07 July 2021
EMA/HMPC/3914/2021
Committee on Herbal Medicinal Products (HMPC)

Overview of comments received on draft revised Public statement on the use of herbal medicinal products containing toxic, unsaturated pyrrolizidine alkaloids (PAs) (EMA/HMPC/893108/2011 Rev. 1)

Table 1: Organisations and/or individuals that commented on the draft revised Public statement on the use of herbal medicinal products containing toxic, unsaturated pyrrolizidine alkaloids (PAs) including recommendations regarding contamination of herbal medicinal products with pyrrolizidine alkaloids as released for public consultation on 15 August 2020 until 15 November 2020

	Organisations and/or individuals
1	Medicines and Healthcare products Regulatory Agency (MHRA); UK
2	AESGP (The Association of the European Self-Medication Industry)
3	G. Pohl-Boskamp GmbH & Co. KG, Germany
4	Kooperation Phytopharmaka GbR (Koop Phyto); Germany

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Table 2: Discussion of comments

General comments to draft document

Interested party	Comment and Rationale	Outcome
MHRA	The MHRA agrees and supports the recommendations made in this public statement and has the following additional comments. It is noted that no mention of skip testing has been made in this 2020 Public statement, unlike the 2016 public statement with transitional arrangements. In relation to this, it would be helpful if the guideline could include further clarity on acceptability of skip testing and under what circumstances this would be considered appropriate. The type of factors that could be discussed could include the nature of the herbal substance (type of plant/plant part), risk minimisation measures, the number of historical batches for which data would be presented relative to the proposed frequency of skip testing and if/how much data would be provided to cover each supplier of the herbal substance. A discussion of potential derogations would be useful, for example essential oils, seaweed or plant parts such as whole fruits where PA contamination is unlikely.	Partially endorsed. The requirements for skip testing were given in the PS version ("Transitional recommendations for risk management and quality control") as follows: "Consideration should be given to the need for routine vs periodic controls (skip testing) depending on the risk assessment and the available evidence base". Furthermore, it was referred to risk-based scenarios of some MS. With the version of the PS now available, the reference to "provisional" is no longer necessary. For any "skip-test"-scenarios, the same requirements for "skip testing" should apply as for all other tests for impurities. The prerequisites etc. for such a design are presented in the corresponding quality guidelines of the EMA. Potential derogations are hard to define per se. From literature it is known, that even a horizontal transfer via roots can take place, PA containing pollen can be deposited on other structures etc. Concerning essential oils see below.
G. Pohl-Boskamp GmbH & Co. KG	We encourage HMPC to include a specific section in the Public Statement that reflects the particularities regarding HMPs with essential oils of pharmaceutical quality as active ingredients. For this purpose, we like to	See below.

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	provide additional data obtained by PB in an investigation on the PA-stripping ability of the steam distillation process step in the manufacture of essential oils. The following documents will be submitted to HMPC: 01 Cover letter 02 PA-study report along with 6 associated annexes 03 Statement on analytical results of PA-testing of essential oils	
Koop Phyto	Koop Phyto appreciates the re-drafting of the public statement on pyrrolizidine alkaloids (PAs), given that in the last few years there was considerable scientific progress in the fields of the assessment of the pre-existing toxicological data on PAs, and of the generation of new data, especially on the mechanisms of action of the different PA isomers and their different genotoxic potency, and on the feasible extent of the reduction of PA entry to herbal drugs. These data show convincingly, that keeping the provisional limit of 1 µg/day now as a permanent limit, is very clearly on the precautionary side from a toxicological perspective and less likely to disrupt supply chains. In addition, the inclusion of contamination as a source of PAs in herbal drugs to the statement is an advantage of this new draft. Given the extent and complexity of the subject of the statement, there is still a broad range of points to comment for further improvements. These comments take the scientific projects and international scientific workshops initiated by Koop Phyto in the field of PA toxicology into account and are focused predominantly on aspects of toxicological risk assessment and risk management.	-

Specific comments on text

Section number and heading	Interested party	Comment and Rationale	Outcome
1. Introduction, lines 57-59	Koop Phyto	The inclusion of the contamination of herbal drugs with wild herbs to the public statement is appreciated.	-
1.4. Contamination of herbal medicinal products	G. Pohl-Boskamp GmbH & Co. KG	As mentioned above (general comment) section 1.4. should be complemented with a chapter dealing with the particularities of HMPs utilizing essential oils of pharmaceutical quality as active ingredients. Therefor the following proposal is made, in analogy to lines 240 to 242 please include after line 263: *Investigations proved that essential oils with pharmaceutical quality are free of PAs. Potential PA-contaminants in precursors (plant material) cannot be transferred into the corresponding essential oils due to the rather hydrophilic nature of PAs and the two-step manufacturing process for essential oils (initial process step is steam distillation or cold pressing, which is typically followed by a refinement by rectification). Since essential oils of pharmaceutical quality employed as active ingredients do not pose any risk of carrying PA-traces, HMPs manufactured thereof are basically out of scope and can be regarded as safe with respect to PA-contamination.*	Endorsed in regard to the general outcome. However, the explanations concerning essential oils are included in chapter "4.2. Specifications for herbal substances, herbal preparations, HMPs" and furthermore it is to highlight, that although appreciated, the documents provided by Pohl-Boskamp are not be seen suitable for proving this beyond doubt and were therefore considered as supportive only.
2.3.3. Genotoxicity and Carcinogenicity of PAs,	Koop Phyto	There are several references attached, which are of relevance for this section of the statement and are listed in the following (in alphabetical order):	The references presented do not contradict what is stated in the PS. Aboud Hadi *et al*. (2020); GA (2020); Gao (2020);

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line 627 ff.		• Aboud Hadi NS *et al.* (2020) Genotoxicity of selected pyrrolizidine alkaloids in human hepatoma cell lines carcinoma HepG2 and Huh6. Mutat. Res. Submitted. *Comment: Supports REPs and underlines the existence of a threshold of genotoxicity in some PAs.* • GA (Society for Medicinal Plant and Natural Products research), Ed.: Abstract volume of the GA eSymposium on Novel Insights into Pyrrolizidine Alkaloid Toxicity And Implications for Risk Assessment, September 29-30, 2020. *Comment: Several contributions at this symposium underlined the large differences of genotoxic potency of PAs, which are not taken into account in present MOE approaches, so that these approaches can be rated to be highly on the safe side.* • Gao L. (2020) Structure-dependent hepato-cytotoxic potencies of selected pyrrolizidine alkaloids. *Comment: Confirms differences of PAs in genotoxic potencies.* • Hartwig A *et al.* Mode of action-based risk assessment of genotoxic carcinogens. *Archives of Toxicology* 2020, 94:1787–1877. *Comment: On risk assessment methodology.* • Kopp. Extracting and Analyzing Pyrrolizidine Alkaloids in Medicinal plants. *Toxins* 2020, 12, 320. *Comment: Review on extraction and analysis of PAs.* • Rutz l *et al.* Structure-dependent genotoxic potencies of	Rutz *et al*. (2020); Schrenk (2020) (2x) deal with questions concerning potential different genotoxic potency of single PAs. This research focus is already addressed in the PS. Hartwig *et al*. (2020) formulated: "For future, it is necessary to elucidate structure–activity relationships referring to different endpoints to proper assess the risk of PAs for humans and livestock. This includes on the one hand clear data for oral bioavailability of mono-, di- and cyclic diesters at human-relevant doses in dependence of their respective structure. On the other hand, more data for the mode of action, especially in the target organ liver, are needed." These aspects of missing information are covered in the PS. Kopp (2020) reviews on extraction and analysis methods of PAs. The conclusion "This review shows that both standardized extraction and sensitive determination of PAs is required for achieving appropriate safety levels concerning public health in future." is not contradicted. Rather, the explanations in the Ph. Eur. on the validation of the measurement method, to which reference is made in the PS, are applicable here. Xia (2020) describes a method to identify and quantify metabolites formed from the metabolism of senecionine in biological systems. This is not considered to substantiate the PS on limits for PAs in

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		selected pyrrolizidine alkaloids. *Archives of Toxicology* 2020, 94:4159–4172. *Comment: The work is on metabolic activation of PAs and on Relative Potency Factors and shows, that in toxicological studies, the genotoxic and cytotoxic potency of PAs go very much in parallel.* • Schrenk D. Final Report of the research project TU-KL 1, Investigation of the hepato-cytotoxic and genotoxic potency of selected pyrrolizidine alkaloids, relevant in medicinal plants and preparations thereof. Study Report, University of Kaiserslautern, Germany 2020. *Comment: Research report, University Kaiserslautern, supports REPs and the existence of a genotoxicity threshold in the range of the PAs most relevant as contaminants in herbal drugs.* • Schrenk D. (2020) Lecture PA-Workshop The bad ones and the not so bad ones GA eSymposium. *Comment: Supports REPs and at toxicological threshold of PA genotoxicity and shows, that the present threshold is very clearly on the safe side or even overly precautionary.* • Xia Q. Quantitation of DNA reactive pyrrolic metabolites of senecionine. *J. Food Drug Anal* 2020, 28:167-174. *Comment: On genotoxicity of senecionine in vitro.*	drugs.
3.2. Recommendations, line 843 ff.	Koop Phyto	When it is stated that HMPC decided to follow the $BMDL_{10}$ approach of EFSA, it needs to be taken into account, that the Margin-of-Exposure approach of EFSA is intended to be	Not endorsed. It is noted that the wording might be misunderstanding, however, in ICH M7 it is explained,

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		used to determine, whether concentrations of genotoxic substances in products are of low concern or not. EFSA considers that the MOE approach is connected to a high uncertainty, so that only orders of magnitude can be rated as of low concern. Risk management, in case that the MOE is lower than 10.000, would then follow the ALARA principle, so that, depending from the feasibility of lowering the PA content of a given product, product specific maximum values could be negotiated. Using the MOE approach in a reverse way for setting limits, as is sometimes done, as e.g. here by HMPC, is accordingly not in line with this concept of EFSA. Another point is, that, given that reference is taken to ICH M7, the question comes up, why the less-than-lifetime approach, which has an important place in this guideline, is not applied here. Given that most HMPs are used only short-term, and by far less than lifetime, this approach would allow to set maximum values in a more appropriate way. While, as discussed above, the concept of relative potency factors (RPFs) for different PAs may not yet elaborate enough to allow inclusion in this version of the public statement, we would like to encourage HMPC to follow the future developments in that field with an open attitude, and to revise this statement accordingly as soon as the development status of the RPF concepts allows. A similar	that the $BMDL_{10}$ approach can be used in the field of medicinal products to derive limits. The differences in concepts might be explained by the different regulatory systems of EMA and EFSA (see also Assessment report Procedure under Article 5(3) of Regulation EC (No) 726/2004 "Nitrosamine impurities in human medicinal products" (EMA/369136/2020)). Accepting the LTL approach could lead to high acute PA intake, especially with medicines given at high doses and for a short period of time. Furthermore, patients may take more than one PA-containing medicinal product, which would further increase their daily PA intake. In addition, environmental exposure varies based on lifestyle. Patients with a certain lifestyle may potentially have higher than average exposure to PA. Furthermore, the LTL approach relies on strict linearity of the dose response even in the higher dose ranges, which is not proven so far. Therefore, the LTL approach described in ICH M7 is currently not used for PAs.

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		concept was also developed years ago for many dioxin derivatives and is now considered to be tried and tested. Taking these considerations into account would allow to safe resources now needed to assure PA limits, which are most likely overly precautionary in many products and have therefore no relevant additional positive impact on public health. At the same time overly precautionary limits can easily lead to an inappropriate allocation of resources and enhanced costs for our society. This in different ways, by potentially leading to prohibitive retail prices of products, so limiting the access by populations with low income, and by potentially leading to excessive agricultural measures to protect cultures against weed entry, so counteracting biodiversity and leading to a less favourable carbon dioxide footprint of the production of herbal drugs.	
3.2. Recommendations, line 869 ff.	Koop Phyto	For the use in children, an adjustment according to the body weight of the age group is asked for. In most medicines, doses for children are lower than those in adults and adapted to age groups. This might not fully compensate for the lower body weight, but has been still seen appropriate for other dose-dependent safety parameters of the products. Adding an additional fixed body-weight related adjustment of daily PA intakes, can, in an arbitrary way, lead to the need to lower PA contents in products as compared to those set for adults.	Not endorsed. The limit for adults is derived from body weight. It has not been proven why this reference to body weight should not apply to children. For both limits listed, the HMPC used rounding to avoid too many decimal places: adults (50 kg) = 0.0237 µg/kg bw/day x 50 kg = 1.185 µg/day= ~1.0 µg/day children (20 kg) = 0.0237 µg/kg bw/day x 20 kg = 0.474 µg/day= ~0.5 µg/day

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		So, the usefulness and feasibility of the children-related adaptation of doses to the body weight would deserve to be re-checked. Independent from this point, the example of 0.5 µg PAs / 20 kg is hard to understand calculatory.	
3.2. Recommendations, line 878 ff.	Koop Phyto	Given that it is stated in this section of the text, that cutaneous penetration is much lower than oral absorption, not adapting the permitted dose to this lower absorption, but to request product-specific studies, seems overly complex and deserves a re-check.	Not endorsed. To date, no studies are available from which a general factor can be derived.
3.3. Quality measures to reduce contamination with PAs, line 909	Koop Phyto	The statement that, in addition of the MOE approach warranting a dose of low concern, the concept of ALARA should be applied, is incompatible with a reasonable risk management strategy. Given that PA-doses with a sufficient MOA are of low concern, further measures to lower PA contamination will generate no relevant additional benefit for the patient. The mentioned ALARA approach may also result in higher retail prices excluding low income populations from access, and have an additional negative impact on biodiversity in agriculture and on carbon dioxide footprint. This becomes clear when looking e.g. to the list of agricultural measures under 4.3., lines 971 ff, which are likely to have an additional negative impact both from the perspective on biodiversity in agriculture and on carbon dioxide footprint.	Not endorsed. The ALARA principle is mentioned under the heading with the contaminations. The measures mentioned later are part of the Code of Practice, which is implemented by the industry, as far as it is presented. It should be noted, that PA-containing plants as contamination should be avoided as much as possible.
4.2.	MHRA	In cases where a herbal preparation is used, batch data for the herbal preparation would be expected to be provided, as the herbal substance data could not be translated into an	Not endorsed. It should be pointed out, that the absolute amount of PA couldn't increase. Therefore, even if the PA content

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		equivalent content of PAs in the finished product. It is stated that the most appropriate stage for testing to take place should be considered; i.e. whether at the level of the herbal substance, the herbal preparation or the herbal product. If cases where an extract is used in a herbal product, PA data from the herbal substance would not be useful because the levels cannot be translated into an equivalent content in the herbal product. In these cases, it would be expected to see PA data on the herbal preparation used in the herbal product. It would be useful to make this point clearer in the public statement.	is measured in the herbal substance, the concentration (DER) should be taken into account and so the numerical amount of PA should be calculated for the final product, also keeping in mind the daily dose of the product. Although the problems with the test in the herbal substances are known (e.g. spot contamination), it is the task of the MAH/applicant to present a coherent concept to reliably determine the PA content.