on this therapy have considerably increased, showing that an enhanced carcinogenic risk, if any, is strictly dose dependent and is connected only to patient groups with the highest exposure in PUVA therapy, while lacking in lower dosed PUVA. These lower doses are still orders of magnitude higher than those applicable with herbal medicinal preparations. So, the data from PUVA therapy are no suitable basis for the risk assessment for preparations from Angelica archangelica L.

- While not leading to any decrease of a risks for consumers or patients, the proposed dose limit would lead to a ban of the save and well established use of herbal medicines from e.g. Angelica archangelica L. and Angelica sinensis Oliv..

Taken together, the risk assessment in the reflection paper is not in accordance with the HMPC draft concept paper on the development of a guideline on the assessment of genotoxic constituents in herbal substances/preparations (EMEA/HMPC/413271/2006), lines 76 to 79, according to which the authorities should not ban the use of herbal medicinal preparations used in self medication on the basis of extrapolated suspicions, but their remit is to develop sound risk-benefit approaches for HMPCs, with which to protect consumers.

So, the draft reflection paper cannot be rated as acceptable and should be replaced by a paper in accordance with the existing toxicological risk assessments for orally applied furocoumarins from official bodies, as are the COT (1996) or the SKLM (2006).

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Specific Comments on Text

1. Introduction (background)

As stated in the first paragraph, the paper may be used by national authorities when evaluating the safety of herbal medicinal products containing preparations of Angelica archangelica L. or other herbal preparations containing furocoumarins with a phototoxic potential. This paragraph as well as the following paragraphs do not take into account the majority of publications on the toxicological relevance of plant furocoumarins (as summarized in COT 1996, SKLM 2006). Instead of this, the paper is mainly based on risk assessments of PUVA therapy. This therapy of psoriasis and other skin diseases is based on the use of high doses of isolated mono-substances (8-MOP, 5-MOP) in combination with UV A radiation.
So, the recommendation of the paper, as it is, for risk assessment of herbal preparations is not appropriate.

2. Safety evaluation of furocoumarins

Other than stated, basing the risk assessment of herbal furocoumarins only on data derived from the use of 5-MOP and 8-MOP in PUVA therapy is not appropriate, but has to be accomplished by specific data on plant forocoumarins. This concept has been followed by the risk assessments of COT (1996) and SKLM (2006) and should be applied here, too.

2.1 Phototoxicity

Other than in PUVA therapy, phototoxicity after oral intake of herbal medicines has never been described, so that the conclusions of the actual reflection paper, based solely on the occurrence of such reactions in PUVA therapy, using very high doses of isolated furocoumarins with a different chemical profile, are obviously not applicable to the therapeutic use of HMPCs.

2.2 Carcinogenic potential of furocoumarins

This section of the paper is mainly based on IARC monographs dating from 1986 resp. 1987. There is a large amount of data on that theme, published since that time until today, that has not been taken into account in the actual reflection paper. According to these data, several studies did not confirm the assumption of an increased carcinogenic risk due to the furocoumarins used in PUVA therapy, 8-MOP and 5-MOP. If there is any risk, this is obviously restricted to the highest exposition to PUVA, applied several hundred times, while no association of lower dosed PUVA to an enhanced cancer risk could be confirmed (Stern et al. 1998).
As is pointed out in the SKLM assessment (2006), the potential genotoxic resp. carcinogenic risk of furocoumarins is clearly coupled to phototoxic doses, while lower doses have never been described as carcinogenic, so that any influence of furocoumarin intake with herbal preparations on the carcinogenic risk would have been recognised due to evident symptoms of phototoxicity.

2.3 Mechanism of action

It should be mentioned, that a photo-activation of furocoumarins by UV A irradiation, causing its binding to DNA, is based on the same chemical mechanisms as the binding to other intracellular components, so that genotoxicity can not be expected to occur without phototoxicity (SKLM 2006).

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2.4 Human toxicity

The "rule of thumb" opinion mentioned is not backed by recent publications (Stern et al. 1998), according to which a putative carcinogenic effect of PUVA is limited to the patient groups with the highest exposure, while lower exposure had no putative carcinogenic effect.

2.5 Various considerations for risk assessment

The statement, that oral exposure to furocoumarins from herbal preparations may pose a significant health risk to humans is not backed by scientific data, as they were evaluated by SKLM (2006).

Neither the MOE approach nor the TTC concept, using safety factors, have been designed for use in pharmacologically active substances from medicines, but for the assessment of environmental toxins or impurities of otherwise pure chemical substances. In case of preparations from Angelica archangelica L., both concepts cannot be expected to give results relevant for risk reduction in consumers or patients, as the average uptake of furocoumarins from other sources, which is in the range of 1.4 mg/day (COT 1996, SKLM 2006) is several orders of magnitude higher than any dose limits resulting from the use of these concepts.

2.6 Problems in risk assessment of other derivatives

Indeed, there are data on plant furocoumarins pointing to a phototoxic potential significantly below that of 8-MOP or 5-MOP (SKLM 2006), but even if these are not taken into account (the SKLM is based on the conservative assumption that all furocoumarins are as active as 8-MOP), there is no indication of a relevant toxicological potential of furocoumarin doses as taken up with usual food or with herbal medicines.

Conclusions

The dose limit of 15 µg, which is rated as posing no risk to consumers, is far below any limits of concern from toxicological assessments, while resulting in a ban of the well established therapeutic use of preparation from Angelica archangelica L.. As it is not based on any data on herbal preparations, but solely on contradictory data on a possible carcinogenic risk potential of the therapeutic use of certain furocoumarins in PUVA, it is apparently not in accordance with the HMPC draft concept paper on the development of a guideline on the assessment of genotoxic constituents in herbal substances/preparations (EMEA/HMPC/413271/ 2006), as mentioned above.

So, this reflection paper cannot be considered acceptable from a scientific point of view.

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HMPC. Draft reflection paper on the risks associated with furocoumarins contained in preparations of Angelica archangelica L. (EMEA/HMPC/317913/2006)

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With kind regards
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Remarks to the HMPC draft reflection paper on the risks associated with furocoumarins contained in preparations of *Angelica archangelica* L.

HMPC sees a carcinogenic risk associated to the use of preparations derived from *Angelica archangelica* containing furocoumarins. A maximum daily dose of 15 µg is considered acceptable. The reason given for this limitation are reports of an enhanced incidence of skin tumours in psoriasis patients after long term therapy with 8-methoxypsoralen (8-MOP) in high doses (0.4-0.6 mg/kg b.w.) and UVA radiation, Stern et al. 1998, 2002).

This suspicion of an enhanced carcinogenic risk after therapy with 8-MOP is extrapolated to the uptake of furocoumarins from preparations of *Angelica archangelica*, with furocoumarin contents of very low magnitude, using the TTC approach for risk assessment. Such a use of the TTC approach seems to be not admissible here:

- Preconditions for a genotoxic risk or even carcinogenicity of these compounds are phototoxic reactions. Such reactions are observed only at doses of at least 14 mg 8-MOP, whereas such reactions were never observed in lower doses (Schlatter et al, 1991, COT Report 1996, SKLM 2006).

  This is plausibly explained by the fact, that only the genuine furocoumarins show phototoxic reactions, but not their metabolites (Schmid et al. 1980a). In dosages below the 14 mg mentioned above, 8-MOP and other furocoumarins are metabolised already in their first hepatic passage and therefore do not occur in the systemic circulation (Schmidt et al 1980 b, Brickl et al. 1984). Therefore, as a different metabolism exists in lower doses, an extrapolation of a possible risk from high doses to lower doses is not admissible.

  In association with the use of herbal preparations derived from *Angelica archangelica* phototoxic reactions were never observed, so that, as mentioned above, also the preconditions for a carcinogenic risk do not exist.

  The Scientific Committee on Consumer Products (SCCP) assessed total concentrations of furocoumarins exceeding 1 ppm in externally applied products as of concern with regard to consumer safety. A transfer of this limit to oral uptake is not admissible, as topical application results in very high concentrations in the skin, as opposed to oral administration of the same product.

- Moreover, the enhanced carcinogenic risk of the psoriasis therapy with 8-MOP is still under discussion, as apparently already the disease itself is connected with an enhanced risk of skin cancer (Leonardi et al. 2006).

- Also with other reasons, data obtained with 8-MOP can not simply be transferred to herbal preparations. A risk assessment for herbal preparations simply based on the furocoumarin content is not admissible, as

- bioavailability of furocoumarins from herbal matrices is significantly lower than that of isolated chemical compounds (studies with foodstuffs containing furocoumarins, COT report 1996, statement of SKLM 2006).
- the relative phototoxic potential of furocoumarins from Angelica is to be assessed as about 10-12 times lower than that of 8-MOP (see also Bordin et al. 1991, Ojala 2001)

Risk assessments of herbal furocoumarins based on the complete available scientific information were performed by the British Committee on Toxicity (COT 1996) and the supra-national Senate Commission on Food safety (SKLM 2006). These scientific bodies rated a daily uptake of up to 14 mg furocoumarins from plant products as without a relevant risk.

As since of then no relevant new data have been published, the divergent risk assessment in the current draft reflection paper is therefore not understandable. At the same time, it contradicts the HMPC draft concept paper on the development of a guideline on the assessment of genotoxic constituents in herbal substances/preparations (EMEA/HMPC/413271/2006), which states under item 3, lines 76 to 79: "the authorities should not ban the use of herbal medicinal preparations used in self medication on the basis of extrapolated suspicions, but their remit is to develop sound risk-benefit approaches for HMPCs, with which to protect consumers".

Taking into account the aspects mentioned above, a revision of the actual draft reflection paper based also on the existing risk assessments of COT and SKLM is necessary and justified.

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