European Medicines Agency
Post-authorisation Evaluation of Medicines for Human Use

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OVERVIEW OF COMMENTS RECEIVED ON DRAFT 'REFLECTION PAPER ON THE RISKS ASSOCIATED WITH FUROCOUMARINS CONTAINED IN PREPARATIONS OF ANGELICA ARCHANGELICA L.' (EMEA/HMPC/317913/2006)

Table 1: Organisations that commented on the draft Reflection paper as released for consultation

	Organisation
AESGP	Association Européenne des Spécialités Pharmaceutiques Grand Public
EFCAM	European Forum for Complementary and Alternative Medicine
GCRN	German Council for Responsible Nutrition e.V.
BPI	German Pharmaceutical Industries Association (Bundesverband der pharmazeutischen Industrie)
KP	Kooperation Phytopharmaka
PHC & RIMP	Polish Herbal Committee and Research Institute of Medicinal Plants
UK-HF	UK Herbal Forum
IGEPHA	Austrian Self-Medication Industry Association (Interessengemeinschaft österreichischer Heilmittelhersteller und Depositeure)
University of Münster (DE)	University of Münster (Germany)

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Table 2: Discussion of comments

GENERAL COMMENTS - OVERVIEW
General responses to comments received during the consultation period: Because many comments from various organisations were rather similar, if not identical, general responses to these comments are presented in this document. Nevertheless, takes this opportunity to thank all the commentators for their valuable comments which have helped, and will help, to develop the work of HMPC on the issue concerned to the full benefit of all concerned parties. The comments received have enabled the HMPC to revise the reflection paper in different sections as it is presented below. For transparency, all the comments received during the consultation period are published in a separate file on the EMEA website. **General comments:** <u>1. "Ordinary" toxicities vs. genotoxicity and carcinogenicity:</u> Commentators do not give full appreciation to crucial differences between "ordinary" toxic outcomes that may be identified in studies on acute or chronic toxicity or, to some extent, on the basis of long-standing use and genotoxicity or carcinogenicity. Genotoxicity and carcinogenicity are difficult (and sometimes close to impossible) to ascertain in adequate human studies and consequently proactive risk assessment has to be based mainly on experimental studies and in vitro tests and modeling and extrapolation (which contain assumptions, which may be true or false, but that are still based on current scientific thinking). <u>2. Risk of skin cancer associated with PUVA treatment</u> The risk of skin cancer associated with PUVA has been questioned, but the author of the latest review (Stern RS Psoralen and ultraviolet a light therapy for psoriasis. N Engl J Med. 2007; 357: 682-690.) is of the opinion that the risk is real with an extended use (as it is also stated in the reflection paper). A very recent case report published in New English Journal of Medicine points out a possibility of phototoxicity after dietary exposure of lime (Pomeranz MK, Karen JK. Images in clinical medicine. Phytophotodermatitis and limes. N Engl J Med. 2007; 357(1): e1). Because of large interindividual variability in pharmacokinetics and pharmacodynamics, it is possible that rare individuals are very sensitive to furocoumarin-containing materials, including diet and herbal medicinal products. <u>3. Link between phototoxicity and genotoxicity/carcinogenicity</u> There are some reasons to think that manifested phototoxicity is a prerequisite for genotoxicity and carcinogenicity, although this has not been unequivocally demonstrated and there may be situations in which genotoxicity is induced without any other apparent toxicity (see Brendler-Schwaab et al, Photochemical genotoxicity: principles and test methods. Report of a GUM task force. Mutat Res 2004; 566: 65-91). Thus, genotoxic insults, if of stochastic nature, may be manifested at concentrations, in which no phototoxicity can be observed. There is also some evidence that first-pass metabolism of dietary furocoumarins prevents the systemic exposure to unmetabolised parent substances at least to a certain exposure level. However, there is very little comparative information about bioavailability and metabolism of furocoumarins between food and herbal medicinal preparations. If bioavailability from these two different sources are rather similar, it is possible to argue that there exists a certain relative limit for the systemic exposure to furocoumarins.

4. The need for extrapolation:
Commentators do not appreciate that when dealing with genotoxicity and carcinogenicity risk assessment, the risk assessments are always based on some assumptions (i.e. there is no threshold for stochastic processes) and toxicology uses modeling, simulation and extrapolation, also with respect to exposures, which means extrapolation from high doses to low "human" exposures.
The HMPC does not agree with the view of some commentators that e.g. TTC or MOE or safety factor approaches are intrinsically unsuitable for the risk assessment of herbal medicinal preparations. Toxicologically speaking, there is very little difference between 'toxic constituents from herbal medicinal preparations' and 'environmental toxins and impurities', because both are usually constituents of complex mixtures.

5. Complex mixtures vs. pure substances:
Commentators do not appreciate that chemicals are chemicals whether they are "impurities" or minor constituents in complex mixtures and it is possible to use data on single constituents when assessing the complex mixture containing this single constituent. It is certainly possible that in complex mixtures, interactions at all phases of kinetics and dynamics could occur, which have consequences to risk assessment. However, little or no information on these potential interactions is usually available and this also concerns furocoumarins in *Angelica archangelica*, L.. In absence of specific studies with extracts from *Angelica archangelica*, L, an "index-compound"-approach (i.e. 5-MOP and 8-MOP) has been chosen. This enables assessors and applicants to perform risk-assessments on the basis of comparative studies on phototoxicity (e.g. in-vitro studies) or to adopt a "worst-case" scenario (based on analytical data and specifications) assuming that the mixture will have the same effects as 8-MOP .

6. The ability of pharmacovigilance to detect genotoxicity or carcinogenicity:
Commentators do not appreciate that genotoxic potential cannot be detected by pharmacovigilance or long-standing use and experience. Carcinogenic potential may be realised sometimes in human studies, but this happens always *post festum*, retrospectively. It has to be stressed, too, that there has been no organised pharmacovigilance concerning many traditional herbal medicinal preparations and a very strong under-reporting of cases can be expected.

7. Level of understanding:
Commentators do not appreciate or they neglect uncertainties and gaps in the current knowledge. It is true that first-pass metabolism of furocoumarins affects systemic exposure (however, there probably are large differences between various furocoumarins in this respect) and that UV light is needed for the realisation of potent genotoxicity and carcinogenicity of furocoumarins and this scenario might be a threshold phenomenon. However, many details of these processes are still mostly assumptions based on our general state of science and not fully established facts.

8. Dietary vs herbal medicinal products exposure:
Commentators do point to a very important area: natural substances in diet and in herbal (or pharmaceutical) preparations. What is the significance of background exposure through diet? How should it be taken into consideration? Because many herbal substances and preparations are derived from plants which are also used as food, it is apparent that exposure to various herbal constituents can also occur via diet. It is clear that amounts and ratios of these constituents vary enormously, depending on individual and population dietary preferences. For the proper risk assessment, dietary exposures should be assessed and quantified, as far as possible, and comparative assessment of exposures via diet and herbal substances and preparations should be performed. It may be, however, premature to decide that assessments of dietary exposures could be used at face value for the assessment of herbal medicinal products.
It is an unresolved question whether herbal medicinal preparations should be assessed in the more general context of nutrition. There are considerations favouring this approach, but it has to be remembered that in many ways herbal medicinal products are 'drug-like', in distinct pharmaceutical preparations and they are avoidable at will, if deemed risky. Hazards and risks regarding herbal medicinal products should be assessed; assessment concerning dietary exposures is certainly

valuable and helpful, but it may not be so straightforward to equate food and herbal medicinal products.

9. Matrix effects:
Commentators point to a very large difference between dietary exposures to furocoumarins and the limit value reached by HMPC in the draft reflection paper. While this difference is real and should be an important topic of further investigations and assessments, there are several issues which should be remembered in this respect. First of all, It is not really known whether exposures via diet and via herbal preparations are really equivalent. Matrix effects may be of importance for chemicals, as pointed out by many commentators, but there is a lack of evidence about whether matrix effects within dietary exposures are similar to what happens with herbal medicinal products containing extracts etc.. A reasonable expectation is that there are not too large differences in this respect between diet and herbal preparations, but this is mostly an assumption.

10. Avoidable hazards and risks:
There are unavoidable and avoidable hazards and risks. While many exposures via diet belong to the first category, exposures via herbal preparations belong to avoidable risks, or at least are a matter of risk-benefit considerations. Even in the presence of unavoidable risks, extra risks of the same kind pose at least some ethical problems, although actual risk may remain small or practically negligible.

11. Lack of regulatory assessments in the reflection paper:
Commentators point to a lack of some important assessments from national agencies dealing with nutrition and diet. It should be noted that HMPC is not aware of any acceptance limits issued by official bodies of the European Union such as the European Food Safety Authority (EFSA) or the European Commission DG SANCO. The HMPC will follow-up clarification with EFSA and update the document, if necessary. National organisations, have established limits for food where risks seemed to be negligible to those organisations. The HMPC is not aware of any official statement on the "established or proven safety" of these exposures.

On the basis of the comments presented, the following consideration has been added to the new version of the reflection paper:
Furocoumarins are present in various dietary commodities, such as celery, and are thus a regular part of our diet. Risk assessment of dietary furocoumarins has been made by different authorities from Switzerland (Schlatter et al 1991), the US (where Angelica has GRAS status) (Wagstaff 1991), the UK Committees on Mutagenicity and Carcinogenicity (COT 1996), and the German DFG (DGF-SKLM 2005). On the basis of these assessments, an average daily intake of 1.45 mg of dietary furocoumarins has been estimated, with high-exposure peak values of up to 14 mg (DGF-SKLM 2005). This quantity is close to the threshold where phototoxic reactions may be expected in combination with UV irradiation (>14-15 mg) (DGF-SKLM 2005; Schlatter 1991). These evaluations have come to the conclusion that the risk of dietary furocoumarins is very small or insignificant. It should be noted that parts of this assessment was based on very limited information on bioavailability of furocoumarins from the food matrix. The influence of furocoumarin mixtures on the first pass metabolism was not investigated at all. Exposure *via* herbal medicinal preparations was not assessed. It should be noted, however, that exposure through herbal medicinal products will add to the average general exposure through food.

What is (are) pharmacological/therapeutic principles in herbal medicinal products?
This is a difficult conceptual problem, which has been frequently raised in the comments received. Many (most) commentators state that furocoumarins cannot be assessed by “ordinary” risk assessment procedures for toxic substances, because they are active principles in herbal medicinal products and consequently a benefit/risk approach should be adopted. Therapeutic action based on the “wholeness” of the herbal extract should deserve a thorough scrutiny. At present data on Angelica preparations are practically absent. In absence of such data an extrapolation on the basis of available data is unavoidable. In the reflection paper, the HMPC

has adopted a “standard” toxicological approach to assess hazards and risks of furocoumarins in Angelica archangelica preparations.

The reflection paper states very clearly that 8-MOP and 5-MOP have been ‘used as a model for risk assessment’ and ‘different results may be obtained, if genuine mixtures of furocoumarins present in relevant herbal preparations are studied’. This approach had to be adopted because there are no relevant studies with actual genuine preparations available. Appropriate genotoxicity studies would have given experimental results for the risk assessment of the preparation itself, without the need of excessive extrapolation.

The risk assessment considerations and conclusions parts of the reflection paper have been completely revised. Because the document is written in the form of a reflection paper, several potential risk assessment schemes are presented, with widely differing outcomes. In the absence of the approved risk assessment guidelines for genotoxicity and carcinogenicity of herbal medicinal products, the HMPC regards this reflective approach the most useful one in the current situation.

The majority of comments address that a limitation with respect to a maximum content of furocoumarins and pharmacovigilance actions for products exceeding this limit would be inappropriate. The purpose of the reflection paper is clearly stated in the introduction. It is not the intention of the document to establish a strict "acceptance limit" with respect to furocoumarins. The reflection paper identifies one exposure level (<15 µg/day) where risks of phototoxicity are considered to be absent, a second level (<1.5 mg/day) where the risk is considered to correspond the risk through dietary exposure. Any herbal medicinal product exceeding this limit requires a specific benefit/risk assessment. This assessment will have to take into account, among other factors, the structure and content of the furocoumarins present in the herbal preparation, their relative phototoxicity as compared to 8-MOP, their bioavailability, including release e.g. into tea preparations, the evidence on the benefit and the targeted population of users. The reflection paper does *a priory* not "ban" such products. It may be expected that a product-specific benefit/risk assessment will, in many cases, result in a product-specific opinion to the effect that the product can be used safely.