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FINAL

REFLECTION PAPER ON THE RISKS ASSOCIATED WITH FUROCOUMARINS CONTAINED IN PREPARATIONS OF *ANGELICA ARCHANGELICA* L.

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1. INTRODUCTION (BACKGROUND)

On request of a Member State, the HMPC made an assessment of the risks associated with the use of herbal preparations[1] from *Angelica archangelica* L. The result of this assessment is presented in this reflection paper. This document identifies different exposure levels where risks related to phototoxicity are considered to be absent or not relevant. Exposure levels beyond those limits would require a more detailed benefit/risk assessment and additional studies. The assessment may be used by national competent 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. Applicants may use the assessment when preparing applications for the marketing authorisation or registration.

This reflection paper focuses on coumarin-derivatives present in *Angelica archangelica* L., as these substances are the most relevant constituents for phototoxicity (see Appendix 1 - Table 1). In addition to these constituents, there are a large number of other compounds, which have been found e.g. in the essential oil (see Appendix 1 - Table 2). The safety of these constituents is not addressed in this paper.

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. In essence, characterization of systemic exposure needs detailed knowledge of the constituents of a preparation, (bio)transformation of constituents upon administration, bioavailability and pharmacokinetics. Because preparations from *Angelica archangelica* L. contain a large number of furocoumarins, whose kinetic and metabolic properties are incompletely investigated, the assessment of systemic exposure remains fragmentary.

This document has been intended to address risk-assessment and risk-management associated to furocoumarins contained in herbal preparations. Other human medicinal products are excluded from the scope of this reflection paper.

2. SAFETY EVALUATION OF FUROCOUMARINS (CAS NUMBER 66-97-7)

In plants, the most commonly detected linear furocoumarins are psoralen, 8-methoxypsoralen (8-MOP, xanthotoxin) and 5-methoxypsoralen (5-MOP, bergapten). Angular furocoumarins include angelicin (isopsoralen) and its derivatives. All these compounds are detectable in *Angelica archangelica* preparations (Appendix - table 1). As toxicological data on all individual furocoumarins in Angelica and on herbal preparations from Angelica are almost lacking, this assessment is mainly based on the data on 5-methoxypsoralen and 8-methoxypsoralen that are, both, well studied. For this reason both substances were used as a model for risk assessment. Different results may be obtained, if genuine mixtures of furocoumarins present in relevant herbal preparations are studied. However, 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.

2.1 Phototoxicity of furocoumarins

Linear furanocoumarins 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 reactions. These reactions are manifested as itching, pigmentation and erythema. Long term PUVA[2] 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

[1] As defined by Article 1.32 of directive 2001/83/EC as amended by directive 2004/24/EC.

[2] PUVA stands for psoralen (P) and ultraviolet A (UVA) therapy in which the patient is exposed first to psoralens (drugs containing chemicals that react with ultraviolet light) and then to UVA light.

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.

2.2 Carcinogenic potential of furocoumarins

The IARC[3] Working group (IARC 1986) 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). No epidemiological data relevant to the carcinogenicity of 5-MOP were available, whereas on the basis of experiments designed to test the carcinogenicity to mouse skin of 5-MOP in combination with ultraviolet A radiation or solar-simulated radiation, there is sufficient evidence of carcinogenicity to experimental animals. The evidence is inadequate in the absence of ultraviolet A radiation. The overall evaluation was that 5-MOP is probably carcinogenic to humans (Group 2A).

For angelicin and some of its methyl derivatives, limited evidence for the carcinogenicity to experimental animals in combination with ultraviolet A radiation was obtained, but no evaluation could be made of the carcinogenicity to humans.

In the presence of ultraviolet A radiation, both 8-MOP and 5-MOP induced chromosomal aberrations, sister chromatid exchanges and unscheduled DNA synthesis in human cells *in vitro*; sister chromatid exchanges, mutation and DNA cross-links in rodent cells *in vitro*; mutation, gene conversion and DNA cross-links in yeast; and mutation in bacteria. In the absence of ultraviolet A radiation, both psoralen derivatives were weakly mutagenic to bacteria. Also angelicin was genotoxic, but probably weaker than the two methoxypsoralens.

2.3 Mechanism of action

Binding of photo-activated furocoumarins to DNA has been extensively characterised (Loveday 1996). They have also been shown to interact with proteins, lipids in membranes, and ribosomes (Bordin 1999).

2.4 Human toxicity

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). Slight immunotoxicity has also been suggested to occur in some individuals after PUVA treatment.

PUVA as oral 8-MOP plus ultraviolet light A has been a standard treatment of psoriasis since 1974. 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, relative risks being about roughly from 6- to 12-fold after about 8-10 years follow-up (Hannuksela-Svahn 1999; Stern 2007). A "rule-of-thumb" opinion is that about 200 exposures result in an average excess risk of one additional case of squamous cell skin carcinoma in a population of about 3000 treated patients (Hannuksela-Svahn 1999). The risk of other skin or non-cutaneous cancer is much less or cannot be detected.

2.5 Various considerations for risk assessment purposes

Photogenotoxicity and photocarcinogenicity are the most important toxic outcomes of furocoumarins from the risk assessment point of view (Müller 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 consequently health risk to humans associated with the exposure to furocoumarins from herbal preparations should be assessed.

[3] IARC: International Agency for Research on Cancer

Since a detailed scheme of risk assessment for phototoxicity of herbal medicinal products is not available, in this section it is presented first the assessment of several national agencies/committees on dietary exposure to furocoumarins, followed by some potential approaches for assessing the risks of herbal medicinal products.

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.

The European Food Safety Authority Scientific Committee (EFSA 2005) has concluded that "for compounds that have both genotoxic and carcinogenic properties a margin of exposure (MOE) approach for the risk assessment is proposed. The margin of exposure is defined as the point of comparison on the dose-response curve (usually based on animal experiments in the absence of human data) divided by the estimated intake by humans". Furthermore, "The Scientific Committee is currently of the opinion that a compound with a calculated margin of exposure of 10,000 or higher, based on the BMDL and taking into account overall uncertainties in the interpretation, would be of low health risk and therefore could be considered of low priority for risk management actions. A MOE that would be considered acceptable is the responsibility of risk managers". The MOE approach would, however, lead to a very low acceptable exposure to furocoumarins. The approach is not considered to be appropriate for herbal medicinal products that contain furocoumarins.

Recently a framework of thresholds for toxicological concern (TTC) has been suggested for potentially genotoxic and carcinogenic impurities of pharmaceuticals, which for exposures of 1 month and less is maximally 120 µg and for a life-time exposure 1.5 µg (Müller et al 2006). Although constituents of herbal medicinal products are not 'impurities', this approach may offer one possible approach to risk management in the present case.

The standard uncertainty (safety) factor approach needs two assumptions to be fullfilled:
1) there should be adequate evidence for a threshold for genotoxicity and carcinogenicity (there is uncertainty in this respect), and
2) there should be a No Observed Adverse Effect Level (NOAEL) based on an adequate study (there are no such study available).

However, the following calculation serves as an illustration for potential exposures. PUVA treatment is intermittent with usually 1-3 weekly exposures to the drug and UVA. Based on the experiences with a PUVA dose of 30 mg 8-MOP, taken intermittently for about 200 doses over a period of several months, results in an increased (but not exactly quantifiable) skin cancer risk (on top of a relatively high skin cancer incidence due to, e.g. natural UVB). By limiting the dose by a factor of 1000 to 30 µg per day, the skin cancer risk is assumed to be reduced to a very low level.

2.6 Problems in risk assessment of other derivatives

There is very little reliable information about other furocoumarins than 8-MOP and 5-MOP. Furocoumarins are obviously not a homogeneous group. For example, angular furocoumarins may not be as phototoxic as linear derivatives. These differences, however, are difficult to take into consideration in risk assessment. It is well-known that furocoumarin derivatives have an influence on the activity of the cytochrome system. As the safety depends, among other factors, from an

inactivation by the first pass mechanism, mixtures of furocoumarins as they are present in herbal preparations may pose additional challenges.

3. CONCLUSIONS

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

Many furocoumarins are photogenotoxic and photocarcinogenic and pose a potential risk to human health in this respect. A significant exposure via both diet and herbal preparations might occur and consequently the risk to human health should be assessed.

The risk assessment for preparations of *Angelica archangelica* L. that contain furocoumarin derivatives should take into consideration that exposure to furocoumarins via diet is considerable and probably exceeds in most instances that occurring via herbal preparations. Consequently, there are two primary considerations in the risk assessment: first, the risk associated with dietary exposures, and secondly, whether furocoumarin exposure via herbal medicinal products would cause a significant extra burden. The above mentioned assessments on dietary exposures to furocoumarins come to the conclusion that the average daily exposure to about 1.5 mg furocoumarins does not cause significant health risk. Peak exposures to 14-15 mg furocoumarins via diet can still be regarded as a NOAEL, although they are very close to phototoxic limit doses and thus may cause a significant health risk. Tentatively, a 10-fold uncertainty factor with respect to the peak exposure seems to be necessary. It should, however, be stressed that no official acceptance limit value has been assigned to the furocoumarin exposure via diet by the EU or by Member States authorities.

An uncertain factor of 10 with respect to peak exposure through food is necessary for the following reasons.

There are significant uncertainties and gaps in knowledge concerning furocoumarins from herbal medicinal products. It is true that first-pass metabolism of furocoumarins affects systemic exposure and thus phototoxicity and that UV light is needed for the realisation of genotoxicity and carcinogenicity of furocoumarins. It is likely that this scenario might be a threshold phenomenon. However, many details of these processes are still mostly assumptions based on general considerations and not fully established facts. For example, clinical pharmacokinetic studies on which the notion of first-pass effect is based, are rather old and employ only very few subjects. Studies with herbal medicinal products and herbal preparation are absent.

Herbal furocoumarins are a complex group of substances present as variable natural mixtures with highly variable toxicodynamic and toxicokinetic behaviour, toxic effects and potencies. If risk assessment is performed by using, e.g. 8-MOP as a basis for calculating toxic equivalent, this may present a worst-case scenario. However, this is an acceptable approach in risk assessment of many generic classes of toxicants, unless a detailed benefit/risk assessment is performed.

Genotoxic potential cannot be detected by pharmacovigilance or long-standing use and experience. It has to be stressed that there has been no organised pharmacovigilance concerning traditional herbal medicinal preparations in most Member States. Carcinogenic potential may be sometimes discovered in human studies, but it happens always retrospectively in well-designed cohort-studies. Such studies for herbal medicinal products are not available. It cannot be excluded that dietary furocoumarins may be partially responsible for “background” cancer incidence. The exposure by herbal medicinal products will add to this potential risk.

It is not known whether exposures via diet and via herbal preparations are really comparable. Matrix effects may be of importance for bioavailability, but there is a lack of evidence on whether matrix effects within dietary exposures are similar to what happens with herbal preparations.

While exposure via diet belongs mainly to the category of unavoidable risks, exposure via herbal preparations belongs, in principle, to the category of avoidable risks and it is subject to risk-benefit considerations.

In conclusion, the following risk-management strategy is proposed:

1. Based on the TTC concept:

The highest dose of 120 µg furocoumarins that may be derived from the TTC concept cannot be considered acceptable within that concept, 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 an herbal medicinal preparation that is equal or below 15 µg would not be considered to pose any unacceptable risk to consumers. For herbal medicinal products that do not exceed this limit, safety data with respect to phototoxicity should not be required, if the applicant submits analytical data or bibliographic evidence to the effect that a higher exposure is unlikely to occur.

2. Based on the comparison with dietary exposure

Based on the average dietary exposure to furocoumarins a daily exposure of 1.5 mg furocoumarins through herbal medicinal products is not considered to contribute significantly to the overall risk. In view of the uncertainties, sensible groups such as children and pregnant women should be contraindicated. There should be a warning with respect to co-factors, especially exposure to UV light.

3. Preparations with more than 1.5 mg furocoumarins/day

For those preparations a detailed benefit/risk assessment is necessary. Data on comparative phototoxicity with respect to 8-MOP, metabolism and bioavailabilty of the furocoumarins present in the herbal medicinal product might be necessary to come to conclusions with respect to safety.

The limits expressed in scenario 2 and 3 should be ascertained on the basis of the analysis of the contents of the actual herbal preparation and appropriate specifications. The limit is expressed in 8-MOP equivalents. The applicant may choose to calculate the sum on furocoumarins to be equivalent to 8-MOP (thus providing an extra margin of safety) or to submit appropriate in-vitro studies that would compare the phototoxic effect of the preparation with 8-MOP (thus allowing higher exposures through the herbal preparation).

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5. APPENDIX 1

5.1 Table 1: Coumarin content of Angelica species

NOTE: Coumarins can be extracted with methanol or ethyl acetate. Non polaric solvents are not suitable. Liphophilic coumarins like furanocoumarins and pyranocoumarins are not soluble in strong polaric solvents.

The pharmacological activity of Angelica extracts was investigated on the basis of extracts, which were manufactured with ethanol, methanol, ethyl acetate, water, $CHCl_3$ and CH_2Cl_2.

Missing values means that there are no data available in German and English language.

		A. archangelica			**A. sylvestris**	**A. sinesis**	**A. dahurica**	**A. gigas**	**A. edulis**	**A. japonica**	**A. polymorpha**	**A. glauca**	**A. acutiloba**	**A. pubescens**
		root	**fruit** [1]	**herb**[2]	**fruit** [1]									
Coumarin														
	Osthenol	0,37-0,47mg/g												+
	umbelliprenin	+	0,31%	+	0,44%(f)									
	umbelliferone	+	+										+	+
	osthole	+				+				+				+ (r)
	scopoletin						+/ -(h)			+			+	

		A. archangelica			**A. sylvestris**	**A. sinesis**	**A. dahurica**	**A. gigas**	**A. edulis**	**A. japonica**	**A. polymorpha**	**A. glauca**	**A. acutiloba**	**A. pubescens**
		root	**fruit** [1]	**herb**[2]	**fruit** [1]									
	angelol					+								
	angelicone					+								
	angelol I, H						+							
	6-[(1S), 2R-2,3-dihydroxy-1-methoxy-3-methylbutyl]-7-methoxycoumarin						+ (s)							
	peucedanone							+						
	heraclenol					0,38 [3] mg/g (f)								
	heraclinin					3,0 [3] mg/g (f)								
pyranocoumarine														
decursinol								+						
decursin								+						

		A. archangelica			A. sylvestris	A. sinesis	A. dahurica	A. gigas	A. edulis	A. japonica	A. polymorpha	A. glauca	A. acutiloba	A. pubescens
		root	fruit [1]	herb [2]	fruit [1]									
furanocoumarins			1,3%											
	Angelicin	0,08%	0,01%	0,014%										
	Archangelicin	+				0,29 [3] mg/g (r)								
	Bergapten	+	0,59%	0,015%	0,01%	1,81 [3] mg/g (f)				+				
	Imperatorin	+	2,33%	0,057%	0,49%		0,225% in diplontic species (r), 0,46% in teratploidy (r) 22,14% of coumarins 0,7-0,8 mg/g		+					
	Isoimperatorin	+	0,04%	0,011%		0,59 [3] mg/g (r) /2,06 [3] mg/g (f)	> 0,04% (r) 12,12% of coumarins 0,68-0,78 mg/g		+	+				
	Isopimpinellin	+		+										
	Oxypeucedanin	+	0,13%	0,046%	0,15%	0,21 [3] mg/g (r) / 3,8 [3] mg/g (f)	+		+					

		A. archangelica			A. sylvestris	A. sinesis	A. dahurica	A. gigas	A. edulis	A. japonica	A. polymorpha	A. glauca	A. acutiloba	A. pubescens
		root	fruit [1]	herb [2]	fruit [1]									
	(+)-oxypeucedanin hydrate	+				0,35 [3] mg/g (f)	+		+	+				
	oxypeucedanin hydrate-3´´-butyl ether						+							
	marmesin	+												
	Xanthotoxin	+	0,08%	0,087%						+				
	xanthotoxol	+	0,01%											
	ostruthol	+				1,75 [3] mg/g (r)								
	Psoralen	+	0,02%		0,01%	+								
	byakangelicin						+			+				
	byakangelicin						+							
	byakangelicol								+					
	oxyimperatorin						42,4%							
	knidilin						+							

		A. archangelica			A. sylvestris	A. sinesis	A. dahurica	A. gigas	A. edulis	A. japonica	A. polymorpha	A. glauca	A. acutiloba	A. pubescens
		root	fruit [1]	herb [2]	fruit [1]									
	edulisin III, IV, V								+(f)					
	edulitin								+ (dr)					
	cnidicin								+					
	japoangelone									+				
	japangelol A-D									+				
	phellopterin	+												
dihydrofuran ocoumarins														
	Apterin	+												
	Archangelicin	+												

s= stem, r= root/radix; dr= dried root; f= fruit
1: extract: methanol, soxhlet 2h
2: fresh leaves; extract: methanol 60%
3: air dried material: extract: ethyl acetate
A. koreana: cnidicin, isoimperatorin, imperatorin, oxypeucedanin, oxypeucedanin hydrate, byakangelicol wer
A. atropurpurea (amerikanische Engelwurz) and A. heterocarpa (spanischer Engelwurz) : no data found

5.2 Table 2: Constituents of essential oil of Angelica Species

NOTE: Numerous scientific studies have been carried out on several species. Most of these studies have been focused on identification of active compounds present in these plants and preparations, evaluation of their biological, pharmacological and toxicological properties. Only small number of studies deals with the quantification of compounds.

From various studies it has been established that Angelica species contain amounts of coumarins, essential oil, sugars and resigns, bitters and tannins.

Extraction with supercritical carbon dioxide yielded more than 200 compounds of A. archangelica in the extracted oil.

The content of constituents depends on the origin, age, species and extraction method.

The coumarin content of A. archangelica roots can be elevated to the 20- 200 fold of the regular content due to a fungus infection.
Missing values means that there are no data available in German and English language.

		A archangelica			**A. sylvestris**	**A. sinesis**	**A. dahurica**	**A. gigas**	**A. edulis**	**A. japonica**	**A. acutiloba**	**A. polymorpha**	**A. glauca**	**A. pubescens**
		root	**seed/ fruit**	**herb/leave**										
essential oil		0,05-1%:	0,5 -1,5%	0,35-1,3%/0,1%:		0,4-0,7 %:					? :		0,12%:	
	beta-Phellandren	10-30%	35-65%	13-28%/33,8%									0,2%	
	alpha-Phellandren	2-20%		2-14%									13,5%	

		A archangelica			A. sylvestris	A. sinesis	A. dahurica	A. gigas	A. edulis	A. japonica	A. acutiloba	A. polymorpha	A. glauca	A. pubescens
		root	seed/ fruit	herb/leave										
	alpha-Pinene	4,4-31%%		14-31%/27%		0,6-6,1 %					0,1 %		0,5%	
	beta-Pinene	0,2-1,48%		/ 23,9%		2,3 – 17 %					0,4%		11,7%	
	limonen	6-11,53%				1,2- 16%							0,2%	
	p-cymene (Cymene-8-acetat)	3,5-11,3%		/+									0,1% (0,7%)	
	m-cymene										0,16%			
	myrcene	1,4-5,5%		/+									0,1%	
	cis-ocimen	1,0-1,9%		/+									0,5%	
	t-ocimen	0,24-4,9%		/+									0,2%	
	caryophyllen	+											7%	

		A archangelica			A. sylvestris	A. sinesis	A. dahurica	A. gigas	A. edulis	A. japonica	A. acutiloba	A. polymorpha	A. glauca	A. pubescens
		root	seed/ fruit	herb/leave										
	beta-caryophyllene oxide												7,2%	
	alpha-terpinene	+												
	terpinolene gamma-terpinene	0,2-0,39%											6,7%	
	Δ3-carene	4,5-13%											0,7%	
	sabinene	0,4-1,2%				0,4-1,5 %							1,8%	
	camphene	0,2-1,43%				0,8-3,0 %								
	copaene	0,93-1,29%												
	t-carveol												12,0%	
	thujene												7,5%	

		A archangelica			A. sylvestris	A. sinesis	A. dahurica	A. gigas	A. edulis	A. japonica	A. acutiloba	A. polymorpha	A. glauca	A. pubescens
		root	seed/ fruit	herb/leave										
	nerolidol												6,5%	
	bisabolone										0,5%		5,2%	
	germacrene												4,5%	
	Nitrophelland renderivate	4-7%												
	beta-Endesmol												2,5%	
	Linalool										0,1%		0,2%	
	Camphor												0,6%	
	Bornelol												0,1%	
	terpinen-4-ol												0,1%	
	alpha-												0,2%	

		A archangelica			A. sylvestris	A. sinesis	A. dahurica	A. gigas	A. edulis	A. japonica	A. acutiloba	A. polymorpha	A. glauca	A. pubescens
		root	seed/ fruit	herb/leave										
	Teripinene													
	Menthol												0,2%	
	Citronellol												0,3%	
	E,E-Farnesol												3,5%	
	cirtonellyl acetate					3,4- 10,3 %								
	3-methyl-2-octene					4,1-13,8%								

s= stem, r= root/radix; f= folium

5.3 References for Table 1 and Table 2

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