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Committee on Herbal Medicinal Products (HMPC)

Public statement on contamination of herbal medicinal products/traditional herbal medicinal products[1] with pyrrolizidine alkaloids

Transitional recommendations for risk management and quality control

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[1] Throughout the document the term Herbal Medicinal Products (HMPs) includes Traditional Herbal Medicinal Products as defined in Dir. 2001/83/EC

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1. Background

Pyrrolizidine alkaloids (PAs) are nitrogen containing compounds that occur naturally in plants. Several hundred structurally distinct PAs have been found in low concentrations in several thousand different plant species. Many of these plants are common weeds.

Recently, it has been shown that PA-containing weeds contaminate botanical raw materials used for the production of food and herbal medicinal products (HMPs)[2]. The botanical raw materials generally appear to be contaminated by (very) low levels of PAs, but due to newly developed analytical methods (LC-MS/MS) even trace amounts of PAs can now be detected and quantified.

The acute toxicity, genotoxicity and carcinogenic potential of PAs have been known for decades. These alkaloids occur principally in two forms, namely tertiary base PAs and PA-N-oxides (PANOs). Because PAs and PANOs are metabolically interconvertible and both are toxicologically important, it is necessary that both species are included in the analytical determinations. Only the group of PAs which structurally are 1,2-unsaturated are relevant for safety assessment, as the PAs without this structural feature are considered non-toxic.

In a public statement (HMPC, 2014), the Committee on Herbal Medicinal Products (HMPC) recommended that the intake of PAs from herbal medicinal products be limited to 0.35 µg/day (maximum 14 days), calculated for a person with a body weight of 50 kg. This level was originally derived by EFSA using the 'margin of exposure' (MOE) framework according to current guidelines on risk assessment of genotoxic carcinogens in food.

On 1 March 2016 the German Medicines Agency (BfArM) made a public announcement setting out work on-going within Germany to address the issue of PA contamination in herbal medicinal products. The BfArM reported that in order to reduce potential PA contamination to meet the threshold defined in the public statement of the HMPC enhanced measures needed to be put in place beyond the usual Good Agricultural and Collection Practices (GACP). The BfArM stated that this work was underway and a coordinated approach would be put in place to address aspects of cultivation, collection as well as developing standard methods for assaying PAs. Based on the available data the BfArM had introduced a maximum threshold of 1.0 µg PAs daily as a transitional measure. It has later been clarified by BfArM that the transition period is not expected to exceed 3 years, after which the threshold will be set at 0.35 µg/day, in accordance with the HMPC and EFSA recommendations.

On 22 March 2016 the Austrian Medicines Agency (AGES) announced that their action on PAs would follow the strategy implemented by BfArM taking account of the close connection between the markets in Austria and Germany. However, for the initial action, Austria would restrict measures to ten plants associated with a higher risk of PA contamination.

On 6 April 2016 the UK Medicines Agency (MHRA) informed registration holders for traditional herbal medicinal products that the agency had reviewed the information from BfArM and concluded that a maximum threshold of 1.0 µg PAs can be accepted for UK registered products as a transitional arrangement.

The HMPC received further updates at its meeting on 4 April 2016, including detailed information presented by AESGP. The HMPC considered that, following a review of the available data, a Public Statement should be published to enable Member States to consider a harmonised approach in implementing appropriate controls for their markets.

[2] Throughout the document the term Herbal Medicinal Products (HMPs) includes Traditional Herbal Medicinal Products as defined in Dir. 2001/83/EC

2. Brief review of toxicological data

2.1. Acute and subchronic toxicity of PAs

According to EFSA (2011) it is likely that there is a common mode of action for all 1,2-unsaturated PAs. Currently, the data available for the model substances, riddelliine, lasiocarpine and monocrotaline, are therefore used to assess the toxicity of 1,2-unsaturated PAs as a group.

Convincing animal studies have shown that reactive metabolites of the 1,2-unsaturated PAs riddelliine and retrorsine are formed by metabolism via CYP 3A4 enzymes. Available data suggest that the same underlying mechanism accounts for both acute and chronic toxicity following oral intake of 1,2-unsaturated PAs, i.e damage to macromolecules, including DNA, caused by reactive metabolites. The native 1,2-unsaturated PAs are non-toxic prior to metabolic activation and are thus classified as pro-toxins.

Data from toxicity studies (NTP) indicate that the endothelial cells in the liver sinusoids (SEC) are the primary targets for toxicity of 1,2-unsaturated PAs. Data supporting this observation is that acute exposure to high doses of toxic PAs result in a specific form of damage to the microcirculation of the liver, so-called hepatic sinusoidal obstruction syndrome (HSOS), also known as veno-occlusive liver disease, and subsequent liver failure. Exposure to a very high single dose (160 mg/kg bw, p.o.) of monocrotaline is used as a reproducible animal model (rat) of HSOS.

It has been shown that both hepatocytes and SEC form toxic metabolites after exposure to monocrotaline, but SEC are apparently more sensitive to toxic effects than the hepatocytes. It has been suggested that the particular vulnerability of SEC is due to their lower glutathione content and thereby possibly greater intracellular exposure to toxic metabolite(s) due to lower capacity for detoxification. This could explain why SEC become the main targets of 1,2-unsaturated PA toxicity (DeLeve *et al*., 1996). This explanation is supported by the observation that in the monocrotaline model of HSOS, a concomitant infusion of glutathione could dose dependently protect rats from development of HSOS (Wang *et al*., 2000).

High doses (ca 1 mg/kg bw) of 1,2-unsaturated PAs cause HSOS in humans (EFSA, 2011). However, this information is based only on a few documented cases. Clusters of PA poisoning resulting in HSOS have been described from Pakistan, India and Afghanistan (charmak disease) where contaminated wheat flour has been the source of the PAs. There are also documented cases of HSOS from the United States during the 1970s linked to the intake of herbal teas as well as current reports from China related to the use of traditional Chinese medicines. The cases of HSOS in USA and China have been linked to intake of herbal products prepared from PA producing plants.

Having reviewed the available information the HMPC has the following position:
Animal studies have shown that acute toxicity from intake of PAs in high doses leads to the development of HSOS. Similar toxicity findings have also been described in humans, but it is considered that a daily intake of <1.0 µg PAs from herbal medicinal products will not constitute a risk for development of HSOS in humans.

2.2. Genotoxicity

Several PAs have been shown to produce genotoxic effects (mutations, sister chromatid exchanges, chromosomal aberrations) in animals and cell culture systems after metabolic activation. Some PAs induce micronuclei formation in erythrocytes in the bone marrow in mice.

2.3. Assessment of carcinogenic potential by various authorities

NTP conducted 2-year rodent carcinogenicity studies to investigate the potential carcinogenicity of 1,2-unsaturated PAs, using lasiocarpine and riddelliine as model substances (NTP, 1978; NTP, 2008). The main finding in these studies was substance-induced liver hemangiosarcoma in male and female rats, as well as in male mice (riddelliine). Hepatocellular adenoma/carcinoma was also induced by riddelliine and lasiocarpine in rodents, but to a much lesser extent than liver hemangiosarcoma.

Riddelliine was assessed by NTP as reasonably anticipated to be a human carcinogen.

According to the IARC-classification, riddelliine and lasiocarpine are possibly carcinogenic to humans.

EFSA (and EMA/HMPC) point out the risk of cancer development in humans as driving the risk assessment of PAs.

Based on the data from the NTP (1978) study on lasiocarpine, EFSA (2011) used the MOE framework to calculate a permitted daily intake of 0.35 µg PAs/day (50 kg body weight). The BMD_{10} value for lasiocarpine (120 µg/kg x day, male rats) for the development of hemangiosarcoma in the liver (which was the primary finding in the NTP cancer study) was used as reference point on the dose-response curve for the MOE calculation.

2.4. Further considerations on carcinogenicity risk in humans

For riddelliine, NTP concluded that the predominance of hemangiosarcoma was likely due to the greater genotoxicity and toxicity in the endothelial cell than in the hepatocyte. The acute toxic effect of riddelliine, venous occlusion, occurs in the same target cell and the non-cancer effects are likely to involve the same reactive intermediates (NTP, 2008). This mode of action is similarly relevant for other 1,2-unsaturated PAs, and the carcinogenic potency is likely to be related to a combination of the genotoxic potential and the toxicity (EFSA, 2011).

In the NTP-reports on both lasiocarpine and riddelliine, a proliferative effect was observed also on hepatocytes, but this effect was not clearly dose-related, and resulted in malignancy only in the high-dose groups, in a few individuals. In contrast, liver hemangiosarcoma occurred at all dose levels in the rat lasiocarpine study. From a risk perspective, liver hemangiosarcoma is therefore considered the key effect.

The relevance of PA-induced hemangiosarcoma in rodents requires careful consideration when assessing human carcinogenic potential of PAs. The human intake of PAs through food and herbal medicinal products has presumably been fairly constant over the last decades (or longer), yet the incidence of liver hemangiosarcoma in humans is very low. Exact data on the occurrence of liver hemangiosarcoma in the population is difficult to obtain, but all information points to the fact that this is a very rare diagnosis.

Angiosarcoma is a malignant neoplasm of endothelial cells of blood vessels or lymphatic vessels and as such included in the overarching term of soft tissue sarcomas (STS), which in turn is a heterogeneous group of neoplasms of mesenchymal origin that comprise more than 50 histology subtypes, many of them very rare. STS constitutes less than 1 % of all malignancies in adults. In the literature it has recently been estimated that angiosarcoma accounts for approximately 2-3 % of all STS and primary hepatic angiosarcomas in turn accounts for < 5% of all angiosarcomas (Zheng *et al*., 2014).

In a review, Zocchetti (2001) summarised all available epidemiological information on the incidence of liver hemangiosarcoma based on studies in Sweden, UK, USA and Norway. His conclusion was that the incidence of liver hemangiosarcoma was ca 0.5-2.5 cases per 10.000.000 individuals per year. Furthermore, it has been estimated that about 20-25 % of the cases are associated with known

etiologic factors such as vinyl chloride monomer exposure, use of Thorotrast (thoriumdioxid) in angiography, exposure to inorganic arsenic and treatment with androgenic-anabolic steroids (Zocchetti, 2001; Falk *et al*., 1981; Rademaker *et al*. 2000). In the majority of cases the aetiology however remains unknown.

Another risk that cannot be excluded at present is that intake of PAs would result in other forms of neoplasms in humans than in rodents. It is of course difficult to assess this risk, but the MOE framework, used by EFSA and HMPC to arrive at an acceptable daily intake of PAs, has been devised to accommodate such species differences.

3. Concluding considerations

- Contamination of herbal products (food or medicines) with PAs cannot be a new phenomenon, but today new, sensitive analytical methods can detect even very low levels of PAs in food and medicines.
- The human intake of PAs through food and herbal medicinal products has presumably been fairly constant over the last decades (or longer), yet the incidence of liver hemangiosarcoma in humans is very low.
- Once the problem with PA contamination of herbal medicinal products has been identified, regulatory actions to mitigate the problem must be considered.
- In March 2016 DE implemented a limit of intake of PAs from herbal medicinal products of 1 µg/day as a transitional measure. Currently, AT has followed this proposal and UK has also accepted this limit.
- In a public statement (2014) HMPC recommended that the intake of PAs from herbal medicinal products be limited to 0.35 µg/day. This level was originally derived by EFSA using the MOE framework according to current guidelines on risk assessment of genotoxic carcinogens in food.
- The MOE framework involves estimating a reference point (tumor response in 10 % of the animals; BMD_{10}) on the dose-response curve using regression analysis. This is followed by calculating a one-sided confidence interval and from the lower point of this interval ($BMDL_{10}$), a safety factor of 10,000 is applied to obtain the dose in humans that is considered to be of low priority for risk management. Obviously, this human dose is not an experimentally determined dose, but a value estimated using the current paradigm for risk assessment of genotoxic carcinogens. Given these circumstances it appears reasonable to accept the already implemented (DE, AT, UK) higher value of 1.0 µg PAs/day during a 3-year transition period. It is considered that an acceptance of this limit during a transition period will have no negative influence on public health. It may be noted that 1.0 µg/day is below the threshold of toxicological concern for medicinal products (1.5 µg/day), as set out in the ICH M7 guideline on genotoxic impurities.

4. Recommended strategy for risk management

1. The main approach for risk management of the PA contamination of herbal medicinal products should be according to the concept of ALARA, i.e. as low as reasonably achievable.
2. In principle, contamination of herbal substances with PA containing weeds should not occur at all for reasons of requirements on pharmaceutical product quality and compliance with GACP/GMP. However, based on toxicological considerations and the current guidelines for risk assessment/management of genotoxic carcinogens, a contamination level leading to a daily intake

of maximum 0.35 µg PAs/day (life-long exposure for a person with a body weight of 50 kg) is considered of low safety concern.

3. A contamination level of herbal medicinal products leading to a daily intake of maximum 1.0 µg PAs/day during a transitional period of 3 years is acceptable from a public health point of view, for reasons discussed above. During this time period the producers of herbal medicinal products should take actions necessary to reduce the contamination to a level leading to a daily intake not exceeding 0.35µg PAs/day.

5. Quality aspects: control of PAs due to contamination in Herbal Medicinal Products

5.1. Quality Aspects

As stated above, the HMPC view is that patient exposure to PAs from HMPs should be as low possible and should not exceed a daily intake of 0.35 µg. However, for a limited transitional period an intake up to 1.0 µg per day can be accepted.

With regard to actions to be undertaken by Member States arising from the concerns relating to the quality of HMPs, two main aspects needs to be addressed:

1. Implementation of suitable testing procedures to ensure PA levels are controlled in line with limits agreed.
2. Implementation of measures to avoid or reduce PA contamination in HMPs.

6. Implementation of suitable testing procedures to ensure PA levels are controlled in line with agreed limits

Implementation of testing procedures to ensure PA levels are controlled in line with agreed limits requires immediate consideration in view of the available evidence of the widespread contamination in herbal ingredients of HMPs. The key issues to be addressed by individual Member States relate to the choice of analytical methods, available laboratory resource and prioritisation of the herbal ingredients/HMPs for evaluation.

6.1. Analytical methods

Highly sensitive analytical methods are required to provide the level of quantification needed to control PAs due to contamination in HMPs. There are no official test methods currently available for PAs in HMPs.

The HMPC has therefore requested that the European Pharmacopoeia consider development of an appropriate analytical method for PAs in HMPs as a matter of priority.

Until such time as an official analytical method is available Marketing Authorisation Holders (MAHs) are advised to use the SPE-LC-MS/MS method as published by BfR (Federal Institute for Risk Assessment: BfR-PA-Tea-2.0/2014). Other suitable validated methods may be acceptable.

The test method should allow quantification of at least the following toxic PAs:

1. Echimidine	11. Jacobine	21. Senecionine
2. Echimidine-N-oxide	12. Jacobine-N-oxide	22. Senecionine-N-oxide
3. Erucifoline	13. Lasiocarpine	23. Seneciphylline
4. Erucifoline-N-oxide	14. Lasiocarpine-N-oxide	24. Seneciphylline-N-oxide
5. Europine	15. Lycopsamine	25. Senecivernine
6. Europine-N-oxide	16. Lycopsamine-N-oxide	26. Senecivernine-N-oxide
7. Heliotrine	17. Monocrotaline	27. Senkirkine
8. Heliotrine-N-oxide	18. Monocrotaline-N-oxide	28. Trichodesmine
9. Intermedine	19. Retrorsine	
10. Intermedine-N-oxide	20. Retrorsine-N-oxide	

6.2. Prioritisation of the herbal ingredients/HMPs for evaluation

This will require a product-specific and risk-based approach to the quality control on a case by case basis depending on the specific herbal ingredients and the posology of the herbal product. In the light of the safety concerns the strategy should be to focus initially on herbal substances with a high risk of contamination and to ensure availability of herbal medicinal products with a low risk of contamination.

Consideration should be given to the need for routine vs periodic controls (skip testing) depending on the risk assessment and the available evidence base.

An existing database, compiled by the German industry (BAH) can be a valuable resource and provides some preliminary evidence on those herbal ingredients at highest risk of contamination. This may enable Member States to identify those herbal ingredients of highest priority for regulatory action. For example, ten herbal ingredients are identified by BAH to be most affected and likely to require routine controls; these include:

- Hyperici herba, Passiflorae herba, Matricariae flos, Alchemillae herba, Liquiritiae radix, Melissae folium, Menthae piperitae folium, Salviae folium, Taraxaci herba cum radice and Thymi herba

Based on the information available it may be possible to develop a risk based approach to prioritisation and to the extent of testing needed for particular herbal ingredients. This will depend, however, on the supporting data from individual suppliers of herbal substances/preparations.

This type of risk based test scenario has been adopted by some Member States (DE and AT) based on three risk classes (A, B, C) that determine acceptance limits for the finished product as well as the test frequency based on the class. This is summarised in the Table below.

Class	**µg PA/day in the HMP**	**Test frequency**	**Acceptance limit:** with respect to maximum daily dose of HMP
A	≤ 0.1	Skip testing *	90 % of samples below 0.1 microgram/day; none contain > 0.35 microgram/day
B	≤ 0.35	More frequent skip testing*	90 % of samples below 0.35 microgram/day; none contain over 1.0 microgram/day
C	≤ 1.0	Routine testing required	No result over 1.0 microgram/day

* frequency of testing will depend on risk assessment and extent of information available

6.3. Amendment of specifications for herbal substances, herbal preparations, HMPs

The most appropriate stage for testing to take place i.e. at the level of the herbal substance, herbal preparation or herbal product should also be considered. Regulatory specifications should be updated to reflect the controls introduced on PAs. In any event the controls to be applied on PAs should take account of the final posology of the HMPs.

An appropriate sampling plan should be developed depending whether the herbal substance (spot contamination) or the herbal preparation / finished product (homogenous sample) is tested. Sampling should be in accordance with Commission Regulation 401/2006/EC.

7. Implementation of measures to avoid or reduce PA contamination in HMPs

The findings of widespread contamination by PAs in HMPs has confirmed that the situation with PA contamination is serious and on an unprecedented scale. A detailed Code of Practice (CoP) has been developed by FAO and WHO (Joint FAO/WHO Food Standards Programme, Codex Committee on Contaminants in Foods. Code of Practice for Weed Control to Prevent and Reduce Pyrrolizidine Alkaloid Contamination in Food; ftp://ftp.fao.org/codex/meetings/cccf/cccf8/cf08_11e.pdf).

The CoP highlights that PAs are probably the most widely distributed natural toxins and recognises that total eradication of PA-containing plants is not feasible. The CoP focuses on weed control and provides guidance on good management practices to prevent and reduce PA contamination by control measures for the management of PA-containing plants as well as measures for control of plant release and spread.

The challenge to GACP is considerable as very small numbers of PA-containing plants, as few as one *Senecio* plant per hectare in a crop of St John's Wort (Hyperici herba), would suffice to exceed the HMPC recommended threshold. Available agricultural measures to reduce PA-weeds by way of selective herbicides, manual weeding/sorting, seed cleaning, inspection of fields before harvesting etc., need to be put in place as a matter of urgency but will take several growing seasons to be effective.

In view of the considerable challenge to be faced and the need for comprehensive and collaborative efforts to reduce PA contamination the HMPC recognises that a level of significantly enhanced GACP will be needed to address the problem and this cannot be achieved in the short term as a number of growing cycles are needed to allow effective controls. It is accepted therefore that a transitional period is needed to allow implementation.

As an integral part of the risk assessment, MAHs and manufacturers of herbal Active Pharmaceutical Ingredients should be required to provide details of the strategies, including enhanced aspects of GACP, being implemented to reduce levels of PA contamination.

This aspect will need to be kept under review and MAHs should be required to provide information on an on-going basis to enable a comprehensive position to be evaluated during the transition period.

The HMPC is of the view that the transition period, during which the higher PA limit would apply to certain ingredients, should be as short as possible and should not exceed a period of 3 years.

If enhanced GACP measures prove ineffective, a further review of the regulatory position will be instigated.

8. Abbreviations

- AESGP: Association of the European Self-Medication Industry
- AGES: Austrian Medicines Agency
- ALARA: As Low As Reasonably Achievable
- BAH: Bundesverband des Arzneimittel-Hersteller e. V. (German Medicines Manufacturers' Association)
- BfArM: German Medicines Agency
- BfR: The Federal Institute of Risk Assessment/Bundesinstitut fürRisikobewertung, Germany
- BMD_{10}: Bench Mark Dose (giving 10% response)
- $BMDL_{10}$: Bench Mark Dose Lower Confidence Limit
- CYP: Cytochrome P450
- EFSA: The European Food Safety Authority
- GACP: Good Agricultural and Collection Practices
- HMP: Herbal Medicinal Products
- HSOS: Hepatic Sinusoidal Obstruction Syndrome
- IARC: International Agency for Research on Cancer
- LC-MS/MS: Liquid chromatography tandem mass spectrometry
- MHRA: UK Medicines Agency
- MOE: Margin of exposure
- MS: Mass Spectrometry
- MS/MS: Tandem mass spectrometry
- NTP: National Toxicology Program (USA)
- PA: Pyrrolizidine alkaloid.
- PANO: PA-N-oxide
- SEC: Endothelial cells in the liver sinusoids
- SPE-LC-MS/MS: Solid Phase Extraction (SPE) in combination with Liquid Chromatography tandem mass spectrometry (LC-MS/MS)
- STS: Soft Tissue Sarcomas

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