EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 November 2014
EMA/HMPC/577756/2014
Committee on Herbal Medicinal Products (HMPC)

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

Table 1: Organisations and/or individuals that commented on the second draft Public statement on the use of herbal medicinal products containing toxic unsaturated pyrrolizidine alkaloids (PAs) as released for public consultation on 14 November 2013 until 15 February 2014

	Organisations and/or individuals
1	The Association of the European Self-Medication Industry (AESGP)
2	European Botanical Forum (EBF)
3	European Coalition on Homeopathic and Anthroposophic Medicinal Products (ECHAMP)
4	European Scientific Cooperative on Phytotherapy (ESCOP)
5	European Confederation of Pharmaceutical Entrepreneurs (EUCOPE)
6	Kooperation Phytopharmaka (KOOP Phyto)
7	National Institute of Medical Herbalists (NIMH)
8	Swissmedic

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Table 2: Discussion of comments

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Interested party	Comment and Rationale	Outcome
AESGP	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. AESGP appreciates the new and exceptional (second) consultation period and the opportunity to submit comment. In this respect, we refer to the comments submitted by AEGP on the first draft in February 2013.	
AESGP, EUCOPE	Executive Summary We agree that the intake of pyrrolizidine alkaloids (PAs) and their N-oxides should be minimized due to their hepatotoxic and cancerogenic risks and we welcome developing uniform European rules for the use of herbal medicinal products containing toxic 1,2-unsaturated pyrrolizidine alkaloids. However, to our view for the following reasons the proposed conclusion and the recommendations of the 2nd draft Public Statement are not justified and not realistic: • As stated in the HMPC recommendation, the exposure to PAs should be kept as low as practically achievable. This intention, however, shall not result in a limit which cannot be achieved in practice. • The limit of 0.035 µg PAs per day is inadequate and would result in prohibition of many products or batches thereof. Excluding all those products manufactured from plant species that may contain PAs (even in traces and /or	

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	as contaminants) which exceed this limit would lead to depriving patients of effective herbal drugs which are approved according to current scientific knowledge and for which positive monographs have been established. • In accordance with the Less-than-Lifetime (LTL) exposure concept addressed in the new ICH M7 Guideline (EMA/CHMP/ICH/83812/2013), for herbal medicinal products which may contain PAs a differentiated and balanced assessment should be performed with an option to permit higher, more adequate limits in accordance with their duration and frequency of use. • Internationally accepted guidelines should be applied which explain how limits of toxic impurities can be defined. Beyond different EMA Guidelines on impurities in medicinal products, recommendations do exist for the food area which might as well be applied for medicinal products. • Furthermore, as long as appropriate strategies to reduce contamination with PA-containing weeds have not been developed, strict limits as proposed in the HMPC Public Statement cannot be met. For this reason, a sufficient period of time is required to reduce the burden of PA caused by weeds and to meet realistic limits as used e.g. in the food area. Additionally the yet unsolved analytical problems have to be addressed and resolved before setting limits. • In light of the recent developments and discussions initiated by the BfR Study, re-consideration of the HMPC Public Statement is absolutely necessary. Early setting of limits for herbal medicinal products without taking into account the overall problem of potential contamination with PA-containing weed is not realistic. 1. Current situation of potential contamination with PA-containing plants We understand that the HMPC Public Statement mainly deals with herbal	The intake of PAs can occur via different "routes": PA containing plants (medicinal usage) and contamination of other herbal material by PA-containing plants and/or contamination of food (e.g. honey). For the toxicity/carcinogenicity the source of the PAs is not important. Therefore rather a general daily limit should

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	medicinal products produced from plants which naturally contain PA, as described in chapter 1.1 with regard to the natural occurrence of PA in plant species of the families of e.g. Boraginaceae, Asteraceae and Fabaceae. However, bearing in mind the current discussion of a potential contamination of plant material with PA after publication of findings in more than 200 samples of herbal (food and medicinal) teas by the German Federal Institute for Risk Assessment (BfR) [1], the HMPC Public Statement deserves special attention and a careful consideration of potential consequences for all herbal medicinal products. So far the recently published BfR findings [1] have not yet been taken into consideration within the HMPC draft Public Statement. From those findings it can be concluded that apart from a natural content of PA in certain herbal drugs of the above-mentioned families, a coincidental occurrence of PA in cultivated material is suspected which might presumably be caused by contamination through weeds, e.g. Senecio species. In any case, these findings imply the need of a complete re-consideration of the HMPC Public Statement. This is even more relevant in view of the cut-off date of July 2011 for literature references given in the 2nd draft HMPC Public Statement. Otherwise it should be clearly mentioned that the Public Statement applies only to those medicinal products containing herbal drugs known to naturally produce PAs. Although efforts are being made to avoid the occurrence of PA-containing weeds by measures of Good Agricultural and Collection Practice (GACP) [2] and to elucidate the actual burden caused by such weeds in a project initiated by the German Medicines Manufacturers' Research Association (FAH), a complete avoidance is not realistic. In light of this problem re-consideration of the HMPC Public Statement is absolutely required. Early setting of limits which are not suitable in practice is not realistic.	not be exceeded. Strategies for the reduction of contamination have to be developed as soon as possible to meet the requirements of the total intake of PAs. Due to the more recent knowledge about the occurrence of PA (for instance as contamination) the older limits of the German graduated plan from 1992 cannot be supported anymore (e.g. a restriction to 6

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	2. Accepted limits of PAs in medicinal products As stated in previous comments, we regard the limits set by the German graduated plan in 1992 [3] as safe and established. They are in the range of the value established by use of the Margin of Exposure (MoE) approach for food (see 3.1.), differing for short-term and long-term use. With a limitation of application to maximum 6 weeks per year, doses of up to 1 µg for internal and 100 µg for external use are accepted. Such doses are contraindicated for pregnant and breast-feeding women and, in case of topical use, should only be applied on intact skin. Without limitation of duration of use, the maximum daily exposure to PAs by medicinal products should not exceed 0.1 µg for internal use and 10 µg for external use. In the HMPC "Overview of comments" (EMA/HMPC/893108/2011) [4], it was claimed that the limits described in the German graduated plan were based on older studies. On the other hand, it is stated that more recent studies with single PA exist and that the $BMDL_{10}$ value – based on the induction of liver haemangiosarcomas by lasiocarpine in male rats, cited from EFSA (2011), could be used instead (page 3/33). However, the study with the single PA lasiocarpine on which the assessment from EFSA (2011) is based and which was considered as most conservative by the HMPC, is the NTP 1978 Report [5]. This is exactly the same study which was already cited in the German graduated plan in 1992 [3]. Thus, the findings were already included in the risk assessment from the German graduated plan that led to the limits specified above which were regarded are safe and that are still valid in Germany since then. Therefore, there is no reason to question these limit values. During the past 20 years after the establishment of this graduated plan, no basically new scientific knowledge concerning PAs has been published and no new information or signals relevant for assessment are available from	weeks). The intake of toxic, unsaturated PA from herbal medicinal products (for short-term intake) should not exceed the daily limit calculated by EFSA: 0.007 µg/kg. Taken into account a body weight of 50 kg this would lead to a daily intake of 0.35 µg PAs for adults. The body weight of 50 kg is used, since for ~18% of the European population (average) the body weight is given with less than 60 kg [Special Eurobarometer 246/Wave 64.3 "Health and Food" 2006: *ec.europa.eu/public_opinion/archives/ebs/ebs_246_en.pdf.*; found September 2014]. The calculation of EFSA was never challenged by the draft public statement, rather it was tried to focus on the topic of the additional intake of toxic, unsaturated PAs via food and medicinal products. By now this is pointed out more clearly by giving the EFSA limit as

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	pharmacovigilance that would necessitate further action. For this reasons, the limits set in the German graduated plan in 1992 are sufficient to guarantee the safety of PA-containing medicinal products. 3. Toxicological assessment From our point of view, the calculation of the limit given by the HMPC is not adequately justified by current toxicological assessment criteria and regulatory guidelines and has been shown by Schrenk [6]. For the calculation a range of different assessment methods have been used and mixed up, which result in multiple worst case assumptions with respective addition of safety factors, unusual in comparative cases. In his recently elaborated expert report, Schrenk [6] states that extrapolation of animal cancer data obtained from a very narrow high-dose range into a dose range being six orders of magnitude lower is considered as being highly uncertain and obsolete. The approach using a factor of 10,000 as proposed by EFSA [7] provides a rational basis for assessment. Furthermore, the HMPC approach does not take into account the fact that most PAs are likely to exert a lower genotoxicity and carcinogenicity than lasiocarpine which was used by EFSA as reference compound. Herbal medicinal products have a documented benefit which is confirmed by the competent authority during marketing authorisation/registration procedures. Thus, regarding risk evaluation, herbal medicinal products have to be treated at least in the same manner as food, if not even better. In his expert report Schrenk [6] recommends e.g. • To replace the approach to estimate a virtually safe dose from rat cancer data over six orders of magnitude by the EFSA MoE approach considering	such and it is reflected that the additional intake via medicinal products is only seen as short-time intake. See above.

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	a MoE of 10,000 and above to be of low concern. • To take into account that herbal medicinal products have proven beneficial effects to sick patients. • To apply the Less-than-Lifetime (LTL) exposure concept because herbal medicinal products are not used over the whole human lifespan. 3.1 Margin of Exposure approach As stated in previous comments we regard the application of the Margin of Exposure (MoE) approach used by EFSA and BfR for pyrrolizidine alkaloids also as useful for herbal medicinal products. The calculations performed for contamination of food with pyrrolizidine alkaloids show that daily doses of maximal 0.007 µg PAs/kg b.w. are acceptable [8-10]. For an adult of 60 kg b.w. a daily intake of 0.42 µg is judged to be reasonable [8, 10]. Application of this $BMDL_{10}$ takes various safety factors in concern, as it is based on lasiocarpine, a pyrrolizidine alkaloid of high toxicity. In the carcinogenicity study the effect of lasiocarpine was investigated on 24 rats in each group [5]. From this study a Benchmark Dose Lower Confidence Limit 10% ($BMDL_{10}$) of 73 µg/kg b.w/day has been calculated [11]. Based on a MoE of 10,000, corresponding doses of up to 0.007 µg/kg b.w/day are practically not associated with any cancerogenic concern [8, 11]. According to the EMA Guideline on the Assessment of Genotoxicity of Herbal Substances/Preparations, a MoE of 10,000 and higher has been deemed to be of low health risk [12], even more as this approach based on lasiocarpine has been estimated conservative [8]. In the HMPC's Overview of comments [4] it was pointed out that the MoE approach was originally developed for variable, but continuous exposure. As a consequence, its application bears even more safety as the intake of herbal medicinal products is generally limited regarding dosage and their duration of use.	Toxic, unsaturated PAs have to be considered as mutagenic compounds with positive carcinogenicity data. Therefore the TTC is not applicable. Although pyrrolizidine alkaloids do not officially belong to the mentioned high-potency class of compounds, their clear carcinogenicity at relatively low exposures indicate that they resemble the high-potency group. Therefore the limit of 1.5 µg/day cannot be supported. Even though that the HMPC allows the TTC concept for the risk evaluation of herbal preparations containing identifiable genotoxic compounds this applies only to preparations/compounds where an established safety assessment method cannot be applied by the lack of data. For PAs the data existing at the moment were seen sufficient to allow a safety assessment (s. EFSA 2011).

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	3.2 TTC concept Furthermore, as explained earlier, we regard the limit for oral PA intake defined by the German graduated plan 1992 as justified by the Threshold of Toxicological Concern (TTC) concept which, according to the EMEA Guideline on Genotoxic Impurities, is defined by a threshold value of 1.5 µg/day for genotoxic impurities in pharmaceutical products [13]. We do not agree that the TTC and other calculation models are not acceptable because PAs have to be considered as mutagenic compounds with positive carcinogenicity data. Furthermore, toxicology data is available from different animal species receiving defined pyrrolizidine substances (or groups of them) but not the various naturally occurring mixture of PAs. Thus, based on the principle of the TTC concept the specific composition and overall structure of this natural PA mixture is not known. Thus, – in analogy – the basic prerequisite to apply this concept is fulfilled. According to the TTC concept, a daily intake of less than 1.5 µg of a compound of toxicological concern is regarded as associated with an acceptable health risk and no further testing or regulatory measures are necessary at this level, including genotoxic and carcinogenic compounds [13, 14]. In general, the regulatory threshold value of 1.5 µg/day is applicable to all types of chemical compounds. For chemicals with a structural alert for genotoxicity a reduced threshold of 0.15 µg/day is suggested. However, a prerequisite for the application is a comprehensive knowledge of the chemical structure [14]. For compounds with specific structural alerts (i.e. aflatoxin-, azoxy-, N-nitroso-, dibenzodioxin- and dibenzofuran-like structures), which were identified to be of such high potency that intakes even below the TTC limits would be associated with a high probability of a significant carcinogenic risk, the TTC concept cannot be considered [13]. Pyrrolizidine alkaloids do not belong to these excluded	The Less-than-Lifetime approach cannot be applied for the intake of PAs, since the intake occurs also via food and/or contamination of e.g. herbal teas (without PA-containing plant as labelled ingredients). Therefore a restriction to only a certain amount of days/years cannot be assumed, even though that the defined amount or the real burden cannot be given exactly. Therefore a strong discrimination between intake by food and intake by medicinal products cannot be performed, but must be seen as additive, as pointed out in the Public Statement. However, for a short-time usage the limit of 0.007 µg/kg/day might be applicable for medicinal products as well.

<table>
<tr><th colspan="3">GENERAL COMMENTS</th></tr>
<tr><td></td><td>substances but are known chemical structures that allow accurate analysis and application of the TTC concept. Although it has not been accepted by the HMPC that PA do not belong to the mentioned group of high-potency substances [4], we are of the opinion that the TTC concept is applicable.

Even though the TTC concept cannot be interpreted as providing absolute certainty of no risk, it underlines that exposure to PAs corresponding to the German graduated plan is associated with an acceptable risk as the intake is less than 1.5 µg/day [13].

3.3 Less-than-Lifetime approach of ICH M7

The recently published draft ICH M7 Guideline on the assessment and control of DNA reactive impurities – although not obligatory for herbal medicinal products - states that intake of a mutagenic impurity of 1.5 µg per day is considered to be associated with a negligible cancer risk (theoretical risk <1 in 100,000 over a lifetime exposure). However, to address Less-than-lifetime (LTL) exposures to mutagenic impurities in pharmaceuticals, an additional approach is applied which describes the following acceptable intakes for individual impurities [15]:

<table><tr><td>Duration of treatment</td><td>≤ 1 month</td><td>>1-12 months</td><td>>1-10 years</td></tr><tr><td>Daily intake [µg/day]</td><td>120</td><td>20</td><td>10</td></tr></table>
As herbal medicinal products are usually used for a limited time, the application of the LTL exposure concept is fully justified. Thus for herbal medicinal products which may contain PA a differentiated and balanced assessment should be performed with an option to permit higher limits in accordance with their duration and frequency of use. This has also been proposed by Schrenk in his</td><td>The limit for short-time usage is now set with 0.35 µg/Day. As an example, the daily intake of 0.1 µg/day was already mentioned in the German graduated plan (1992) which is valid since many years. Assuming a possible intake of 0.35 µg PA/day via medicinal products (PA-containing plants as active ingredient or contamination), this limit should be possible to maintain.</td></tr>
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	expert report [6]. 4. Analytics of PA According to the HMPC recommendation, the exposure to PA should be kept as low as practically achievable. This intention, however, shall not result in a limit (0.035 µg daily) which cannot be achieved in practice. Generally, the analytical quantification of PA in natural materials is a very difficult challenge, due to the wide variability in structure of different PA and its low concentrations in complex and different plant matrices. At the moment, only 17 reference standards are commercially available whereas in total more than 500 PA exist in more than 6000 plants. Due to the limited availability of reference standards, the analytical results have a large variability as different PA show distinct detector responses in the respective analytical methods. Thus, for special analytical problems of individual plants adequate methods using the corresponding reference substances need to be developed and validated in order to achieve accurate results. An analytical method in the "parts per billion" range has been recently developed for 17 PA compounds occurring in typical weeds [1] and presents the best possible technical level for detection of very low traces of PA. Anyhow, from an analytical point of view, the limit of 0.035 µg per day is not feasible and not realistic. E.g. a daily dose of 5 cups of medicinal tea each prepared with 2 g herbal drug per tea bag (corresponding to 10 g herbal drug per day) would implicate a limit of 3.5 µg PA per kg herbal drug. Due to the fact that in case of PA contamination by weeds typically much more than one PA compound occurs, the limit of 3.5 µg would refer to the sum of, e.g. 5 or even more different PA compounds. The current limits of quantification for single PA compounds are mostly in a range of 5 to 20 µg/kg. Thus it would be feasible to assume a	Measures of the industry to lower the PA burden per se should be presented in the individual application/ documentation.

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	general limit of quantification of 10 µg/kg on average. The sensitivity of the above-mentioned method [1] allows to detect contaminations as low as, e.g., 2-3 Senecio plants in a cultivation area of 1 ha (=10.000 square metres) which - theoretically - might cause an estimated PA contamination of about 50 µg/kg (!). 2-3 Heliotropium plants in a cultivation area of 1 ha would cause a calculated PA contamination even of about 500 µg/kg. Evidently, with regard to these facts a limit of about 3.5 µg PA per kg herbal drug, as implicated by the maximum dose level of 0.035 µg/day proposed by the HMPC, is clearly not feasible. There is no analytical technique available with corresponding lower detection limits. 5. Elucidation of PA burden caused by weeds At present, big efforts are being undertaken to elucidate the actual burden that is suspected to be caused by weeds. Two projects are in preparation, in which the German Medicines Manufacturers' Research Association (FAH) is involved. The first project „Avoidance of introducing pyrrolizidine alkaloid-containing, allergenic and other dangerous weed species into medicinal and spice plants crops via seeds, Phase 1: Quantification of problematic weed seeds in marketed seed of medicinal and spice plants" will be part of the demonstration project "Optimization of Chamomile, Valerian and Melissa production by breeding and cultivation technologies as example for improving the German herb growers' competitive situation (KAMEL)" and focus on the quantification of weed seeds in the seeds of the medicinal and spice plants Chamomile, Thyme, Melissa, Valerian, Fennel, Marjoram and Caraway; special emphasis will be given to the seeds of PA -containing weeds (e.g. Senecio), tropane alkaloid-containing weeds, allergenic weeds and invasive weeds (e.g. Ambrosia). In a follow-up project, methods for seed cleaning will be developed in order to eliminate the	From the pharmacovigilance database it is hardly possible to reflect on development of tumours. Therefore the argument of not known cases of tumour development cannot be taken as rational for general limits for cutaneous use. As stated in the Public Statement absorption rates can be influenced by many factors, such as matrix, excipients etc. Higher contents of PAs within the products for cutaneous use would be possible if for the relevant product low absorption rates (generated with modern analytical techniques; in animal species which are more comparable to human beings in relation to the skin or *in-vitro* human skin preparations) can be shown, not exceeding the daily intake of 0.35 µg PA/kg for adults.

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	seeds of these weeds. This project will probably be financed by the German Federal Ministry of Food and Agriculture (BMELV) via the Fachagentur Nachwachsende Rohstoffe e.V. (FNR). In the second project "Recording of the site-specific weed flora in medicinal plants crops in middle Europe with special emphasis on pyrrolizidine alkaloid-containing weeds" a database will be built up listing the weeds found in medicinal plants crops in middle Europe and their respective amounts of PA. In addition, the database will contain descriptions and as far as possible sketches and photos of the weeds. The database will be in different languages and allow the addition of further weeds. After completion, it will be open for downloading by any party interested so that each organization and company can adjust it to its special needs. Financing of this project is still uncertain but possibly also done by BMELV via FNR. As long as appropriate strategies for reducing or avoiding contamination with PA-containing weeds have not been developed, strict limits as proposed in the HMPC Public Statement cannot be met. For this reason, a sufficient period of time is required to investigate the extent and the risk of a PA-burden caused by PA-producing weeds and to meet realistic limits as used e.g. in the food area. 6. Cutaneous Application Concerning cutaneous use, the German graduated plan [3] specifies concrete and reasonable limits for topical application. Due to a low absorption through the skin the upper limit for topical application was defined 100 times higher (10 µg/d) than for oral (0.1 µg/d) use. According to present scientific knowledge there are up to now no side effects reported regarding cancerogenicity or liver toxicity for topical treatments. So far the limits for PAs in topical applications set in 1992 seem to be sufficient with regard to product safety.	See above. See above.

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	However, the second draft Public Statement of the HMPC has a different approach. It requires a maximum daily amount of PA of <0.035 µg which represents the same threshold as for oral use. Higher contents are possible in cases where lower absorption rates are proven for the specific product. From our point of view, this is not adequate. On the one hand differences existing between oral and topical use have to be taken into consideration in general, on the other hand, as addressed under point 4, even with modern techniques the determination of single PA absorption rates is analytically not feasible due to their extremely low content. 6.1 Low permeation of pyrrolizidine alkaloids through the skin A permeation study with human skin [16] analyzed the permeation of the model pyrrolizidine alkaloid monocrotaline in a solution, added to a comfrey cream, in comparison to the reference substance caffeine which is known to be nearly completely absorbed orally [17] but hardly penetrate human skin [18]. The results showed that the permeability coefficient of monocrotaline was even 10 times less than that for caffeine. Moreover, the absorption rates of monocrotaline in the cream were lower than those from the solution. These very low absorption rates confirm the results of former studies e.g. [19] which showed that the absorption of pyrrolizidine alkaloids in a rat model could be 20 to 50 times lower than after oral application. 6.2 Analytical aspects These studies, however, do not consider the individually different absorption behaviour after topical application between the PAs and their corresponding N-oxides yet. PAs occur in extracts or plant materials also as their corresponding N-oxidated forms which should have a lower penetration because of their more hydrophilic properties. Therefore the following analytical issues for topical	See above. The German graduated plan (1992) reflects only to intact skin. If the usage on broken skin is applied for, the safety should be shown (absorption rates in models for broken skin). The HMPC is not responsible for the assessment of homeopathic medicinal products. However, the same limits of intake should be applicable for homeopathic medicinal products keeping in mind, that due to the often performed potentiation the general burden of PA-content/daily dosage will be lowered.

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	application have to be considered: • The limit of 0.035 µg per 50 kg body weight per day would represent the sum of all PAs and their N-oxides respectively. • PA-containing herbal drugs or extracts do not only contain one single pyrrolizidine alkaloid but a couple of substances, occurring as PA-alkaloids and their N-oxides respectively. • Additionally the dilution within the skin of the PAs and PA N-oxides has to be taken into account for resorption analysis. • Therefore even with advanced techniques the limit of 0.035 µg is not feasible and not realistic from an analytical point of view. Reference is also made to Chapter 4 of these comments regarding the analytical discussion. 6.3 Summary and conclusion for cutaneous application As the absorption rate after cutaneous application is lower than after oral application medicinal products for external use deserve a separate calculation. The limits for oral and for topical application defined by the German graduated plan of 1992 are still appropriate because there are no known safety risks and new scientific knowledge is not available. It is established that the absorption of PAs through the skin in general is very low. However, the currently available penetration model and the assays do not allow real quantification of each single PA on its way through the skin. Due to the lower absorption after application on intact skin higher amounts of PAs should be accepted in medicinal products for external use. This is also in line with the German graduated plan where daily limits for external application on intact skin are 10 µg PAs (with unlimited treatment duration) and 100 µg PAs (with restricted treatment duration of 6 weeks). For the application on non-intact skin (superficial, non-bleeding	At the moment no regulatory measurements regarding PAs in food exist, even though the topic is discussed and European bodies (e.g. EFSA) are aware of the problems. As pointed out in the Public statement the intake of PAs from food cannot be avoided. Therefore the usage of PA containing medicinal products should be strongly assessed.

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	abrasions) the daily limit for oral use (0.1 µg) should be applied. 7. Homoeopathic medicinal products In principle, the public statement is directed to herbal medicinal products and the HMPC is formally not involved in the assessment of homoeopathic medicinal products. Although the public statement does not primarily address homoeopathic medicinal products, starting materials of herbal origin are also used in homoeopathy. From our point of view, in case a risk assessment for homoeopathic medicinal products is performed, they should not be treated in a more restrictive manner than herbal medicinal products. Consequently, according to the known/calculated concentration of PA in different dilutions/potencies, a safe dilution should be calculated analogous to a limit set for herbal medicinal products. Above sufficiently diluted homeopathic preparations there is no need to prohibit the intake of the respective homeopathic medicinal products. E.g., this has also been done by the German graduated plan which in general excluded PA-containing homoeopathic medicinal products with potency from D6 for internal use or D4 for external use from the restrictions [3]. 8. Health risk due to PAs in food compared to PAs in herbal medicinal products The HMPC draft public statement concludes that for herbal medicinal products containing herbal preparations with toxic unsaturated PAs (even in very low amounts) a low limit for intake of PA should be set (0.035 µg/day). As mentioned earlier, in our opinion such an assessment is disproportionate and neglects the fact that medicinal products in contrast to food products are taken in much lower amounts and in most cases for a restricted period of time. From our point of view the HMPC's conclusion unfairly discriminates highly controlled	Not endorsed. As pointed out above, the settings from the German

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	and regulated medicinal products against food products. Compared to the undefined and poorly controlled exposure to PAs by food, the impact through herbal medicinal products is of very low toxicological concern. Efforts should be concentrated on reducing PA contamination in food, as this is a source of uncontrolled and potentially very high intake. It is generally difficult to compare health risk due to contamination of food with the risk arising from the intake of herbal medicinal products containing such compounds. In contrast to food, pharmacovigilance measures required for medicinal products ensure a constant survey of safety. Also for herbal medicinal products rules ensuring their quality and safety have been established, e.g. the EMEA guideline on Quality of Herbal Medicinal Products/Traditional Herbal Medicinal Products [20] or the HMPC guideline on Good Agricultural and Collection Practice (GACP) [2]. Based on these regulations PA content of herbal medicinal products can be controlled and reduced to a sufficiently low level. Furthermore, PA intake by drugs is usually in terms of short-term use and in a defined dose. On the other hand, exposure by food is not predictable and might occur during a long period of time and in much higher doses. It should therefore be emphasized that efforts must focus on establishing methods and regulations to minimize PA exposure by food. This has already been realized by the Committee, as stated in the HMPC Guideline on the assessment of genotoxicity [12], the exposure to constituents of herbal medicinal products is rather low as compared to the background exposure by food: *"… the stepwise approach presented in this guideline takes into account the fact that HMPs are mixtures of natural substances for which some background exposure through food and other environmental factors can be expected. In those cases the exposure to these constituents can a priori not be avoided or*	graduated plan (1992) cannot be seen as substantiated anymore. A general limit of intake of 0.007 µg toxic, unsaturated PAs/kg/day (0.35 µg PAs/day for adults) should be met (for short time usage).

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	the contribution of the HMPs to the general exposure may be not relevant. Secondly, HMPs are indicated for the use in relatively minor health complains for short durations, i.e. the use is mostly sporadic and/or intermittent. Thus the exposure, vis-a-vis the natural background exposure to dietary constituents, probably remains in most cases relatively low." With regard to a potential background exposition, information is available about an approach applied by the German Commission D. It indicates that additional intake of a toxicological relevant substance from further sources (e.g. by administration of homeopathic medicinal products) should not exceed 10% of estimated inevitable background exposition [21]. As stated in chapter 2.1 of the HMPC draft, the BfR identified that for 1.2-unsaturated PA a daily intake of 0.007 µg/kg (0.42 µg/60 kg adult) should not be exceeded. This recommendation should also be valid for herbal medicinal products. Moreover, the daily intake of 0.007 µg/kg should not be regarded as a limit but as a warning threshold. In cases of short-term use, the BfR considers in a worst case of an intake of even more than 0.2 µg PA/kg body weight daily (!) an acute damage of health as improbable [1]. 9. Conclusion In light of the recent developments and discussions initiated by the BfR Study, re-consideration of the HMPC Public Statement is absolutely necessary. Early setting of limits for herbal medicinal products without taking into account the overall problem of potential contamination with PA-containing weed is not realistic. For the assessment of herbal medicinal products that might (potentially) contain PA, it is suggested to apply the existing limits of the German graduated plan [3]. In the past 20 years no obvious risks have been observed by using the	

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	respective products. Thus the limits ensure a sufficient level of safety. Furthermore, the application of these values can be justified by the MoE approach and the TTC concept, two scientifically approved and internationally accepted methods for establishing limits for toxic substances in pharmaceuticals. In case this is not acceptable the limits used in the food area should be applied. That means that a daily intake of 0.007 µg/kg (0.42 µg/60 kg adult) for adults and children, respectively should not be exceeded. This approach is in line with the current recommendations applied in the food area. Setting a limit for herbal preparations of 0.035 µg/day which is less than a factor of 10, is disproportionate and neglects the fact that medicinal products in contrast to food products are taken in much lower amounts and in most cases for a restricted period of time. It is not justified to set a very low PA limit for herbal medicinal products which discriminates medicinal products against food products. Furthermore, as long as appropriate strategies to reduce contamination with toxic weeds have not been developed, strict limits as proposed in the HMPC Public Statement cannot be met. For this reason, a sufficient period of time is required to reduce the burden of PA caused by weeds, to establish and validate analytical methods with corresponding reference substances, to obtain accurate data concerning the PA content and to meet realistic limits as used e.g. in the food area. During this period and in accordance with the Less-than-Lifetime (LTL) exposure concept used in the new ICH M7 Guideline, for herbal medicinal products which may contain PA a differentiated and balanced assessment should be performed with an option to permit higher limits in accordance with their duration and	

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	frequency of use. 10. References (References not included in the HMPC reference list, not submitted at an earlier occasion or not available on the HMPC/EMA website are printed in bold.) [1] BfR (Bundesinstitut für Risikobewertung) 2013: Pyrrolizidinalkaloide in Kräutertees und Tees. Stellungnahme 018/2013 des BfR vom 5. Juli 2013. www.bfr.bund.de [2] Guideline on Good Agricultural and Collection Practice (GACP) for starting materials of herbal origin (EMEA/HMPC/246816/2005) of 1 August 2006 [3] Bekanntmachung über die Zulassung und Registrierung von Arzneimitteln vom 05. Juni 1992 Abwehr von Arzneimittelrisiken – Stufe II, hier: Arzneimittel, die Pyrrolizidin-Alkaloide mit einem 1,2-ungesättigtem Necin-Gerüst enthalten. Bundesanzeiger Nr. 111 vom 17. Juni 1992 [4] Overview of comments received on the draft Public statement on the use of herbal medicinal products containing toxic unsaturated pyrrolizidine alkaloids (PAs) (EMA/HMPC/893108/2011) [5] Bioassay of Lasiocarpine for possible Carcinogenicity. National Institutes of Health (NTP) 1978. Technical Report Series No. 39:1-66 [6] Schrenk D. Toxicological evaluation of the issue of repeated exposure towards pyrrolizidine alkaloids. Expert Report. University of Kaiserslautern. Kaiserslautern, Germany. December 2013 [7] EFSA (2005) Opinion of the Scientific Committee on a request from EFSA related to a harmonised approach for risk assessment of substances which	

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EBF	Although the work concerns medicinal products, it may be useful to also consider the discussion paper WHO/FAO by Codex Alimentarius from February 2011, CX/CF 11/5/14: JOINT FAO/WHO FOOD STANDARDS PROGRAMME CODEX COMMITTEE ON CONTAMINANTS IN FOODS	Added to LoR.

GENERAL COMMENTS		
	5th Session The Hague, The Netherlands, 21 – 25 March 2011 DISCUSSION PAPER ON PYRROLIZIDINE ALKALOIDS (Prepared by Electronic Working Group led by The Netherlands)	
ECHAMP	ECHAMP is interested in commenting, because in the past regulations concerning herbal medicinal products have also been used for assessment of homeopathic and anthroposophic medicinal products. Our experience is that limits given in guidelines for herbal medicinal products are mostly even tightened in the assessment of homeopathic and anthroposophic medicinal products. Unfortunately, the second draft of the HMPC Public Statement means no change of consequences compared to the first statement. The newly introduced limit of 0.035 µg/day is not achievable, since it is below the detection limit of PAs. In practice this limit leads to a complete ban on PA-containing herbal medicinal products. We still see a different and unbalanced risk assessment, which discriminates herbal medicines compared to food in an unreasonable and unacceptable manner. The calculation method is not scientifically based compared to other current guidances (e.g. Guideline on the Assessment of Genotoxicity of Herbal Substances/Preparations; ICH M7 Guideline). Regarding HMPC-comment on stakeholders comments on first draft: ECHAMP again suggests considering the German graduated plan of 1992 or at least the TTC concept. The argument that the German graduated plan is based on invalid data is not reasonable, since it considers the same study on	See the responses to AEGSP above.

GENERAL COMMENTS		
	Lasiocarpin, which is also given as most conservative assessment base for the current proposal of HMPC. Considering that only a small portion of PAs shows the cyclic diester structure, which is responsible for severe hepatotoxicity we deem it as disproportionate to exclude them from assessment based on the TTC concept.	
ESCOP	The proposal of the 2nd draft Public Statement to reduce the content of PAs in herbal medicinal products to a lower amount than food is disproportionate. As stated in our previous comments, herbal medicinal products are strongly regulated with regard to the legal requirements particularly for safety and pharmacovigilance. Furthermore, herbal medicinal products are normally consumed in lower quantities than foods and for a restricted period of time. Therefore we strongly plead against a discrimination of herbal medicinal products against food by setting a much lower limit for the daily intake (0.035 µg).	See the responses to AEGSP above.
KOOP PHYTO	Kooperation Phytopharmaka, a German scientific organisation, would like to comment on the revised draft public statement on the use of herbal medicines containing toxic, unsaturated pyrrolizidine alkaloids (PAs). As is mentioned in the problem statement of this draft, the decision to prepare it was triggered by the need to assess a medicinal plant, *Symphytum officinale*, known to contain PAs. Since then, the situation has considerably changed due to the continuing scientific progress in the field. The scientific community becomes increasingly aware of the presence of PAs in different categories of products. Earlier examples of publications were reports of the occurrence of PA containing plants in pre-mixed salads in 2007 (BfR 2007), of PAs in honey from different countries in 2010 (Kempf *et al*. 2010a, b; BfR 2011), and in food plants of cattle (EFSA 2007, 2011), a more recent publication was on PAs in herbal teas (BfR	See the responses to AEGSP above.

GENERAL COMMENTS		
	2013) and on the PA uptake from food (Frankfurter Grüne Soße, Cramer *et al*. 2013). In parallel there have been different approaches published for the assessment of substances with toxic and mutagenic properties in food from different sources (e.g. Benford *et al*. 2010; EFSA 2012) showing the wide-spread exposure to such substances in our diet. With regard to medicines, as has been shown by the data of the BfR from 2013, PA-containing weeds as an impurity in drugs prepared from medicinal herbs, even if contained in small amounts only, can lead to measurable concentration of PAs in these drugs. Therefore now measures are ongoing and starting to be taken, with the aim to find out how to minimize specifically PA-containing weeds in cultivation and harvesting of herbal drugs, but data on the results are not yet available. On the other hand, by the ICH, a guideline draft on genotoxic impurities in medicines (ICH M7, 2013) has been published, which defines values for acceptable intakes of mutagenic impurities for pharmaceuticals and so also shows which amounts of such substances are acceptable in medicinal products. The theme of the current draft public statement is therefore presently undergoing a rapid scientific development, which has not yet yielded a clear picture, neither to which extent the different sources from food contribute to human PA uptake, nor how and to which extent the uptake of PAs can be realistically minimized (in the sense of the ALARA principle resp. the recommendations of regulatory bodies as the BfR or the ANZFA) and to which extent it will have to be tolerated (as that of many other known genotoxic impurities e.g. in food, see e.g. Benford *et al*. 2010).	

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	For the determination of the tolerable intake from medicinal products, using the limits from the ICH M7 guideline seems to be reasonable, as it seems to be logical that for mutagenic impurities in herbal medicinal products, with their comparatively well-known properties, there is primarily no need for other limits different from that for chemically defined products with impurities which in contrast often have new and unknown properties. Given the fact, that the scientific knowledge on the occurrence of PAs is at the moment rapidly advancing, due to the use of more powerful analytical methods, it seems to be most efficient to first develop further measures for minimizing the uptake, which then can be the basis of new limits which could complement the existing regulations.	
NIMH	We agree that exposure to pyrrolizidine alkaloids (PA) should be minimized. However we argue that the benefit of certain herbs used by herbal practitioners, with recognized precautions, means that their usage entails an acceptable risk.	Endorsed Not endorsed. Medical use is not the only criterion to define an adequate risk-benefit-ratio. See the responses to AEGSP above.

SPECIFIC COMMENTS ON TEXT			
Section number and heading	Interested party	Comment and Rationale	Outcome
Line number 43-44	Swissmedic	Wording Proposed change (if any): Furthermore, both the composition and concentration of PAs may fluctuate according to climatic and environmental conditions, the age and part of the plant as well as the variety (genotype/chemotype) [Hoogenboom et al.	Endorsed.

SPECIFIC COMMENTS ON TEXT			
		2011].	
Line number 45-46	Swissmedic	Wording Proposed change (if any): Thus, all known PAs of a PA-containing plant are not necessarily present at the same time.	Endorsed.
Line number 59-60	Swissmedic	wording, Refers to C-1 and C-7 Proposed change (if any): Esterification can take place in these positions.	Endorsed.
Line number 82-83	Swissmedic	Please clarify/ rephrase: Excluding otonecine alkaloids, which cannot form N-oxides, together with the N-oxides of the other alkaloids more than 660 alkaloids are known [Roeder 2000].	Not endorsed. Wording taken from the original literature.
2	KOOP PHYTO	The section gives an overview, also of food sources of PAs, which, in developing countries, lead to epidemic poisoning after high doses of PAs in e.g. ranges of 0.01-10 mg/kg b.w./d, and which need to be urgently avoided. It also refers to studies showing that the carcinogenic properties anticipated for e.g. riddelliine are based on preceding veno-occlusive toxic effects and hypoxia, subsequently leading to mutations and carcinogenesis. As the veno-occlusive toxic effects of PAs are generally accepted to be dose dependent, this seems to point to thresholded mechanisms of carcinogenicity of PAs and even to the rating that there is no evidence that PAs cause liver cancer in humans (ANZFA 2001).	

SPECIFIC COMMENTS ON TEXT			
Sections 2.4. Single and repeat dose toxicity in animals (line 258)	EBF	To be amended the **immunotoxicity** from animal studies showing immunosuppressant activity of dehydroheliotridine and monocrotaline from Codex Comm. E paper: CX/CF 11/5/14 February 2011 (cited above)	Endorsed.
Section 3	KOOP PHYTO	Up to now diverse approaches have been followed for defining acceptable limits for the daily uptake of PAs. Therefore it could seem to be an easy solution to apply the ALARA principle and zero tolerance to this group of compounds. But when taking into account the highly complex situation, it turns out, that this approach is not feasible, and that it is in many cases also not appropriate. *Approaches to limit PAs in food* For example, PAs are widespread mainly in plant derived products and dishes like e.g. Frankfurt Green Sauce (used in and around Frankfurt/M., Germany and containing 1.9-6.7 µg of PAs), Aragonese borrage with garlic (used in Spain), and many other products, which are in widespread use within the EU and, although they contain PAs (Cramer 2013) do not seem to expose consumers to inacceptable risks. This may be the reason why by now no binding limits for PAs in food have been established, despite several recommendations have been published as e.g. that of BfR from 2013 based on a	See the responses to AEGSP above.

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		MOE approach (0.42 µg/day in adults) or that of ANZFA using human data on the incidence of veno-occlusive disease and based on a PTDI approach (1 µg/kg bw/day). Recently, it has turned out that PAs are even more common in herbal products than it was previously known, since they have been found in salads (BfR 2007) and herbal teas (BfR 2013). This is obviously due to PA-containing weeds through which measurable amounts of PAs can find their way to herbal products. This is presumably now leading to new activities to establish specific measures for weed control. It will presumably take some time until the results of these activities will be available and will support realis-tic limits for PAs. Approaches to limit PAs in medicinal products In contrast to the food situation, there exist established PA limits for herbal medicinal products. A first attempt was made by CHMP in 1992, which never came to full action. At the same year, German BfArM established a Graduated Plan for HMPs with PA-containing plants as active substances, which limited the daily uptake to 1 µg for internal and 100 µg for external use, and, when the duration of use exceeds 6 weeks, 0.1 µg for internal and 10 µg for external use. This is in force till date. The approach of the present HMPC draft public statement (HMPC 2013), based on the same exposure data already published in 1978 by NTP, comes to a limit of 0.035 µg for a person with 50 kg b.w. This is transferred, adjusted to the	

<table>
<tr><th colspan="4">SPECIFIC COMMENTS ON TEXT</th></tr>
<tr><td></td><td></td><td>body weight, also to children and to external products.

As it has turned out (BfR 2013), that the presence of PAs in herbal products can be also due to weeds, accidentally harvested as an impurity to the herbal drug, it seems appropriate to rely on the M7 guideline draft of ICH on mutagenic impurities in medicinal products, which has also been published in 2013. It is setting different limits depending on the intended duration of use of a medicinal product:

<table><tr><td>Duration of treatment</td><td>Daily intake of an individual genotoxic impurity [µg/day]</td></tr><tr><td>< 1 month</td><td>120</td></tr><tr><td>> 1 – 12 months</td><td>20</td></tr><tr><td>> 1 – 10 years</td><td>10</td></tr><tr><td>> 10 years to lifetime</td><td>1.5</td></tr></table>
Only for compounds belonging to cohorts of concern, lower limits are recommended.

A comparison of the limit from the M7 guideline draft of 1.5 µg/day to the HMPC draft public statement of 0.035 µg/day shows, that for PAs from herbal medicines, independent of the approach used (MOE vs. TTC etc.) obviously much higher uncertainty factors have been involved.

This raises questions. The PAs obviously do not belong to the cohort of concern, and their pharmacological and toxicological properties are comparatively well known. In contrast, the</td><td></td></tr>
</table>

SPECIFIC COMMENTS ON TEXT			
		impurities in scope of the M7 guideline are often newly discovered synthetic substances with unknown properties. It therefore seems plausible not to set a new special limit for PAs in herbal medicinal products, as is done in the HMPC draft public statement, but to relate to the limit given in the M7 guideline draft. In addition, reference could be made to the limits of the German graduated plan of 1992 and of the assessment of the ANZFA of 2001. Finally, whereas in the near future the availability of new scientific information is to be expected, both regarding the PA contents in food and the PA content in herbal medicinal products, it seems to be premature to set a limit already now. It seems to be better now to refer to existing limits and revise the paper as soon as a broader body of information is available.	
ECHAMP It is to ensure that the amount of PA within the daily dose is 0.035 µg for adults. The use is restricted to intact skin.	ECHAMP	The identical limit for external and internal use is not justified from our point of view. No data are given which show that the absorption via (intact) skin is comparable to oral intake. Therefore, we ask the HMPC to include the data which substantiate this approach into the public statement. Also, there have been no cases reported suggesting poisoning by external application of PA-containing preparations.	See the responses to AEGSP above.

SPECIFIC COMMENTS ON TEXT			
3. Conclusion and recom-mendations	ESCOP	We do not agree with the conclusion of the threshold for the daily oral dosage of 0.035 µg per (50 kg) person. From our point of view the application of the Margin of Exposure (MoE) approach used by EFSA for PAs [1] can also be used for herbal medicinal products. It has been shown by EFSA that contamination of food with PAs leading to daily doses of maximum 0.007 µg PAs/kg b.w. are acceptable, resulting in a daily intake of 0.42 µg for an adult of 60 kg b.w. This calculation already includes various safety factors and is based on one of the most toxic PAs, lasiocarpine, as a "worst case". Most PAs, however, are supposed to have a lower genotoxicity and carcinogenicity risk than lasiocarpine. For these reasons, herbal medicinal products should not be treated in a more restrictive manner than the EFSA approach for food, taking into account also the quantities and the period of use which result in an overall lower intake of PAs by herbal medicinal products as compared to food. [1] Scientific Opinion on pyrrolizidine alkaloids in food and feed. EFSA Panel on Contaminants in the Food Chain (CONTAM). EFSA Journal 2011;9(11):2406.	See the responses to AEGSP above.
4 (References)	KOOP PHYTO	References printed in bold italic letters are not listed in the list of reference of HMPC and are enclosed as copies to this statement. • ANZFA (2001) Pyrrolizidine alkaloids in food. A toxicological review and risk assessment. Australia New Zealand Food Authority, Technical report series No. 2.	

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