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Opinion

of the French Food Safety Agency on the use of botanical food supplements which have been the subject of drug safety monitoring reports

DIRECTOR GENERAL

The French Food Safety Agency (Afssa) was requested on 30 May 2007 by the Directorate General for Competition, Consumer affairs and Fraud Control (Dgccrf) to examine the use of botanical food supplements which have been the subject of drug safety monitoring reports.

Botanical food supplements are covered by decree 2006-352 of 20 March 2006. These food supplements may be present on the French market because they are marketed in other Member States of the EU and because of the principle of free trade. Adverse effects have been reported relating to the consumption of botanical based products (products containing *Hoodia gordonii*, *Cimicifuga racemosa, Viola tricolor*, *Desmodium*, *Echinacea,* or *Polygunum multiflorum*).

The Dgccrf has requested that Afssa firstly identifies and describes the risks from the use of these botanical preparations in food supplements and secondly, insofar as possible, presents the scientific data to define the conditions of use under which these botanical preparations may be used in food supplements. Details are provided botanical by botanical.

In 2003, Afssa published an assessment process on the safety, utility and claims for foodstuffs containing botanicals intended for human consumption (Afssa, 2003) which recalled the bases for assessing these substances. Particular attention must be paid to the safety of use of these substances which (i) are not essential for staying healthy (they are not nutrients), (ii) but are usually presented for the purposes of improving health although the system stipulated by Regulation No. 1924/2006 on claims will not be operational for several years (the claimed effects of the 6 botanicals in this request are very varied and diffuse in formulation and communication means). This assessment must take account of the specific features of the botanicals themselves, indeed, it is complicated by often limited knowledge about products, which have variable and occasionally very different chemical profiles. However, they remain of key importance in terms of risks and physiological effect.
The risk factors from consuming food supplements containing botanicals can be divided into 4 categories: (i) the botanical, (ii) the extraction, (iii) exposure and conditions of consumption, (iv) quality control of the consumed product. Finally, a reference text and specific features relating to the safety of use assessment for the botanicals must be taken into account.

At botanical level, the wide range of species, varieties, ecotypes and chemotypes are such that botanically very similar botanicals may be available although these may have chemically very different compositions. The parts of the botanical (stem, flower tip, root, etc.) often differ in chemical composition. The chemical profile is often complex in composition and the constituents are not always known. A precise identification of the genus and species by scientific name (occasionally supplemented by the name of the author and occasionally the variety), the nature of the organ, the geographical origin and possibly the harvesting period, growing method, botanical treatment methods and external contaminants all need to be taken into account.

In additional to natural variability, the processing methods for the fresh botanicals into a raw extract followed by the selective extractions (generally aqueous-alcoholic or alcoholic extractions) or even very specific extractions (for example supercritical gas extraction) for some specific constituents are liable to result in very different preparations in terms of activities and risks. The type of solvent used

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plays an essential role by selecting ranges of lipophilic and/or hydrophilic substances and therefore substances of different activities. In the case of more or less purified microconstituents, the risk assessment can be based on demonstrative studies consistent with the conventional approach developed for isolated chemically defined molecules. However, the specific features of the "totum[1]" of these botanicals limit the possibility of using this approach.

It is particularly important to take account of the level of exposure in the food sector in light of the potentially very wide scale distribution of food supplements. This point is crucial in terms of the adverse effects of some botanical preparations on particular population groups: allergic people, people of specific physiological status (for example pregnant women) or people suffering from a potentially serious disease which requires drug therapy with which the chemical constituents extracted from some botanicals can interact.

In terms of the many procedures used to obtain preparations from botanicals, through which the chemical profile may vary, it would appear essential for the professional to be able to provide the proof for a given food supplement that he/she has managed the risk issues highlighted above. It is essential that the professional rigorously defines the identification of the raw material, the processing procedure and the production conditions up to the finished product. Standardisation of raw material quality and the application of procedures up to the finished product are essential to ensure data reproducibility.

Assessment of the safety of use of botanicals therefore requires a system of reference which is in part specific to their particular features. This assessment is a more recent development in the foodstuffs sector, although a specific and in-depth system of reference for the assessment and safety of use of botanicals has been in use for many years in the medicines sector. This system of reference includes reference works such as the European Pharmacopoeia which offers the ability to identify the characteristics of botanicals and their preparations, particularly in extract form. For those botanicals which are best understood, knowledge about their use is based on the European tradition. This tradition can help to combat inappropriate uses or the use of poorly understood or even toxic botanicals liable to cause harmful short or long term health effects. Conversely, it cannot combat emergent risks such as interactions between chemical constituents of the botanicals with new medicines. The assessment must also therefore be based on available experimental findings. These include *in vitro* and *in vivo* toxicological and pharmacological studies, clinical studies, and drug safety monitoring data where these exist. The utility and ability to establish a no adverse effect level in animals or human beings must be considered. Apart from the conventional safety studies described above, which are often difficult to apply to these substances, the warning pointers must be identified: overt or potential toxicity of some constituents, existence of reported adverse effects, possible contra-indications, known therapeutic interactions, risks associated with galenic forms and questions relating to the claim.

Finally, it must be highlighted that all of the adverse effects reported for botanical based substances are collected from drug safety monitoring networks established for medicinal health products[2]. These networks do not exist at present in the food sector. It is often very difficult or even impossible to specifically characterise the preparations involved in drug safety monitoring notifications and thus the nature and amounts of substances ingested, in view of the very wide range of food supplements and the lack of marketed product registration.

The following assessments have been based on these principles.

Bibliography

Assessment process on the safety, utility and claims for foodstuffs containing botanicals, intended for human consumption (Afssa, 2003)
Regulation (EC) No 1924/2006 on nutritional and health claims for foodstuffs.

[1] Totum: all of the constituents of a botanical contributing to the activity attributed to this plant.
[2] Afssaps

Hoodia gordonii

CONTEXT

One case of clinically poorly defined malaise with gastro-enteritis has been described in drug safety monitoring reports after ingestion of food supplements containing *Hoodia gordonii*.

The Dgccrf request is for a risk assessment from ingestion of food supplements containing the powder and/or aqueous extract of *Hoodia gordonii* stem in amounts of up to 1g/day. The Dgccrf also asks whether it is possible to establish conditions under which ingestion of this botanical does not carry risks or whether the scientific information about the risk requires the use of this botanical to be prohibited in food supplements.

According to information provided by Dgccrf, *Hoodia gordonii* has recently appeared on the French market through a large number of food supplements, particularly from Internet sites. The *Hoodia gordonii* extracts on the market are generally powdered stems or aqueous extracts dried onto maltodextrin and presented in the form of capsules and tablets. The doses recommended by the companies generally range from 100 mg to 800 mg/day (one product recommends up to 1600 mg/day). An infusion form consisting of 2 g sachets containing a mixture of tea and 100 mg of *Hoodia gordonii* has also been reported. Most of these supplements are in the "slimming" sector, referring to the effect of a "P57" molecule said to act directly on the hypothalamus by stimulating a sensation of satiety.

In regulatory terms, the European bodies consider that *Hoodia gordonii* is subject to regulation (EC) No. 258/97 on new foods and new ingredients. It is not currently recognised as a medicinal botanical in France by the French Health Products Safety Agency (Afssaps).

BOTANICAL AND PHYTOCHEMISTRY INFORMATION

Hoodia gordonii is defined botanically as a botanical originating from the Kalahari dessert belonging to the Asclepiaciae family. The fresh stems are traditionally eaten to relieve hunger by the Bushmen tribes.

On the other hand, phytochemically, only the molecule "P57AS3" is relatively well known in terms of its structure, quantification in the botanical and some of its extracts (Pawar *et al.*, 2006). Some of its effects are also known, as it has been shown that when injected into the cerebral ventricles it has a direct action on the hypothalamus (MacLean *et al.*, 2004). Since this publication, 11 other oxypregnane glycosides have been identified. They have been called hoodiglycosides (A,B,… K) and their structures have been determined although only their cytotoxicity has been assessed on cell lines and found to be negative. No other information about the toxicity of these substances (the concentrations of which are unknown) are known at present and no other potential pharmacological effect has been assessed. One other team (Dall'Aqua *et al.*, 2007) simultaneously published the identification of 10 similar steroidal C21 steroidal derivatives called A-L gordonosides (of which 9 are keto-steroids).

This botanical therefore contains many glycosides, some described as saponosides, although these are in fact more novel structures (in the botanical kingdom), more complex and degraded into functional C21 cetone nuclei with some analogy to animal hormones (steroids). This should encourage considerable caution as their toxicity (acute, sub-acute and chronic, teratogenicity, mutagenicity, carcinogenicity, etc.), activities and bioavailability (absorption, distribution, metabolism, elimination of the substances and their metabolites) have not been assessed.

The possibility that this botanical contains other unknown new compounds must not be excluded in view of its novel biosynthetic pathways and the recent nature of the research upon it.

Finally, 5 recent patents involve *Hoodia gordonii*. One of these uses a particularly selective procedure for molecules which can interact with human hormone receptors by steroid extraction with supercritical carbon dioxide (Gunning *et al.*, 2005).

OTHER INFORMATION

Daily doses are proposed for food supplements containing *Hoodia gordonii* on the market although the material to which the dose refers is unclear (botanical, extract containing several chemical constituents and in this case which ones, specific constituents). It is therefore absolutely impossible to describe the risk from consuming the stated amounts.

CONCLUSION

Afssa considers that within the current information available:

1) *Hoodia gordonii* is insufficiently understood in terms of its phytochemistry and beneficial or deleterious effects. The risks from consuming *Hoodia gordonii* cannot therefore be described. In particular, the possible effects of oxypregnane glycosides on steroid receptors within the body must be investigated in more depth.
2) As a result it is impossible to set risk-free conditions of use for *Hoodia gordonii*: constituents which may cause a harmful effect, part of the botanical and extracts which may be ingested without risk, dose equivalent to ingestion of *Hoodia gordonii* constituents at a level estimated to be risk-free, tracer enabling extracts defined as being risk-free to be standardised;
3) According to the scientific information available, it is recommended that ingestion of *Hoodia gordonii* as a food supplement be avoided.

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Black cohosh
Actaea racemosa or *Cimicifuga racemosa* (L.) Nutt.

CONTEXT

Cimicifuga racemosa has been the subject of several health warnings. On 18 July 2006, the European Medicines Agency (EMEA) distributed information about 42 cases of hepatic disease associated with cohosh, collected from the European Health Authorities or reported in the scientific literature (EMEA, 2006). The majority of these cases were poorly documented, or involved patients with concomitant diseases or treatments which may have explained the hepatic injury. In 4 cases, however, it was not possible to exclude the responsibility of cohosh. An assessment was recently published in 2007 (EMEA, 2007). Afssaps has been aware of 2 French cases of liver impairment reported in 2 patients who had received the "stock" tincture of *Cimicifuga racemosa* and a food supplement.

The Dgccrf request is for an assessment of risk from ingestion of food supplements containing the powder and/or extracts of black cohosh. The Dgccrf also asks whether it is possible to establish conditions under which ingestion of this botanical does not carry risks or whether the scientific information about the risk requires the use of this botanical to be prohibited in food supplements.

According to the information provided, black cohosh is present in the market in around twenty food supplements (capsules) sold in shops. It is also contained in products offered on the Internet.

Cohosh is a North-American medicinal botanical which has received media attention on its possible use in menopausal disorders, although it has not to date been clinically demonstrated to be effective. Most of the commercial food supplements containing *Cimicifuga racemosa* contain the powdered root (1 supplement contains a dry aqueous-alcoholic bark extract) in amounts of between 30 and 300 mg of powder per capsule. The recommended daily doses for these products are not readily available. Internet searches also show the existence of standardised extracts containing 1% actein recommended to be consumed at amounts of 80 mg/day, and standardised extract equivalent to 2.5% of tritepene glucosides.

In regulatory terms the status of cohosh has not been discussed in terms of Regulation (EC) No 258/97 on a Community level, although the national bodies consider that it cannot claim to be recognised as a traditional food substance. The botanical appears on list 3 of the Belgian Royal Decree (1997) establishing a positive list of botanicals of which may be present in the composition of food supplements. This text stipulates the conditions for use to be observed, particularly the fact that the recommended daily dosage should not result in ingestion of more than 3 mg of triterpene glycosides per day.

Several countries have also produced recommendations on the consumption of *Cimicifuga racemosa*. In February and July 2006 respectively, Australia and Great Britain stated that food supplements containing black cohosh should display a warning about potential liver toxicity (Blumenthal, 2006 ; American Botanical Council, 2006). In August 2006, Health Canada distributed a warning recommending caution to people taking black cohosh (Health Canada, 2006). The Minister stated that "although the cases of liver injury reported are rare and the relationship between black cohosh and liver toxicity are not clear, Health Canada opts for caution and is examining the safety and efficacy of black cohosh".

BOTANICAL AND PHYTOCHEMISTRY DATA

Black cohosh is defined botanically and also has the name *Actea racemosa* and *Cimicifuga racemosa* (L.) Nutt. This botanical is also widely called "herbe aux punaises " in French and "black cohosh" in English. It belongs to the family of Ranuncuculaceae. The rhizome and dry roots of *Cimicifuga racemosa*, which are not traditionally eaten are nevertheless traditionally used for minor gynaecological problems (pre-menstrual and menopause-related disorders).

In France, an aqueous-alcoholic extract containing 8% *Cimicifuga racemosa* (L.) Nutt. triterpenoids is used as a herbal medicine called Cimipax®, traditionally used in the symptomatic treatment of

anxiety, particularly for mild sleep disorders. In Germany, alcoholic 40-60% extracts have been accepted by the E Commission (treatment limited to 6 months).

It has been proposed that the underground parts of *Cimicifuga racemosa* contain phyto-estrogens (particularly fomonometin) (Bruneton, 1999). These molecules have not however been confirmed in the most recent research. The main constituents are triterpene glycosides such as cycloartane (actein, cimiracemoside, etc.), and phenol acid esters (fukinolic acid, cimicifugic acid etc.). It now appears that the botanical contains constituents which may be partial serotonin receptor agonists (Burdette, 2003).

Tests performed on black cohosh food supplements (Jiang *et al.*, 2006) show variable triterpene profiles due to the existence of Asian and North-American varieties. It would be appropriate to standardise extracts, quantifying the total triterpene saponosides, which may be measured as actein equivalents. The Belgian regulations permit ingestion of more than 3 mg of triterpene glycosides and it may be wise to restrict the use of low titre aqueous and aqueous-alcoholic extracts in order to avoid the presence of free genins, the gastro-intestinal absorption of which appears to be much greater than that of the heterosidic forms (generally low for the heterosides in the absence of hydrolysis by the intestinal flora). Non-specific assay of the total derivatives would risk failing to distinguish between free and bound forms.

ADVERSE EFFECTS

In 2007 the EMEA published an assessment of the adverse effects of consuming *Cimicifuga racemosa* rhizome according to the so-called "Roussel UCLAF causality assessment" method (RUCAM) (EMEA, 2007). This involved 31 drug safety monitoring cases collected from the competent national authorities from the European Union (EU). 5 cases did not come from the EU and 8 cases were published in the literature. The drug safety monitoring cases and those from the literature were poorly documented (sequence of treatment with products containing *Cimicifuga racemosa*, relationship with development of symptoms, etc.). Results from clinical trials were also considered. The deleterious effects were generally hepatic: in some cases these required transplantation. By the RUCAM method, 3 cases were classified as possible and 2 as probable. The EMEA concluded that the connection between medicinal products containing *Cimicifuga racemosa* and hepatotoxic effects must be considered a warning sign and the EMEA draws the public's attention to the fact that adverse hepatic effects may occur in patients taking *Cimicifuga racemosa*.

Apart from the drug safety monitoring cases described above, a publication in 2007 reported cases of vasculitis in people consuming food supplements containing *Cimicifuga racemosa* (L.) Nutt (Ingraffea *et al.*, 2007).

OTHER INFORMATION

Daily doses are proposed for commercial food supplements containing *Cimicifuga racemosa* (L.) Nutt although the material to which the dose refers is unclear (botanical, extract containing several chemical ingredients, in this case which ones, specific ingredient). It is therefore absolutely impossible to describe the risk of consuming the stated amounts.

CONCLUSION

Afssa considers that:

1) *Cimicifuga racemosa* is insufficiently understood in terms of its phytochemistry and beneficial or deleterious effects. Risks from consuming *Cimicifuga racemosa* cannot therefore be described. In this respect, the recent findings published by the EMEA (EMEA, 2007) call for caution.
2) As a result it is impossible to set risk-free conditions of use for *Cimicifuga racemosa*: constituents which may cause a harmful effect, part of the botanical and extracts which may be ingested without risk, dose equivalent to ingestion of *Cimicifuga racemosa* constituents at a level estimated to be risk-free, tracer enabling extracts defined as being risk-free to be standardised;
3) An extract for this botanical is currently used in France in a medicine, the summary of product characteristics of which has just been supplemented by strong warnings and precautions for use in terms of the risk of liver injury: this botanical is subject to attentive drug safety monitoring in the medicines area ;

4) According to the scientific information available, it is recommended that consumption of *Cimicifuga racemosa* as a food supplement be avoided.

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"Desmodium"

CONTEXT

"Desmodium" has been the subject of a drug safety monitoring report on hepatic injury occurring in a person consuming food supplements containing "Desmodium" and extracts of grapefruit seeds.

The Dgccrf request is for an assessment of risks from consuming food supplements containing the powder and/or extracts of *Desmodium adsendens* The Dgccrf also asks whether it is possible to establish conditions under which ingestion of this botanical does not carry risks or whether the scientific information about the risk requires the use of this botanical to be prohibited in food supplements.

According to the Dgccrf around thirty food supplements (vials, bottles, capsules) containing a botanical described under the name "Desmodium" are sold on the French market. The name used can cover 2 species: *Desmodium gangeticum* and *Desmodium adscendes*.

Most of the food supplements containing "Desmodium" contain aqueous extracts (vials or bottles) and powders (capsules) of leaves and in some cases, stems of the botanical. They claim "hepatic protection" and immunostimulant activities. The proposed daily intake is between 400 mg and 2g of "dry botanical equivalent".

In regulatory terms the European bodies consider *Desmodium gangeticum* to fall within the scope of Regulation (EC) No. 258/97 concerning novel foods and novel food ingredients. The working group of national experts responsible for new foods in terms of Regulation (EC) No. 258/97 concluded that *Desmodium gangeticum* must be deemed to be a novel food. The status of the species *Desmodium adscendes* was not discussed in terms of Regulation (EC) No. 258/97: this botanical appears on list 3 of the Belgian Royal Decree (1997) establishing a positive list of botanicals which may be present in the composition of food supplements.

BOTANICAL AND PHYTOCHEMISTRY DATA

Desmodium adsendens is a Fabaceae originating from West Africa, the leaves and stems of which are used for medicinal purposes and not in traditional foods. The botanical contained in the food supplements cannot be defined unequivocally as it appears that it may be substituted by *Desmodium gangeticum*.

Knowledge about the phytochemistry of *Desmodium adsendens* is extremely limited and only a few secondary metabolites of *Desmodium adsendens* have been quantitatively characterised: flavonoids (vitexin and isovitexin), saponosides (soyasaponin I) (Pothier *et al.*, 2006)) and phenylethylamine alkaloids. There appears to be a degree of variability of the chemical constituents depending on origin (Ghana, Nigeria, Sierra Leone, or Togo). In the absence of an assay method for a specific relevant tracer to confirm their authenticity, the issue of standardisation of the botanical or its extracts has not been resolved. Their quality and safety have not therefore been established.

DATA ON THE ACTIVITY OF THE BOTANICAL AND ITS EXTRACTS

There are no experimental toxicological, bioavailability or pharmacological data published (reference text, scientific publication).

On the other hand *"Desmodium"* is described as a "hepatic protector" and "immunostimulant". Its consumption is described as being beneficial in the treatment of serious disorders (hepatitis), possibly in association with major medicinal products such as chemotherapy. The botanical constituents of *Desmodium adsendens* which can be associated with this claimed activity are unidentified and there are no methodologically robust published studies demonstrating these effects. A daily intake of 400 mg to 2g of dry botanical equivalent is generally stated, although the benefits and risks of consuming these doses have not been demonstrated nor has an opinion been expressed by a scientific body.

Whilst certain constituents of *Desmodium adsendens* have been shown to have activity on the liver, the risk of interference with the metabolism of medicinal products should be assessed as, should enzyme induction occur, the efficacy of these medicinal products could be reduced. The contra-indications and interactions which may be suspected in this context must therefore be documented without fail.

Assessments conducted by the French Health Products Safety Agency have not recognised a favourable beneficial risk ratio for *Desmodium adsendens* and no marketing authorisation or medicinal botanical status has been granted.

CONCLUSION

Afssa considers that :

1) The phytochemistry and beneficial or deleterious effects of *Desmodium adscendes* are insufficiently understood and the risks of consuming *Desmodium adscendes* cannot therefore be described;
2) As a result it is impossible to set risk-free conditions of use for *Desmodium*: constituents which may cause a harmful effect, part of the botanical and extracts which may be ingested without risk, dose equivalent to ingestion of *Desmodium* constituents at a level estimated to be risk-free, tracer enabling extracts defined as being risk-free to be standardised.
3) The effects attributed to *Desmodium adscendes* should undergo detailed studies both to demonstrate that these effects are real and to demonstrate possible deleterious effects to consumers on medicinal treatment from interactions. If these interactions were identified they should as a minimum lead to consumer information in terms of contra-indications;
4) According to the scientific information available, it is recommended that ingestion of *Desmodium* as a food supplement be avoided.

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Viola tricolor L. or *Viola arvensis* Murray *(wild pansy)*

CONTEXT

The Dgccrf has been informed of a case of hepatic injury from taking a product containing a strong aqueous-alcoholic extract of wild pansy.

The Dgccrf request is for an assessment of risks from consuming food supplements containing the powder and/or extracts of *Viola tricolor*. The Dgccrf also asks whether it is possible to establish conditions under which ingestion of this botanical does not carry risks or whether the scientific information about the risk requires the use of this botanical to be prohibited in food supplements.

According to the information provided by Dgccrf, a large number of food supplements containing *Viola tricolor* are present on the French market. In France, capsules of powdered botanical (freeze ground botanical), vials of aqueous extract (maceration in water followed by filtration) to be diluted in a glass of water and capsules or tablets of dry aqueous extracts are found. The maximum recommended daily intakes of these food supplements are 1500 mg of powdered botanical and 80 to 500 mg of dry botanical equivalent for the aqueous extracts.

Food supplements containing *Viola tricolor* are also marketed in other EU Member States.

BOTANICAL AND PHYTOCHEMISTRY DATA

Viola tricolor is a botanical originating from temperate regions, traditionally used in seborrhoeic skin conditions, adjuvant treatment of the painful component of functional bowel disorders and the symptomatic treatment of coughs (Cahiers de l'Agence no. 3 (Medicines Agency, 1998)).

The aerial parts of the flower have been used for more than 30 years in Europe as an infusion. Their polysaccharide, flavonoid and saponoside composition is known. *Viola tricolor* appears in the monograph in the European Pharmacopeia and a minimum content of 1.5% flavonoids expressed as violanthine ($C_{27}H_{30}O_4$;*Mr*578,5) (dried drug) is defined. It is therefore possible to standardise commercial extracts. *Viola tricolor* also appears in the Cahiers de l'Agence no. 3 (Medicines Agency, 1998) for aqueous extracts, weak aqueous-alcoholic extracts (prepared from ethyl alcohol, concentration 30% or less (v/v) and strong aqueous-alcoholics extracts (prepared from ethyl alcohol, concentration of more than 30% (v/v)).

Recent information however has revealed the presence of cyclopeptides, i.e. cyclical peptides containing approximately 30 mostly lipophilic amino acids, some of which have been shown to be highly cytotoxic (IC_{50} from 0.6 to 6 µmol) (Svangard *et al., 2004*). Their content in *Viola tricolor* varies from 0.01% to 0.1%. Some fifty different structures are believed to exist in species of the *viola* genus (Goransson *et al.*, 2003).

Cyclopeptides are very difficult to extract by infusion, which is the traditional form of consumption in Europe and can be considered to be risk-free and of traditional use. Similarly, the strict aqueous extracts do not appear to carry a risk as the doses ingested would not exceed an equivalent in the region of 1500 mg/day of botanical. On the other hand any extract with a solvent more lipophilic than water (including weak aqueous-alcoholic extracts and particularly strong alcoholic extracts) should be prohibited. The "powdered botanical" form is not a traditional form and must not be recommended as ingestion may result in absorption of nonpolar cyclopeptides.

CONCLUSION

Afssa considers that :

1) Consumption of *Viola tricolor* in its traditional form of use (infusion) or with strict aqueous extracts at doses less than an equivalent of 1500 mg of dry botanical/day does not carry risks;
2) Ingestion of *Viola tricolor* in the form of powdered botanical or extracts prepared from any solvent other than water must not be recommended.

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Echinacea angustifolia DC, *Echinacea pallida* (Nutt.), *Echinacea purpurea* (L.) Moench

CONTEXT

Various, particularly allergic, adverse effects have been reported after consumption of Echinaceae.

According to the Dgccrf, 3 species of Echinaceae are of interest to food supplement manufacturers in France: *Echinacea angustifolia*, *E. pallida*, *E. purpurea*. These products are positioned as an immunostimulant in the "prevention of winter illnesses" sector.

The Dgccrf request is for an assessment of risks from consuming food supplements containing one or other of these 3 species of Echinaceae. The Dgccrf also asks whether it is possible to establish conditions under which ingestion of this botanical does not carry risks or whether the scientific information about the risk requires the use of this botanical to be prohibited in food supplements.

These 3 species have various uses in different EU Member States. In Belgium the Echinaceae appear on list 3 of the Royal Decree establishing a positive list of botanicals which may be present in the composition of food supplements, with the following restrictions: *E. angustifolia* daily amount less than 2.4 g of dried root, *E. pallida* daily amount less than 720 mg of dried root, *E. purpurea* daily amount less than 2 g of dried herb. In Italy the 3 species are used without a dose limit: the aerial parts and roots for *E. angustifolia* and *E. purpurea,* and the roots alone for *E. pallida*. In Germany the E commission placed the aerial parts of *E. purpurea* and the roots of *E. pallida* onto a positive list whereas the aerial parts of *E. angustifolia* and *E. pallida*, and the roots of *E. angustifolia* and *E. purpurea* appear on a negative list. Traditional use in Germany above all involves fresh botanical juices. As a result many food supplements are liable to be found in the French market.

In France, *E. purpurea* and *E. angustifolia* appear in the Pharmacopeia list A although none has been included in the Cahiers de Afssaps. The EMEA has initiated an evaluation of the aerial parts of *E. purpureae* (L.) Moench in order to establish an available monograph in a public enquiry. Variable qualifications (well established use and traditional use) with different levels of evidence are proposed depending on the products in question. Several adverse effects associated with the possible immunological activities of *E. purpureae* are highlighted and contra-indications are noted.

The Dgccrf does not state the extent of marketing of supplements containing this species in France. The proposed daily doses are generally 900 mg of *E. pallida* or *E. purpurea* root and 6 to 9 ml of juice from the aerial parts of *E. purpurea*.

BOTANICAL AND PHYTOCHEMISTRY DATA

Echinacea angustifolia, *Echinacea pallida*, and *Echinacea purpurea* are botanicals belonging to the Asteraceae family, originating from North America. The drug from the root requires an essential microscopic examination to identify the species and examine for common falsification from another Asteraceae : *Parthenium intergrifolia* L..
The botanical contains many constituents including sesquiterpene lactones (which may be responsible for allergies), indolizidinine alkaloids, a large number of unsaturated aliphatic compounds and phenolic compounds derived from cafeic acid. This composition varies in particular depending on the species, organ and geographical origin.

ADVERSE EFFECTS

The adverse effects reported notably involve immunological hypersensitivity reactions (anaphylactic shock, urticaria, rash, Stevens-Johnson syndrome). These adverse effects have led the EMEA to recommend warnings for use in children and contra-indications such as hypersensitivity to Asteraceae, auto-immune diseases, immunodeficiencies and haematological diseases.

The EMEA notes that these products must not be used concomitantly with immunosuppressant medicinal products such as ciclosporin or methotrexate.

Serious effects have also been reported in the scientific literature (Mullins *et al.*, 2002 ; Logan *et al.*, 2003; Lee *et al.*, 2004 ; Huntley *et al.*, 2005) such as a case of thrombotic thrombocytopenic purpura after consuming an aqueous-alcoholic drink of *E. pallida* (George *et al.*, 2006) and

therapeutic interactions from inhibition of cytochromes P450 (Budzinski *et al.*, 2000 ; Ernst *et al.*, 2000 ; Tumova *et al.*, 2000 ; Gorski *et al.,* 2004).

CONCLUSION

In conclusion, Afssa considers that :

1) *Echinaceae angustifolia*, *Echinaceae pallida*, *Echinaceae purpurea* (hereafter called "the Echinaceae") are insufficiently understood in terms of their phytochemistry and their beneficial or deleterious effects. The risks from consuming *Echinaceae* cannot therefore be described. On the other hand the deleterious effects which have been seen encourage caution and the risks of therapeutic interactions should be established in more detail.
2) As a result it is impossible to set risk-free conditions of use for *Echinaceae*: constituents which may cause a harmful effect, part of the botanical and extracts which may be ingested without risk, dose equivalent to ingestion of *Echinaceae* constituents at a level estimated to be risk-free, tracer enabling extracts defined as being risk-free to be standardised.
3) According to the scientific information available, it is recommended that ingestion of *Desmodium* as a food supplement be avoided.

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Polygonum multiflorum Thun

CONTEXT

Many cases of liver problems associated with consuming *Polygonum multiflorum* have been reported, particularly by the English Medicines Agency.

The Dgccrf request is for an assessment of risks from consuming food supplements containing *Polygonum multiflorum*. The Dgccrf also asks whether it is possible to establish conditions under which ingestion of this botanical does not carry risks or whether the scientific information about the risk requires the use of this botanical to be prohibited in food supplements.

According to the Dgccrf, *Polygonum multiflorum* is traditionally used in Chinese medicine as a "tonic" and to "combat ageing" (particularly hair loss).

Some species of Polygunum are freely marketed in some Member States of the European Union. In particular, *Polygonum spp.* appears on list 3 of the Belgian Royal Decree establishing a positive list of botanicals which may be present in the composition of food supplements. As a result, food supplements are liable to be found on the French market. The storage and sale of supplements containing *Polygonum multiflorum* has not recently been identified in France according to the Dgccrf.

BOTANICAL AND PHYTOCHEMISTRY DATA

Polygunum multiflorum is a Polygonaceae originating from Asia used in traditional Chinese medicine.

Knowledge about the phytochemistry of *Polygonum multiflorum* is extremely limited. *Polygonum multiflorum* is believed to contain anthraquinones (emodine, aloe-emodol, chrysophanol, physciol). Stilbene heterosides including resveratrol and gallic acid derivatives are also believed to have been identified. No analytical or toxicological data are available.

WARNING POINTERS

In March 2006, 7 cases of hepatic injury associated with consuming the botanical were reported to the English Medicines Agency. Other cases are also reported in the literature (But *et al.*, 1996 ; Park *et al.*, 2001 ; Battinelli *et al.*, 2004 ; Panis *et al.*, 2005 ; Cardenas *et al.*, 2006).

CONCLUSION

Afssa considers that :

1) *Polygonum multiflorum* is insufficiently understood in terms of its phytochemistry and beneficial or deleterious effects and the risks associated with consuming *Polygonum multiflorum* cannot therefore be described;
2) As a result it is impossible to set risk-free conditions of use for *Polygonum multiflorum*: constituents which may cause a harmful effect, part of the botanical and extracts which may be ingested without risk, dose equivalent to ingestion of *Polygonum multiflorum* constituents at a level estimated to be risk-free, tracer enabling extracts defined as being risk-free to be standardised.
3) According to the available scientific information, it is recommended that consumption of *Polygonum multiflorum* be avoided as a food supplement.

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