



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 November 2017
EMA/HMPC/679440/2017
Committee on Herbal Medicinal Products (HMPC)

Overview of comments received on “Reflection paper on Polycyclic Aromatic Hydrocarbons in herbal medicinal products/traditional herbal medicinal products” (EMA/HMPC/300551/2015)

Final

Table 1: Organisations and/or individuals that commented on the “Reflection paper on Polycyclic Aromatic Hydrocarbons in herbal medicinal products/traditional herbal medicinal products” (EMA/HMPC/300551/2015) as released for public consultation on 29 June 2016 until 15 December 2016.

	Organisations and/or individuals
1	Association of the European Self-Medication Industry (AESGP)
2	European Herb Growers Association (EUROPAM)



Table 2: Discussion of comments

General comments to draft document

Interested party	Comment and Rationale	Outcome
AESGP	<p>AESGP represents the manufacturers of non-prescription medicines of either chemical or herbal origin at European level. It counts 29 national associations and 25 associate members. Through its national and associate members, it represents many small and medium-sized companies operating in the self-care sector.</p> <p>General comments</p> <p>In principle we welcome the draft document as a starting point to promote the discussion on PAHs in herbal substances, herbal preparations and herbal medicinal products. The manufacturers act responsibly on the basis of a risk assessment. If applicable, testing of selected relevant products for PAHs is performed and necessary measures are introduced.</p>	<p>HMPC noted the supportive comments from the interested parties and welcomed the stepwise approach proposed by IPS as well as the willingness to contribute to the collection and sharing of data.</p> <p>It is also evident from the comments that, at present, the data available on levels of contamination found in herbal medicinal products (HMPs) is limited and is not yet sufficient to serve as a basis for discussion on the need for introduction of appropriate controls. However, taking into account the existing regulations in the food sector (including established limits and testing requirements) the HMPC will consider introducing information/consideration of potential PAH contamination in the framework of the revision of the quality guidelines for HMPs.</p>
EUROPAM	<p>EUROPAM, the European Herb Growers Association, represents the interests of European primary producers of perfumery, aromatic and medicinal plants of which a large part of the raw material is used for herbal medicinal products. Thus, all kinds of quality criteria including the assessment of potential contaminants are of high importance for our association. The producers act responsible on the basis of a risk assessment.</p> <p>EUROPAM welcomes the reflection paper as a starting point to initiate the</p>	<p>HMPC noted the supportive comments from the interested parties and welcomed the stepwise approach proposed by IPS as well as the willingness to contribute to the collection and sharing of data.</p> <p>It is also evident from the comments that, at present, the data available on levels of contamination found in herbal medicinal products (HMPs) is limited and is not yet sufficient to serve as a basis for discussion on the need for introduction of appropriate controls.</p>

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	<p>discussion on PAHs in herbal substances, herbal preparations and herbal medicinal products. People are exposed to very high levels of PAH by certain food products and cooking habits (grill) and smoking. Therefore, we agree to limit any possible other contamination to the lowest level that can be practically achieved.</p> <p>The (direct) drying process of starting materials was identified as one of the main sources of PAH contamination. In direct drying, exhaust fume from combustions of the heating source comes into direct contact with the dried product whereas the use of heat-exchangers in indirect drying avoids a direct contact with the product. EUROPAM developed over the last decades a good agricultural and wild collection guideline in which direct drying has been specifically mentioned as bad practice (EUROPAM, 2010): "When drying with oil, the exhaust fumes must not be reused for drying. Direct drying should not be allowed except with butane, propane, or natural gas." The majority of our members already changed from direct to indirect drying. We are convinced that this measure significantly decreased the level of PAHs in our products.</p> <p>However, drying is not the only process influencing PAH levels and even in some products regarded as unproblematic outliers may occur (as demonstrated by Schulz et al., 2014 with peppermint). Often, the source of PAH contamination in those outliers is difficult to determine. Therefore, EUROPAM started recently collecting analysis data to verify publications with limited sample numbers and to identify so far unknown sources of contamination, but we are not in a situation to share this data at the present time, mainly because the dataset is too small and not yet representative for the European production.</p>	<p>However, taking into account the existing regulations in the food sector (including established limits and testing requirements) the HMPC will consider introducing information/consideration of potential PAH contamination in the framework of the revision of the quality guidelines for HMPs.</p>

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	<p>EUROPAM suggests to continue collecting data about PAH occurrence in starting material as well as in finished herbal products in a more systematic way to come to sound conclusions and (if necessary) to actions. Especially the transfer rates into herbal products should be taken into account and closely examined. It is also important to consider environmental PAH contamination where producers can take no influence. The European herb growers are willing to contribute in the future to systematically coordinated efforts.</p> <p>References</p> <ul style="list-style-type: none"> • EUROPAM, 2010. Guidelines for Good Agricultural and Wild Collection Practices for Medicinal and Aromatic Plants (GACP-MAP). Available at http://www.europam.net/documents/gacp/EUROPAM_GACP_MAP_8.0.pdf (Accessed 18.11.2016). • Schulz, C.M., Fritz, H., Ruthenschrör, A. (2014): Occurrence of 15 + 1 EU priority polycyclic aromatic hydrocarbons (PAH) in various types of tea (<i>Camellia sinensis</i>) and herbal infusions. Food Addit Contam Part A Chem Anal Control Expo Risk Assess. 31: 1723-1735. Doi: 10.1080/19440049.2014.952785. 	

Specific comments on text

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2.4 Legislative framework	AESGP	<p>Regulation 1881/2006 (EC) has recently set maximum levels for benzo(a)pyrene and PAH4 in dried herbs, spices and food supplements of respectively 10.0 and 50.0 µg/kg. As regards “dried herbs”, the Regulation does expressly not include herbs for preparation of herbal infusions [1] since it has been shown in experimental studies that transfer rates of PAH16 into hot water infusions are very low:</p> <p>In a publication [2] PAH were analysed in 91 tea and herbal infusion samples. The levels of PAHs ranged from below 0.5 (LOQ) to 460 µg/kg, with a median of 4.7 µg/kg and a mean of 39 µg/kg for benzo(a)pyrene, and from below 1.0 (LOQ) to 2700 µg/kg, with a median of 39 µg/kg and a mean of 250 µg/kg for total PAH. For the brews prepared under normal house preparation (20 g material in 2 L boiling tap water for 10 min), it was shown none of the examined PAH could be detected above the LOQ. With an extended brewing time of 30 min, a transfer rate between 0.25 % and 0.52 % was determined, resulting in PAH levels which did not even exceed the maximum limits of the European Union Directive for drinking water.</p> <p><u>In conclusion, transfer rates of PAH into infusions of medicinal herbs as well as into aqueous extracts are reasonably expected to be very low.</u></p>	<p>Agreed</p> <p>These findings should be confirmed by experimental data relevant to the specific mode of preparation of infusions/herbal aqueous extracts of HMPs.</p>

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	AESGP	<p>Background PAH exposure from food, drinking water and other sources</p> <p>In 2008, EFSA [3] published estimates of foodborne PAH exposure based on occurrence data from roughly 10,000 samples of 33 food categories. 50 % of the samples contained benzo(a)pyrene (plus other PAH) while 30 % of the samples did not contain benzo(a)pyrene but other PAH. On average, benzo(a)pyrene accounted for ca. 30 % of the total PAH content. EFSA estimated an average daily exposure for PAH4 of 1,168 ng/day and 2,068 ng/day for high consumers. 95th percentile estimates for high consumers reached 4,486 ng PAH per day.</p> <p><u>EFSA concluded that food is by far the most important source of PAH exposure for non-smokers. For smokers, smoking may contribute significantly to overall PAH intake.</u></p> <p>Due to the intake of only small daily doses of herbal drugs/preparations as compared to food, the contribution of herbal medicinal products to the overall human PAH exposure is reasonably expected to be small. Consumption of 200 g smoked meat (limit according to Regulation 1881/2006 (EC) as amended: 30 µg/kg PAH4) will provide an intake of 6 µg PAH4. Assuming a daily dose of 3 g, the same amount could be reached by consumption of an herbal powder with a content of</p>	<p>Agreed</p> <p>Knowledge of growing conditions of the medicinal plants and processing conditions of the herbal substances/preparations would, together with a body of data from analytical testing, serve as the basis for a risk based approach to the issue.</p>

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		<p>1,998 µg/kg of PAH4. Obviously such levels are far above what can reasonably be expected for most medicinal herbs. An exception is mate leaf, an herbal drug known to be produced in a process involving application of unshielded fire.</p> <p>It will be important to establish a representative body of data and replace assumptions on the occurrence of PAH in herbal substances/preparations – however reasonable they may be – by knowledge. In the light of common PAH background exposure levels from food, this does not appear to be a matter of urgency and should thus allow for a systematic and controlled proceeding including collection of data as a first step.</p> <p>There is no doubt that PAH, being genotoxic carcinogens, should be as low as reasonably achievable in any product. There is currently no basis for defining limits for PAH in herbal substances/preparations for use in herbal medicinal products. Limits established recently for benzo(a)pyrene and PAH4 in dried herbs, spices and food supplements are not directly transferable to herbal substances or herbal medicinal products. It is also not clear on which empirical and/or toxicological basis they have been established. If it had been done on an empiric basis, the plants represented may not be comparable with the plants relevant for medicinal use. In addition, herbal preparations used for medicinal purposes differ from those used as food ingredients. Moreover, their intake levels and</p>	

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		<p>duration of use differ considerably from those representing the food (supplement) use of herbs.</p> <p>Moreover, due to the low transition rate of PAH into herbal infusions as well as into aqueous extracts, the risk of relevant contamination of these preparations with PAH can be regarded as low. The same applies to homeopathic and anthroposophic medicinal products due to the low transition rate of PAH into mother tinctures [4,5] as well as the dilution factor.</p> <p><u>Taking into account the utilization of limited resources to perform testing, we would recommend to first build up a reliable data source to evaluate whether or not and/or to which extent for which herbs/preparations regulatory action is required beyond the approach depicted above. Based on experience gathered from the case of pyrrolizidine alkaloids (PA) establishing a solid data base will require some years in order to be sufficiently representative.</u></p>	
	AESGP	<p>First Step: Risk based approach</p> <p>With regard to potential PAH contamination, an individual risk assessment should be performed. This should take into account major potential sources for PAH in herbal substances/preparations which are probably similar to those for food of vegetable origin: contaminated soil, combustion of wood or fossil fuels for the generation of heat for drying</p>	Agreed

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		<p>processes in product vicinity, drying/roasting of herbal materials by direct application of open fire, PAH emitting industrial processes close to cultivation/drying areas or – not least predominant domestic coal heating. For herbal preparations the dilution factor (of the starting material) should also be considered.</p> <p>If in specific cases the risk assessment leads to the conclusion that PAH contamination is expected to occur regularly at significant levels or occasionally at very high levels measures should be initiated to reduce frequency and levels of PAH occurrence. (Note: While certain changes of production processes or cultivation areas may seem easily manageable from a mere technical point of view, they are not as such in real life. Such changes may require high investments into machinery and infrastructure as well as time for process implementation and for education and training of personnel).</p> <p>Where risk assessment leads to the conclusion that potential sources of PAH contamination can be excluded and thus risk for PAH contamination is negligible or low, routine testing is not required.</p>	
	AESGP	<p>Second Step: Data collection</p> <p>The available scientific literature provides some publications on PAH occurrence in (medicinal) herbs or extracts. These sources</p>	Agreed

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		<p>cover a broad variety of approaches to sample preparation and analytical methodology and PAH coverage ranges from PAH4 to PAH16 or more. While results are reported for a large range of different herbs and preparations, only few data are available for each single herb and only some of the herbs are of significant importance for the European herbal medicinal products market. Data shows that PAH contamination may be both relatively high and frequent in some herbs while other herbs do not seem to be affected at all. Therefore, it is at present not possible to draw sound conclusions from this published data as regards the relevance in general of PAH for herbal drugs/herbal preparations/herbal medicinal products.</p> <p>Companies represented in our German member association BAH have recently started to test herbal substances and herbal preparations. However, further research is necessary in order to identify under which production conditions and in which herbal drugs from which origins PAH can occur. Establishing a sufficiently representative and conclusive body of data will require an analytical screening of herbal substances and herbal preparations based on an agreed coverage of PAH congeners and an agreed setting of methodological parameters and performance criteria. In the absence of pharmaceutical guidance documents covering specifically herbal drugs/preparations the principles established for PAH analysis in food based on Commission Regulations (EC) 333/2007 and (EC) 836/2011 [6,7] should be applied. When sufficient</p>	

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		<p>knowledge about a potential correlation between origin/production process and findings is available, respective data can be submitted.</p> <p>Where risk assessment leads to the conclusion that potential sources of PAH contamination can be excluded and thus risk for PAH contamination is negligible or low, routine testing is not required.</p>	
	AESGP	<p>Conclusion and recommendation</p> <p>Today, PAH are ubiquitous contaminants of our environment and food. Based on monitoring results, food is considered the most relevant source of PAH exposure for the common consumer – even for low or average consumers of those food items with particularly high PAH content. Given the common knowledge on possible PAH sources and some published data, it is reasonable to assume that PAH may possibly occur at significant levels in some herbs used for medicinal purposes, too. Therefore, it would appear advisable for the herbal medicinal products industry to draw attention to this matter by performing an assessment of the risk of PAH occurrence for herbal drugs/preparations and to collect data on PAH occurrence in herbs/herbal preparations in a systematic, coordinated approach in order to establish within a reasonable timeframe an authoritative body of data which can serve as a basis for further conclusions and, where necessary, action.</p>	Agreed

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		<p>References</p> <p>[1] COMMISSION REGULATION (EU) 2015/1933 of 27 October 2015 amending Regulation (EC) No 1881/2006 as regards maximum levels for polycyclic aromatic hydrocarbons in cocoa fibre, banana chips, food supplements, dried herbs and dried spices. Official Journal of the European Union No. L 282/11 of 28 October 2015.</p> <p>http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv%3AOJ.L_.2015.282.01.0011.01.ENG</p> <p>[2] Schulz CM, Fritz H, Ruthenschrör A. Occurrence of 15 + 1 EU priority polycyclic aromatic hydrocarbons (PAH) in various types of tea (<i>Camellia sinensis</i>) and herbal infusions. Food Additives & Contaminants Part A; 2014; 1-12. (attached)</p> <p>[3] EFSA (European Food Safety Authority), Scientific Opinion of the Panel on Contaminants in the Food Chain on a request from the European Commission on Polycyclic Aromatic Hydrocarbons in Food. The EFSA Journal, 2008, 724: 1-114.</p> <p>[4] IUPAC. Solubility Data Series. Volume 58. Polycyclic aromatic hydrocarbons: binary non-aqueous systems. Part I: Solutes A-E. Oxford University Press 1995 (attached).</p> <p>[5] Yap CL, Gan S, Ng HK. Evaluation of solubility of polycyclic aromatic hydrocarbons in ethyl lactate/water versus ethanol/water mixtures for contaminated soil re mediation applications. J Environm Sci 2012; 24(6): 1064–1075.</p>	

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		<p>(attached)</p> <p>[6] COMMISSION REGULATION (EC) No 333/2007 of 28 March 2007 laying down the methods of sampling and analysis for the official control of the levels of lead, cadmium, mercury, inorganic tin, 3-MCPD and polycyclic aromatic hydrocarbons in foodstuffs. Official Journal of the European Union No. L 88/29 of 29 March 2007.</p> <p>http://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2007:088:0029:0038:DE:PDF</p> <p>[7] COMMISSION REGULATION (EU) No 836/2011 of 19 August 2011 amending Regulation (EC) No 333/2007 laying down the methods of sampling and analysis for the official control of the levels of lead, cadmium, mercury, inorganic tin, 3-MCPD and benzo(a)pyrene in foodstuffs. Official Journal of the European Union No. L 215/9 of 20 August 2011.</p> <p>http://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:215:0009:0016:DE:PDF</p> <p>Where risk assessment leads to the conclusion that potential sources of PAH contamination can be excluded and thus risk for PAH contamination is negligible or low, routine testing is not required.</p>	