

– Translation –

Pharmaceutical companies
(see Distribution list)

Ref.: 75-3822-V12617-118994/09
Phone: (0228) 99307-3232
Bonn, 07 December 2009

Prevention of drug-associated risks, Stage II
Medicinal products manufactured using plants of the *Aristolochiaceae* family with the genera *Asarum*, *Aristolochia*, *Saruma* and *Thottea*

– for products see Annex –

Notification of the BGA (*Bundesgesundheitsamt* / Federal Health Agency) dated 03 June 1981 (GV4-7251-01-5383/81)

Dear Madam/Sir

In a hearing in writing (*schriftliche Anhörung*) according to the graduated plan (*Stufenplan*), you are given the opportunity to comment, within four weeks of receipt of this letter, on the facts described in the following and the resulting measures.

In homeopathy it is possible to administer homeopathic preparations from *Aristolochia clematitis*, *Aristolochia curarina*, *Aristolochia serpentaria* (= *Aristolochia officinalis*), *Aristolochia cymbifera e radice* (= *Aristolochia milhomens*), *Aristolochia rotunda*, *Asarum europaeum* and *Asarum canadense*.

Plants of the *Aristolochiaceae* family and preparations derived thereof are also used in traditional Chinese medicine (TCM), for instance various *Aristolochia* spp., like *Aristolochia fangchi*, *Aristolochia manshuriensis*, *Aristolochia contorta* and *Aristolochia debilis*¹ and *Asarum* spp. like the dried roots and the rhizome of *Asarum sieboldii* and *Asarum heterotropoides*.

The necessity of extending the graduated plan procedure of 1981 (see Notification mentioned above), which referred exclusively to medicinal products derived from *Aristolochia*, is resulting from the circumstance that AA I has been detected in three homeopathic mother tinctures of *Asarum europaeum*, in one mother tincture of *Asarum canadense* and in samples of the TCM drug *Asari radix e rhizoma*. The investigations were made in connection with the revision of the HAB monograph "Asarum europaeum" and the elaboration of the Ph. Eur. monograph "Manchurian Wildginger Root and Rhizome" (*Asari radix e rhizoma*). When investigated by the central laboratory of German pharmacists (*Zentrallaboratoriums Deutscher Apotheker*) in 2007, the TCM drugs *Asari radix* and *Asari radix e rhizoma* were detected to contain AA concentrations of 5.1 µg/g and 2.7 µg/g (DAC sample 7, limit of quantitation: 6 ppm).

¹ European Medicines Agency. (23 Nov. 2005) "Public Statement on the Risks associated with the use of Herbal Products containing *Aristolochia* Species" [online], EMEA/HMPC/138381/2005. Available: <http://www.emea.europa.eu/pdfs/human/hmpc/13838105en.pdf>.

The homeopathic mother tinctures of *Asarum europaeum* and *Asarum canadense* were assayed according to the "Test for aristolochic acid I in herbal drugs" (2.8.21) published as Method C (HPLC/MS/MS) in Pharmeuropa 19.4 of October 2007. *Asarum europaeum* had AA I concentrations of 43.8 µg/kg, 85.0 µg/kg and 128.4 µg/kg, i.e. 0.044 – 0.13 ppm, and *Asarum canadense* of 127.4 µg/kg or ca. 0.13 ppm. This method is claimed to be reliable for homeopathic mother tinctures with contents over 100 µg/kg (= 0.1 ppm). The sensitivity of HPLC Method C according to Pharmeuropa constitutes even 15 µg/kg (= 0.015 ppm) in tests for aristolochic acid in drugs.

By comparison, in connection with the revision of the HAB monograph *Aristolochia clematidis* in three *Aristolochia clematidis* mother tinctures AA I and AA II concentrations of 0.008%, 0.017% and 0.022%, i.e. maximally 220 ppm (the AA II percentage in it was about 33%) were found by HPLC with UV detection at 254 nm.

Genuine occurrence of aristolochic acid in plants is currently only assumed for the *Aristolochiaceae* family¹. Reports of aristolochic acid in species of other families refer to commercially procured samples without proper taxonomic determination, or adulterated samples².

The taxonomic conditions in *Aristolochiaceae* are of a complex nature. Certainty exists about the genera *Saruma*, *Asarum*, *Thottea* and *Aristolochia*. Depending on the author, *Pararistolochia* and *Isotrema* are either included in the expanded genus of *Aristolochia*³ or are seen as a separate unit because they are well identifiable monophyletic groups. However, there is general consent among taxonomists about the four genera mentioned above and about *Isotrema* and *Pararistolochia* as sub-genera.

Lactoridaceae and *Hydnoraceae* are currently seen as separate families although their molecular genetic data would rather qualify them for the *Aristolochiaceae* family. *Aristolochiaceae* comprise more than 700 species, which can be classified into the two sub-families *Asaroideae* and *Aristolochioideae*. *Asaroideae* comprise the genera *Asarum* with ca. 85 species and *Saruma* with 1 species; *Aristolochioideae* comprise the genera *Aristolochia* with ca. 500 species and *Thottea* with ca. 30 species⁴.

According to the literature aristolochic acid has been detected in the species of the following genera:

² K.M. Wu, J.G. Farrelly, et al. (2007) "Complexities of the herbal nomenclature system in traditional Chinese medicine (TCM): Lessons learned from the misuse of *Aristolochia*-related species and the importance of the pharmaceutical name during botanical drug product development." *Phytomedicine* 14 (4): 273-279

³ Kelly, L.M. & Gonzalez, F.A. (2003) „Phylogenetic relationships in *Aristolochiaceae*” . *Syst Bot.* 28: 236-249

⁴ Wanke, S. (2006). "Evolution of the genus *Aristolochia* - Systematics, Molecular Evolution and Ecology." Dissertation, Technische Universität Dresden, Dresden

• *Aristolochia*:

Aristolochia fangchi is reported to contain 581 – 5.480 ppm of AA I and II, with AA I being the main component^{5,7,9,10}. Contents of 1300 ppm of AA I and 97 ppm of AA II, related to the dry weight, were detected in *Aristolochia serpentaria* (underground parts)⁶. AA I was found in at least 20 other species in concentrations of up to 9720 ppm (*Aristolochia manshuriensis*)⁷, related to the dry weight, most of them in the 4-digit ppm range^{2,5,6,7,8,9,10}.

• *Asarum*:

A great number of the *Asarum* species^{6,7,11,12} are reported to contain aristolochic acid (almost only AA I). In *Asarum canadense* (underground parts of various origin) AA I contents amounted to 0.01 – 18.40 ppm¹³ with a maximum of 370 ppm, related to the dry weight.

In at least 40 other species AA I concentrations reached values of up to 3377 ppm (*Asarum crispulatum*)¹¹ related to the dry weight, most of them in the 2-digit ppm range^{6,8,9,11}.

• *Saruma*:

AA I contents amounted to 130 - 560 ppm (depending on the plant part, with higher contents in the underground tissue), related to the dry weight⁸.

• *Thottea*:

Aristolochic acid was also detected in two not precisely defined species of *Thottea*; specifications of content are not available¹⁴.

⁵ Lee, T. Y., M. L. Wu, et al. (2001). "High-performance liquid chromatographic determination for aristolochic acid in medicinal plants and slimming products." J. Chromatogr. B. Analyt. Technol. Biomed. Life. Sci. 766 (1): 169-174

⁶ Schaneberg, B. T., W. L. Applequist, et al. (2002). "Determination of aristolochic acid I and II in North American species of *Asarum* and *Aristolochia*." Pharmazie 57 (10): 686-689

⁷ Zhang, C., X. Wang, et al. (2006). "Simultaneous determination of five aristolochic acids and two aristolactams in *Aristolochia* plants by high-performance liquid chromatography." Biomed. Chromatogr. 20 (4): 309-318

⁸ Kawamura, T., Y. Osada, et al. (2003) "Contents variation of aristolochic acid in the plants of Aristolochiaceae; About the related plants of Chinese herb Xixin." Nat. Med. 57 (3): 105-109

⁹ Hashimoto, K., M. Higuchi, et al. (1999) "Quantitative analysis of aristolochic acids, toxic compounds, contained in some medicinal plants." J. Ethnopharm. 64 (2): 185-189

¹⁰ Yuan, J., Q. Liu, et al. (2007). "Characterization and determination of six aristolochic acids and three aristolactams in medicinal plants and their preparations by high-performance liquid chromatography-photodiode array detection/electrospray ionization mass spectrometry." Rapid Commun. Mass. Spectrom. 21(14): 2332-2342

¹¹ Jong, T. T., M. R. Lee, et al. (2003). "Analysis of aristolochic acid in nine sources of Xixin, a traditional Chinese medicine, by liquid chromatography/atmospheric pressure chemical ionization/tandem mass spectrometry." J. pharmaceut. biomed. 33 (4): 831-837

¹² Schaneberg, B. T. and I. A. Khan (2004). "Analysis of products suspected of containing *Aristolochia* or *Asarum* species." J. ethnopharmacol. 94 (2-3): 245-249

¹³ McMillin, D.L., C.D. Nelson, et al. (2003) "Determination of Aristolochic Acid in *Asarum canadense* (Wild Ginger)" [online], Meridian Institute. Available: <http://www.meridianinstitute.com/reports/wgreport.html> [19th March 2008]

¹⁴ Nishida, R., J. D. Weintraub, et al. (1993). "Aristolochic acids from *Thottea* spp. (Aristolochiaceae) and the osmeterial secretions of *Thottea*-feeding troidine swallowtail larvae (Papilionidae)." J. chem. ecol. 19 (7): 1587-1594

It must be assumed that aristolochic acid is present also in the not yet examined species of *Aristolochia*, *Asarum*, *Saruma* and *Thottea* or in the respective species examined in which AA could not be detected. . Therefore, our risk assessment cannot be confined to homeopathy and the *Aristolochia* and *Asarum* species used in TCM according to current findings. On the contrary, the entire *Aristolochiaceae* family with the genera *Aristolochia*, *Asarum*, *Saruma* and *Thottea* should be included in the risk assessment.

Toxicological assessment

Aristolochic acid is the main alkaloid of *the Aristolochia* species. According to recent knowledge, the acid is also present in the *Asarum*, *Saruma* and *Thottea* species. AA occurs among others as AA I and its demethylated derivative AA II.

In in-vitro and in-vivo tests aristolochic acid has proved to be genotoxic^{15, 16}, and in animal experiments it has shown carcinogenic effects. Its carcinogenicity is associated with the formation of DNA adducts. Reductive metabolism activates aristolochic acid by nitroreductases to the nitrenium ion (the finally carcinogenic cyclic N-acylnitrenium ion¹⁷) forming the N6-adenosine and N2-guanosine adducts. Via mutations in the proto-oncogen *H-ras* these DNA adducts induce tumour development in the forestomach and auditory canal of rats.

Some findings suggest a tumourigenic effect in the human ureter: aristolochic acid is assumed to be the trigger of the cancers in a Belgian patient group with terminal renal failure (*Chinese herb nephropathy patients (CHN)*), treated in a slimming cure, among others, with Chinese medicinal herbs including *Aristolochia fangchi*). The DNA adduct pattern in the renal tissue of these patients was similar to that found in animals that had developed tumours after administration of aristolochic acid. Of particular importance was the detection of a DNA adduct that is mainly formed by aristolochic acid, viz. a desoxyadenosine adduct [7-(desoxyadenosine-N6-yl)-aristolactam I, dA-AA I], in the kidneys and ureters of all CHN patients, even where the exposure to aristolochic acid during a slimming cure dated back 10 years^{18, 19, 20, 21, 22}.

¹⁵ Kevekordes et al., 2001: Micronucleus formation in human lymphocytes and in the metabolically competent human hepatoma cell line Hep-G2: results with 15 naturally occurring substances. *Anticancer Research* 21, 1A, 461-469

¹⁶ Robisch et al., 1982: Aristolochic acid is a direct mutagen in *Salmonella typhimurium*. *Mutation Research* 105, 4, 201-204

¹⁷ NTP-Report on Carcinogens, Draft Background Document for Aristolochic Acid-Related Exposures: (1) Aristolochic Acid & (2) Botanical Products Containing Aristolochic Acid, U.S. Department of Health and Human Services Public Health Services National Toxicology Program Research Triangle Park, NC 27709, Scheduled Peer Review Date: January 24-25, 2008

¹⁸ Arlt et al., 2002: Aristolochic acid as a probable human cancer hazard in herbal remedies: a review. *Mutagenesis* 17, 265–277

¹⁹ Cosyns et al., 1994. Urothelial malignancy in nephropathy due to Chinese herbs. *Lancet* 344 (8916): 188. (Support not reported. Authors affiliated with University of Louvain Medical School, Belgium)

²⁰ Mengs et al., 1982 : The carcinogenic action of aristolochic acid in rats. *Archives of Toxicology* 51 (2), 107-119

²¹ Mengs, U., 1983: On the histopathogenesis of rat forestomach carcinoma caused by aristolochic acid. *Archives of Toxicology* 52 (3), 209-220

²² Nortier et al., 2000: Urothelial carcinoma associated with the use of a chinese herb -*Aristolochia fangchi*- *N. Engl. J. Med.*, 342, 1686-1692

Two prevalence studies (data from Belgium) and a multitude of case reports concerning tumours of the ureter confirm the carcinogenic effect of AA on humans after ingestion of AA containing products^{17, 22, 23, 24}.

Mechanistic aspects of DNA adducts

DNA-adducts are seen as premutagenic damages and, thus, as precursors of mutations. Such structural changes to the genetic material are often the first step in the multi-stage process of chemical carcinogenesis (initiator effect). The multi-stage concept of carcinogenesis, i.e. the distinction between tumour initiation, tumour promotion and tumour progression in the process of tumour development, presupposes the distinction between genotoxic and non-genotoxic/epigenetic risk factors²⁵.

DNA adduct formation is caused by covalent binding of reactive molecules to the DNA, with the result that modified nucleotides develop. Attachment to DNA components changes the spatial structure of the DNA.

The DNA adduct formers are direct mutagens, which, in the process of replication at the positions of these modifications or in direct neighbourhood, cause base substitutions, deletions, shifts in the reading pattern, and are able to prevent correct DNA replication. These genetic faults are irreversibly fixed by DNA replication. Theoretically, every mutation has the potential to trigger the development of cancer. Therefore it is impossible to define threshold values for direct mutagens²⁶.

Modifying factors

Cells possess repair mechanisms to eliminate adducts. If their repair capacity is insufficient or lacks efficient repair mechanisms for a certain type of damage, DNA damage may have serious effects on the cells: they can degenerate and, eventually, the noxa is able to induce tumour growth.

Persistence of AA-DNA-adducts

The main AA-DNA-adduct, a desoxyadenosine adduct [7-(desoxyadenosine-N6-yl)-aristolactam I, dA-AA I], was detected in the kidneys and ureters of all CHN patients (see above) even when the exposure to aristolochic acid during a slimming cure had taken place 10 years earlier^{18, 27}.

²³ Cosyns JP, Jadoul M, Squifflet JP, Wese FX, van Ypersele de Strihou C. 1999 Urothelial lesions in Chinese-herb neuropathy. *Am J Kidney Dis* 33 (6): 1011-1017 (Support not reported. Authors affiliated with Universite Libre de Bruxelles, Belgium)

²⁴ Nortier JL, Vanherweghem JL. 2002. Renal interstitial fibrosis and urothelial carcinoma associated with the use of Chinese herb (*Aristolochia fangchi*). *Toxicology* 181-182: 577-580 (Support not reported. Authors affiliated with universite Libre de Bruxelles, Belgium)

²⁵ Wörth C. C. T., 2000, Entwicklung eines Nachweis-Verfahrens für DNA-Addukte basierend auf Fluoreszenzderivatisierung und kapillarelektrophoretischer Trennung, Dissertation molekulare Toxikologie, Leiter Prof. Manfred Wießler am Deutschen Krebsforschungszentrum Heidelberg

²⁶ Neumann HG (2006a) Die Risikobewertung von Kanzerogenen und die Wirkungsschwelle. Teil I. *Bundesgesundheitsblatt* 49: S. 665–675

Neumann HG (2006b) Die Risikobewertung von Kanzerogenen und die Wirkungsschwelle, Teil II. *Bundesgesundheitsblatt* 49, S. 818–823

Neumann HG (2006c) Die Risikobewertung von Kanzerogenen und die Wirkungsschwelle, Teil III. *Bundesgesundheitsblatt* 49, S. 911–920

²⁷ Arlt et al., 2001: Analyses of DNA adducts formed by ochratoxin A and aristolochic acid in patients with Chinese herbs nephropathy. *Mutation Research-Genetic Toxicology and Environmental Mutagenesis* 494, 143-150

Evaluation of DNA adducts

Adduct formation indicates exposure to genotoxic substances, but not whether the exposure will trigger toxic effects.

Threshold of Toxicological Concern (TTC) is not applicable

Aristolochic acid has been proved to be a direct mutagen and one of the most potent carcinogens^{16, 20, 28, 29, 30}.

The mutagenic activity of aristolochic acid was compared with that of N-methyl-N'-nitro-N-nitrosoguanidine following systemic administration. Activity was markedly higher in aristolochic acid than in the comparative substance³¹. Therefore, aristolochic acid belongs to the group of highly potent genotoxic carcinogens and is explicitly excluded from the TTC approach, in accordance with the *GUIDELINE ON THE LIMITS OF GENOTOXIC IMPURITIES (EMEA/CHMP/QWP/251344/2006)*:

"Some structural groups were identified to be of such high potency that intakes even below the TTC would be associated with a high probability of a significant carcinogenic risk³². This group of high potency genotoxic carcinogens comprises aflatoxin-like-, N-nitroso- and azoxy-compounds that have to be excluded from the TTC approach."

(For exclusion see also POINTS TO CONSIDER ON NON-CLINICAL SAFETY OF HOMEOPATHIC MEDICINAL PRODUCTS OF BOTANICAL, MINERAL AND CHEMICAL ORIGIN, ADOPTION BY HMA, July 2007: *"Additionally, Aristolochia species are excluded from the TTC approach for homeopathic medicinal products of botanical origin in compliance with the Position Paper on the Risks Associated with the Use of Herbal Products containing Aristolochia species (EMEA/HMPWP/23/00)."*)

Estimation of virtually safe doses

In accordance with the estimates derived from human data by Prof. Schmeiser from the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ), an aristolochic acid limit of 0.36 ng/d, with a residual cancer life-time risk of less than 1:1,000,000, is acceptable.

Derivation of the virtually safe dose according to the DKFZ by Nortier et al. (2000)²²:

- 50% tumour risk for cumulated intake of ca. 200 g of *Aristolochia fanghi* for ca. 2 years
- assuming a content of 0.65 mg of aristolochic acid per gramme of herb, the intake per patient amounts to 130 mg of aristolochic acid in the course of 2 years.

This is equivalent to a daily exposure of 0.18 mg of aristolochic acid. Assuming a body weight (b.w.) of 50 kg this is equivalent to a daily dose of aristolochic acid of 0.0036 mg/kg b.w.

Assuming a residual risk of 1:1,000,000 and a 50% tumour risk, the virtually safe dose of aristolochic acid is 0.36 ng per day.

²⁸ Schmeisser et al., 1984: Cancer Lett 23: 97-101

²⁹ Pezzuto et al., 1988: Mutat Res 206: 447-454

³⁰ Mengs et al., 1988: Arch Toxicol 61: 504-505

³¹ Maier et al., 1985: Mutat Res 143: 143-148

³² Kroes et al., Food and Chemical Toxicology 42 (2004): 65-83

Calculation of potencies considered safe for homeopathic *Aristolochia* preparations

According to the 1981 graduated plan procedure for *Aristolochia* species, homeopathic preparations from *Aristolochia* are marketable from an arithmetical potency of D11 and higher related to the finished product.

Based on the above findings about aristolochic acid, potency D11 for the maximum daily dose of *Aristolochia* preparations is under review considering:

- the highest known content of aristolochic acid in *Aristolochia manshuriensis* of 9720 ppm (=3227 ppm in the mother tincture = 0.3227%). Calculation on the basis of the maximum content is necessary because the data available come from as few as three homeopathic mother tinctures of *Aristolochia clematitis*. In view of the high toxic potential of aristolochic acid it is impossible to determine a potency limit alone on the basis of these three samples;
- the highest daily dose for “worst-case” conditions,
- the liquid dilution/mixture and tablet dosage forms.

The fresh aerial parts are the starting material for the mother tincture of *Aristolochia clematitis*. The mother tincture is prepared according to HAB, manufacturing method 2a. Decimal dilution (D) 1 is prepared from 2 parts of mother tincture and 8 parts of ethanol 43% (m/m), D2 from 1 part of D1 and 9 parts of ethanol 43% (m/m). Procedures for the following dilutions are similar.

Assuming 9720 µg or 9.72 mg of aristolochic acid in 1 g of dried plant:

With a loss of drying of 60% this is equivalent to 3.88 mg of aristolochic acid in 1 g of fresh plant. If prepared according to HAB, manufacturing method 2a, 0.83 g of fresh plant is processed in 1 g of mother tincture. Thus, 1 g of mother tincture contains ca. 3.23 mg.

Liquid dilution/mixture (dose specification as in Commission D monograph):

Dose of 5-10 drops half-hourly to hourly.

10 drops x 24 x 2 = 480 drops

minus 8 hours of sleep: 10 x 8 x 2 = 160 drops

Thus the maximum dose/day is 480 – 160 = 320 drops.

(30 drops, according to drop table, equivalent to 1 g of liquid dilution)

A maximum daily dose of 320 drops of mother tincture (UT) would amount to 11 g of UT.

11 g UT contain maximally ca. 35 mg of aristolochic acid.

This is equivalent to ca. 7.1 mg in D1 and ca. 0.071 ng in D9.

Hence, potency D9 is below the virtually safe dose of 0.36 ng/d of aristolochic acid.

Tablets (each 250 mg of active substance):

Dose of 1-3 tablets half-hourly to hourly.

3 tablets x 24 x 2 = 144 tablets

minus 8 hours of sleep: 3 x 8 x 2 = 48 tablets

Thus the maximum dose/day is 144 – 48 = 96 tablets (equivalent to 24 g of active substance).

Derived from the content of aristolochic acid in the mother tincture, D1 contains ca. 15.5 mg and D9 ca. 0.155 ng of aristolochic acid.

Hence, potency D9 is below the virtually safe dose of 0.36 ng/d of aristolochic acid.

Derived from these calculations and the reasons mentioned above, a justifiable risk from *Aristolochia* species can be assumed for potency stages beginning at D11, not lower. This is equivalent to a maximum exposure of 3.6 µg/day of aristolochic acid.

Calculation of potencies considered safe for homeopathic *Asarum* preparations

Calculations take into consideration:

- the highest known content of aristolochic acid in *Asarum crispulatum* of 3 377 ppm (= 750 ppm in the mother tincture = 0.075%). Calculation on the basis of the maximum content is necessary because data are only available for three homeopathic mother tinctures from *Asarum europaeum* and one mother tincture from *Asarum canadense*. In view of the high toxic potential of aristolochic acid it is not possible to determine a potency limit alone on the basis of these four samples;
- the highest daily dose for “worst-case” conditions,
- the liquid dilution/mixture and tablet dosage forms.

The fresh underground parts of either *Asarum* species are the starting material for the mother tinctures from *Asarum europaeum* and *Asarum canadense*. The mother tinctures are prepared according to HAB, manufacturing method 3a. Decimal dilution (D) 1 is prepared from 3 parts of mother tincture and 7 parts of ethanol 62% (m/m), D2 from 1 part of D1 and 9 parts of ethanol 62% (m/m). Procedures for the following dilutions are similar. From potency D4 on, use of ethanol 43% (m/m) is prescribed.

Assuming 3377 µg or 3.377 mg of aristolochic acid in 1 g of dried plant:

With a loss of drying of 60% this is equivalent to ca. 1.35 mg of aristolochic acid in 1 g of dried fresh plant. If prepared according to HAB, manufacturing method 3a, 0.55 g of fresh plant is processed in 1 g of mother tincture. Thus, 1 g of mother tincture contains ca. 0.75 mg of aristolochic acid.

Liquid dilution/mixture:

The maximum daily dose of 320 drops of mother tincture (UT) is equivalent to 11 g UT (see “Calculation of potencies considered safe for homeopathic *Aristolochia* preparations”).

11 g UT contain a maximum of 8.25 mg of aristolochic acid.

This is equivalent to ca. 2.48 mg in D1 and ca. 0.248 ng in D8.

Hence, potency D8 is below the virtually safe dose of 0.36 ng/d of aristolochic acid.

Tablets:

A maximum daily dose of 96 tablets, each of 250 mg, is equivalent to 24 g of active substance (see “Calculation of potencies considered safe for homeopathic *Aristolochia* preparations”).

This is equivalent to 5.4 mg of aristolochic acid in D1, to 0.54 ng in D8, and 0.054 ng in D9.

Hence, potency D9 is below the virtually safe dose of 0.36 ng/d of aristolochic acid.

Derived from these calculations and the reasons mentioned above, a justifiable risk from *Asarum* species can be assumed for potencies beginning at D11, not lower. This is equivalent to a maximum exposure of 3.6 pg/day of aristolochic acid.

Summary

Aristolochic acid has been detected not only in homeopathic mother tinctures from *Aristolochia clematidis*, but also from *Asarum europaeum* and *Asarum canadense* as well as in the TCM drug *Asari radix e rhizoma*. These findings are confirmed in the literature stating the presence of aristolochic acid in numerous *Asarum* species, in a *Saruma* species and in two not precisely defined *Thottea* species.

Therefore it is necessary to extend the measures ruled in the graduated plan procedure of 1981 to all medicinal products prepared by using plants of the *Aristolochiaceae* family including the *Aristolochia*, *Asarum*, *Saruma* and *Thottea* genera.

A potency limit of D11 is necessary in view of the following facts:

the high toxic potential of aristolochic acid (whereby the establishment of the potency limit was based on the highest contents of AA found so far in *Aristolochia manshuriensis* and *Asarum crispulatum*); conversion of the virtually safe dose into a potency stage under the conditions of worst-case doses and in consideration of the 1981 graduated plan procedure for *Aristolochia*. This means that safety concerns are raised by products derived from plants of the *Aristolochiaceae* family up to and including the 10th decimal power (D10), related to the finished product. Therefore, it is intended to revoke the authorisations/registrations of the products listed in the Annex.

It is explicitly stated here that the present graduated plan procedure does not only apply to finished medicinal products liable to registration or authorisation in accordance with Section 5 sub-section 1 of the German Medicines Act (AMG). It also applies to the sale of the medicinal drug itself and to those homeopathic medicines that are exempted from the obligation to authorisation due to the provisions in Section 38 sub-section 1 AMG if marketed in quantities of not more than 1000 packages per year. The pharmaceutical companies concerned are obliged to immediately implement the measures also for the mentioned products. The competent authorities will control the implementation.

Standard registrations

According to pharmaceutical legislation the present ruling is valid for individually registered medicinal products. Users of relevant standard registrations are requested to immediately adopt the above mentioned changes on their own account in order to adapt to the up-to-date findings, in anticipation of a change of the ordinance for standard registrations on the basis of Section 39 sub-section 3 in connection with the provisions of Section 36 sub-section 1 AMG.

Further procedure

You can avoid a further procedure under the graduated plan and, consequently, a notification liable to fees, if you notify the BfArM bindingly, within the deadline for the hearing, of your renunciation of the authorisation/registration for the medicinal products in question (please refer to the *Aktenzeichen* mentioned below).

Holders of drug marketing authorisation/registration are reminded that they are obliged also by the legal principle of sole responsibility, to manufacture and market their products in compliance with the scientific knowledge of the time and to take any necessary precautions at the earliest possible time, independently of any restricting decisions of the federal higher authority.

Yours sincerely
Dr. A. Thiele
on behalf of the BfArM

Annex

Annex

Medicinal products:

Asarum europaeum

- Medicinal products on the market

Potencies < D11: 5 products

| Processing Number | Product name | Pharmaceutical company | Calculated potency | Dosage form | Type of application |
|--------------------------|---------------------------------------|-------------------------------|---------------------------|--------------------|----------------------------|
| 0250814 | Monoplex 9 - Asarum europaeum - | Pflüger | D4 | Liquid dilution | ZULP105 |
| 0826898 | Xanthoxylon N Oligoplex | Madaus | D4/5 | Mixture | ZULP105 |
| 2141470 | ANTIMIGREN tablets | Pascoe | D4/5 | Tablet | ZULP21 |
| 2157030 | WigaCim | Kattwiga | D4 | Mixture | REGP38 |
| 2512425 | 165 Inula Komplex | Nestmann | D4/5 | Mixture | REGP105 |