Ref. Ares(2010)892815 – 02/12/2010

Annex 2 to 5-3539-02-5591315

Scientific assessment of Ephedra species *(Ephedra spp.)*

Purpose of assessment

The Federal Office of Consumer Protection and Food Safety (BVL), in collaboration with the ALS working party on dietary foods, nutrition and classification issues, has compiled a hit list of 10 substances, the consumption of which may pose a health risk. These plants, which include Ephedra species *(Ephedra* L.*)* and preparations made from them, contain substances with a strong pharmacological and/or psychoactive effect. The Federal Ministry of Food, Agriculture and Consumer Protection has already asked the EU Commission to start the procedure under Article 8 of Regulation (EC) No 1925/2006 for these plants and preparations, for the purpose of including them in one of the three lists in Annex III. The assessment applies to ephedra alkaloid-containing ephedra haulm. The risk assessment of the plants was carried out on the basis of the Guidance on Safety Assessment of botanicals and botanical preparations intended for use as ingredients in food supplements published by the EFSA[1] and the BfR guidelines on health assessments[2].

Result

We know that ingestion of ephedra alkaloid-containing Ephedra haulm represents a risk from medicinal use in the USA and from the fact that it has now been banned as a food supplement in the USA. Serious unwanted and sometimes life-threatening side effects are associated with the ingestion of food supplements containing ephedra alkaloids. Due to the risks described, we would recommend that ephedra alkaloid-containing Ephedra haulm be classified in List A of Annex III to Regulation (EC) No 1925/2006.

Opinion

1. **Identity of plant** (HagerDIGITAL, 2008; USDA-ARS GRIN Taxonomy, 2010)
   - Family: *Ephedraceae* (Ephedra)
   - Genus: *Ephedra* L.
   - Species: Data on the number of species vary from 20 to 44, broken down into 5 sections; the species from which the drug is obtained come under the Ephedra and Monospermae PACHOM sections.

     Species (examples):
     - *Ephedra sinica* STAPF
     - *Ephedra intermedia* Schrenk & C.A. Mey
     - *Ephedra shennungiana* T.H. Tang (synonym: *Ephedra equisetina* Bunge)
     - *Ephedra distachya* L. (synonym: *Ephedra vulgaris* Rich.)
     - *Ephedra major* HOST
     - *Ephedra regeliana* FLORIN
     - *Ephedra viridis* Coville

[1] European Food Safety Authority (2009) Guidance on Safety assessment of botanicals and botanical preparations intended for use as ingredients in food supplements. http://www.efsa.europa.eu/en/scdocs/doc/1249.pdf.

[2] http://www.bfr.bund.de/cm/221/bfr_leitfaden_fuer_gesundheitliche_bewertungen.pdf.

- *Ephedra californica* S. Watson
- *Ephedra monosperma* J.G. Gmel. ex C.A. Mey
- *Ephedra lomatolepis* Schrenk

- Synonyms: Ephedra
- Common names: English: Mormon Tea, Ephedra sinica, Epitonin, Herbal Ecstasy, Ma Huang, Muzei, Popptillo; Chinese: ma huang shu.
- Parts used: ephedra alkaloid-containing Ephedra haulm
- Geographical origin: moderate and sub-tropical regions of Asia, Europe, North and Central America, South America (along the Andes from Ecuador to Argentina and Patagonia), North Africa (HagerDIGITAL, 2008; Abourashed et al, 2003)
- Cultivation/harvest: some collected from wild stock, mostly cultivated; air-dried, where possible in the sun (HagerDIGITAL, 2008).

2. Manufacturing process

There are no known manufacturing processes for use in foods.

3. Chemical composition

Toxicologically relevant ingredients of the Ephedra haulm are ephedra alkaloids (see Table 1). The relative composition of the alkaloids varies considerably between the Ephedra species and within individual species (see Table 2) (Kitani et al, 2009; Lake et al, 2001).

The total alkaloid content, depending on the species, origin and time of harvest, may be between 0.5 and 49 mg/g (see Table 2) (Kitani et al, 2009; Lake et al, 2001; WHO, 1999). The two main alkaloids (ephedrine and pseudoephedrine) account for 70-99% of the total alkaloid content in Ephedra haulm (Cui et al, 1991; Kitani et al, 2009; Long et al, 2005; Trujillo and Sorenson, 2003; White et al, 1997). The ephedrine content may be between 0 and 90% and the pseudoephedrine content may be between 0.1 and 99% of the total alkaloid content (HagerDIGITAL, 2008; Kitani et al, 2009; Long et al, 2005; WHO, 1999).

Table 1: Ephedra alkaloids with synonyms and CAS numbers (HagerDIGITAL, 2008; United States National Library of Medicine, 2008; WHO, 1999)

Name	Synonyms	CAS number
Ephedrine	(1R,2S)-2-methylamino-1-phenyl-1-propanol, (L)-Ephedrine, Ephedrine, Fedrin, I-Sedrin, Manadrin, (-)-Ephedrine	299-42-3
Pseudoephedrine	(+)-(1S,2S)-Pseudoephedrine, D-Pseudoephedrine, Besan, Psi-Ephedrine, Sudafed, Isoephedrine	90-82-4
(-)-Norephedrine	Phenylpropanolamine, Mydriatin	492-41-1
(+)-Norspeudoephedrine	Cathine	492-39-7
(-)-Methylephedrine	N-Methylephedrine, 1-phenyl-2-dimethylaminopropanol	17605-71-9
Methylpseudoephedrine		51018-28-1

Table 2: Ephedra alkaloid content in mg/g and proportion of the two main alkaloids (%) in the total alkaloid content in the Ephedra haulm of various species and ephedra alkaloid-containing products

Species	Ephedra alkaloid content	Ephedrine	Pseudo-ephedrine	Norephedrine	Norpseudo-ephedrine	Methyl-ephedrine	Methylpseudo-ephedrine	Reference
Ephedra sinica	9.7	6.4 (66)	1.4 (15)	0.9	0.8	0.3	0.01	(Trujillo and Sorenson, 2003)
	16.3	12.4 (76)	3.1 (19)	n.a.[3]	n.a.[3]	0.8 (5)	n.a.[3]	(White et al, 1997)
	18.6-41.6	3.8-21.4 (11-78)	2.2-22.4 (8-67)	<0.7-3.4	0.7-7.3	<0.7-3.2	n.a[3]	(Kitani et al, 2009)
	12.6-13.8	7.6-8.1 (58-60)	2.8 (20-22)	1.0	1.1-1.4	0.5-0.7	Traces	(Cui et al, 1991)
Ephedra equisetina	39.8-49.0	1.4-1.5 (3-4)	36.6-44.5 (91-92)	<0.7-1.2	0.7-1.2	0.7-1.0	n.a[3]	(Kitani et al, 2009)
	22.1	12.5 (57)	5.8 (26)	2.0	1.6	0.3	n.d.[4]	(Cui et al, 1991)
Ephedra intermedia	4.6-18.1	0-3.3 (0-30)	1.5-15.6 (3-99)	0.1-0.9	n.a.[3]	n.d.[4]	n.a.[3]	(Long et al, 2005)
	11.2-16.7	1.3-5.5 (12-33)	8.0-9.1 (54-72)	0.3-0.8	1.1-1.3	0.1-0.3	n.d.[4]-0.1	(Cui et al, 1991)
Ephedra regeliana	19.5-31.9	<0.7-5.9 (0-21)	14.4-27.8 (71-89)	<0.7-1.3	<0.7-3.5	<0.7-1.0	n.a.[3]	(Kitani et al, 2009)
	n.d.[4]	n.d.[4]	n.d.[4]	n.d.[4]	n.a.[3]	n.d.[4]	n.a.[3]	(Long et al, 2005)
Ephedra przewalskii	n.d.[4]	n.d.[4]	n.d.[4]	n.d.[4]	n.d.[4]	n.d.[4]	n.a.[3]	(Kitani et al, 2009)
	n.d.[4]	n.d.[4]	n.d.[4]	n.d.[4]	n.a.[3]	n.d.[4]	n.a.[3]	(Long et al, 2005)
	0.5	0.3	0.06	0.03	0.05	0.03	n.d.[4]	(Cui et al, 1991)
Ephedra alkaloid-containing products[5]	0.3-71.0	0.2-66.7	0.05-9.8	0.001-0.4	0.003-0.8	0.001-0.9	0.001-0.2	(Trujillo and Sorenson, 2003)

[3] Not analysed.
[4] Not detected or <0.7 mg/g.
[5] Powdered ephedra extract, capsules with ephedra extract, food supplements with ephedra alkaloids, protein shakes with ephedra alkaloids.

Not all Ephedra species contain ephedra alkaloids (WHO, 1999). The following species contain ephedra alkaloids, the concentrations of which, where known, are given in brackets (Kitani et al, 2009; Lake et al, 2001, Zhang et al, 1989).

- *Ephedra sinica* (10-42 mg/g)
- *Ephedra equisetina* (22-49 mg/g)
- *Ephedra intermedia* (5-18 mg/g)
- *Ephedra distachya*
- *Ephedra regeliana* (20-32 mg/g)
- *Ephedra major*
- *Ephedra monosperma* (28 mg/g)
- *Ephedra lomatolepis* (13.6 mg/g)

Data on Ephedra species which contain no ephedra alkaloids are contradictory. This might be due partly to difficulties in determining the species and partly to the fact that the findings depend on the sensitivity of the analysis used. According to Long et al (2005), *Ephedra regeliana* contains no ephedra alkaloids, whereas Kitani et al (2009) demonstrated the existence of 20-32 mg/g of ephedra alkaloids in this species. Cui et al (1991) found 0.4-0.5 mg/g of total alkaloids in *Ephedra przewalskii* STAPF and *Ephedra lepidosperma* C.Y. Cheng. Other authors assume that these species do not contain or only contain traces of ephedra alkaloids (Kitani et al, 2009; Long et al, 2005; White et al, 1997; Zhang et al, 1989). Compared with *Ephedra sinica*, which contains up to 42 mg/g, these species have very low concentrations of ephedra alkaloids. *Ephedra nevadensis* S. Watson probably contains no ephedra alkaloids (EFSA, 2009; Trujillo and Sorenson, 2003). *Ephedra californica* and *Ephedra viridis* contain pseudoephedrine, but no ephedrine (Adams Jr. and Garcia, 2006).

Ephedra products contain Ephedra haulm or extracts of Ephedra haulm and their ephedra alkaloid content differs widely. They contain 0-26 mg of total alkaloids per dose. The actual quantity may also differ considerably from that stated. Similarly, batches of a product often differ considerably in terms of alkaloid concentrations (Baker et al, 2003; Gurley et al, 2000).

4. Specifications

There are no known specifications.

5. Stability of plant and plant preparations used

There is no information available on the stability of the ingredients.

6. Proposed uses and use levels as food

There is no information available in Germany on use as a food.

7. Other uses

Preparations of Ephedra haulm are used for blocked nose caused by hay fever, allergy-induced rhinitis, acute chills and general colds and sinusitis. The drug is also used as a bronchodilator to treat bronchial asthma. These indications are supported by clinical trials. Other indications described in medical journals are treatment of urticaria, nocturnal enuresis, narcolepsy, myasthenia gravis and chronic postural hypotonia. It is also known to be used in popular medicine, but this is not supported by experimental or clinical data. The effects include pain-relieving, antiviral, antibacterial and expectorant properties and use as an antitussive and immune stimulant (WHO, 1999). Ephedra (Ma Huang) has been used in traditional Chinese medicine for over 2500 years (Mehendale et al, 2004).

The haulm of certain Ephedra species (*Ephedra nevadensis, Ephedra viridis*) has traditionally been used by North American Indians to prepare daily infusions and medicinal teas (USDA-NRCS, 2006a; USDA-NRCS, 2006b).

Food supplements containing ephedra alkaloids are used mostly for weight loss and to enhance athletic performance or in bodybuilding (FDA, 2004; Haller and Benowitz, 2000; Samenuk et al, 2002).

Norpseudoephedrine (cathine) is contained as a hydrochloride in appetite suppressants.

8. Assessments and classification by other committees

National assessments and classifications

Ephedra species and preparations from Ephedra species[6] and ephedrine[7] are prescription drugs (Annex I, AMVV).

Commission E of the Federal Health Bureau has assessed Ephedra haulm, consisting of the dried young switches of *Ephedra sinica, Ephedra shennungiana* or similar Ephedra species harvested in autumn and preparations in effective doses. Ephedra haulm is used for respiratory diseases with slight bronchial spasms in adults and school children. The single dose for adults is 15-30 mg and the maximum daily dose is 300 mg of total alkaloids calculated as ephedrine. The single dose for children is 0.5 mg and the maximum daily dose is 2 mg of total alkaloids, calculated as ephedrine per kg body weight. Ephedra haulm is contra-indicated for persons in a state of anxiety or agitation and for persons with high blood pressure, narrow angle glaucoma, cerebral circulatory disorders, prostate adenoma with residual urine, pheochromocytoma or thyrotoxicosis. Side effects of insomnia, motor disturbances, irritability, headaches, nausea, vomiting, micturition disorders and tachycardia have been reported. Higher doses may lead to a drastic increase in blood pressure, cardiac arrhythmia and addiction. Because of the risk of tachyphylaxis and addition, Ephedra haulm preparations should only be used on a short-term basis. Interactions may occur in combination with cardiac glycosides or halothane (cardiac arrhythmia), with guanethidine (increased sympathomimetic effect), MAO inhibitors (accentuation of sympathomimetic effect of ephedrine) and secale alkaloid derivatives or oxytocin (high blood pressure). Ephedrine has an indirect sympathomimetic effect and indirectly stimulates the central nervous system (Commission E of the Federal Health Bureau, 1991).

Norpseudoephedrine (cathine) is classified as a marketable prescription narcotic in Germany, with the exception of preparations containing up to a 5% solution but no more than 1600 mg per packaging unit or up to 40 mg of norpseudoephedrine per separate form, calculated as the base, with no other substance in Annexes I or II (BtmG, Annex III).

International assessments and classifications

Ephedra alkaloid-containing parts of the plant are classified in Category 1 under the Base Materials Act and Regulation (EC) No 273/2004 and Regulation (EC) No 111/2005, as this raw material can be used for the illegal production of amphetamines and methamphetamines.

[6] For oral use (with the exception of certain homeopathic preparations).

[7] For oral use

- in preparations to which this substance alone or this substance together with caffeine are added as active ingredient;
- in other preparations, insofar as a single dose of over 10 mg or, in the case of slow-release preparations, a daily dose of over 40 mg, calculated as ephedrine base, is stated on the container and outer packaging or the preparation contains caffeine.

Ephedrine, pseudoephedrine and norephedrine are Category I substances under the aforementioned regulations. As mixtures and natural products containing such substances are included in these substances, ephedra alkaloid-containing plant parts are also regulated by these laws. The only exceptions are mixtures, natural products and other preparations which contain listed substances and are so complex that they cannot be used simply or easily and affordably extracted (BfArM, 2007).

The FDA assessed food supplements containing ephedra alkaloids in 2004. According to the FDA assessment, these products represent an unacceptable health risk, bearing in mind the conditions of use. More importantly, an even relatively minor risk of serious harm to health due to misuse is unacceptable (FDA, 2004). Food supplements containing ephedra alkaloids cannot be considered safe at any dose (FDA, 2006).

The National Centre for Complementary and Alternative Medicine (NCCAM) issued a recommendation for users in 2004 warning of the health risks of Ephedra (NCCAM, 2004). The NCCAM also points out that, although the FDA has banned food supplements containing Ephedra, the ban does not extend to its use in traditional Chinese medicine or to products such as herb teas (NCCAM, 2008).

Norpseudoephedrine (cathine) is listed in Annex III of the UN Convention on Psychotropic Substances (1971). This substance does not therefore qualify as a food (Regulation (EC) No 178/2002, Article 2g).

9. Exposure data and assessment

Alkaloid-containing Ephedra haulm is used mainly in food supplements for weight loss. According to a randomised telephone survey carried out in five states in the USA by government health officials prior to the FDA ban, 1% of interviewees (persons over 18 years of age) use Ephedra products. If these data are extrapolated for the entire US population, then around 2.5 million people used Ephedra products between 1996 and 1998. Women, young people (18-34 years old) and persons who are overweight take Ephedra products considerably more often (Blanck et al, 2001). Approximately 0.8% of schoolchildren (classes 7-12) questioned in the USA between 1996 and 2001 admitted that they had used Ephedra products. Use is strongly associated with the use of other stimulants (Henry et al, 2007).
According to another assessment, up to twelve million people are assumed to have taken ephedra alkaloid-containing food supplements in 1999 (Haller and Benowitz, 2000). This assessment is based on an American Herbal Products Association (AHPA) survey. Of the 42 firms contacted which sell food supplements containing ephedra alkaloids, 13 firms responded. Together they sold over three billion portions of these products in 1999, containing between less than 10 mg to over 26 mg of ephedra alkaloids per portion, to be taken 3 times a day for a maximum of twelve weeks. The manufacturer's recommended daily dose of 25-100 mg was not to be exceeded (AHPA, 2000; NTP, 2001).

Food supplements containing ephedra alkaloids and Ma Huang contain around 12 mg of ephedra alkaloids per dose, although the content varies widely from product to product (0-26 mg per dose). The stated quantities often do not tally with the values measured, containing 17-154% of the stated quantity, with a discrepancy for most products of less than 25% (Baker et al, 2003; Gurley et al, 2000). An analysis of products containing Ephedra haulm illustrated that daily doses of over 300 mg of ephedra alkaloids a day were possible in some cases (Lake et al, 2001). In addition to the total alkaloid quantity, large differences were also found in the composition of the alkaloids, even within one product (Baker et al, 2003; Lake et al, 2001). The recommended daily dose is between 12 and 75 mg in relation to the ephedra alkaloids. The

recommended maximum dose ranges from 24 mg/d for seven days to up to 100 mg/d for twelve weeks (Baker et al, 2003).

Medicinal products (for cold symptoms and as appetite suppressants) are another source of ephedra alkaloids.

10. Risk identification and classification

Kinetics

Generally speaking, the pharmacokinetics of pseudoephedrine and norephedrine are similar to those of ephedrine. However, the minor structural differences between the ephedra alkaloids affect the pharmacokinetics (CANTOX, 2000). Table 3 illustrates the results in terms of the pharmacokinetics of ephedrine from various studies with various products (Ma Huang alone or in combination[8] with other substances or ephedrine as a single substance). The pharmacokinetics of ephedrine do not differ substantially between products containing Ma Huang and ephedrine as a single substance; however, it takes around twice as long to reach the maximum concentration in the blood after taking products containing Ma Huang (Gurley et al, 1998; White et al, 1997). Sporting activities have no effect on the pharmacokinetics of ephedrine (Strömberg et al, 1992).

Ephedrine is quickly and completely absorbed by the gastrointestinal tract following oral administration (2-2.5 h). The oral administration of Ephedra haulm may delay the absorption of ephedrine (CANTOX, 2000). There are circumstances (e.g. sauna) which may affect absorption (Vanakoski et al, 1993).

Ephedrine is quickly distributed in the body. Individual plasma levels differ widely after oral administration. Ephedrine does not bind to plasma proteins. It is lipophilic and passes the blood-brain barrier. It also crosses the placenta; foetal blood concentrations are approximately 70% of the mother's blood levels (CANTOX, 2000).

Ephedrine can be partly (8-20%) metabolized to norephedrine by N-demethylation. Oxidative deamination of ephedrine gives 1-phenylpropane-1,2-diol; further oxidation gives benzoic acid and hippuric acid (4-13% of the oral dose) (CANTOX, 2000; Wilkinson and Beckett, 1968).

Methylephedrine is metabolized to give ephedrine and norephedrine (Wilkinson and Beckett, 1968).

Ephedrine is eliminated in the urine mainly unaltered (55-75%), with a half-life of 3-6 hours (95% of the oral dose within 24 hours). Elimination depends on the pH value of the urine. Alkaline urine reduces elimination to 20-35% of the dose. However, the β-hydroxy group reduces the effect of the pH value compared with amphetamines and increases metabolic stability. Norephedrine is mainly eliminated unchanged (CANTOX, 2000; Haller et al, 2002; Wilkinson and Beckett, 1968). Children eliminate ephedrine faster (CANTOX, 2000). Ephedrine passes into breast milk (CANTOX, 2000).

Pharmacological and toxicological properties

It is difficult to predict the active spectrum, active strength and active duration of products made from ephedrine alkaloid-containing Ephedra haulm, due to the variable alkaloid content and variable alkaloid composition. The individual ingredients work in the same or opposite directions, for differing lengths of time and sometimes compete for the same receptor (HagerDIGITAL, 2008).

Ephedrine is an oral sympathomimetic which stimulates both alpha and beta adrenoreceptors (HagerDIGITAL, 2008). This means that it works on various organ systems in the human body, including the heart and blood vessels (increasing the pulse and blood pressure), the airways

[8] Ma Huang, Ma Huang extract, Ephedra extract.

(bronchial dilation), the nervous system (stimulation) and the liver (glycogenolysis and gluconeogenesis). Ephedrine works longer than epinephrine and has a less marked effect on the cardiovascular system and a more marked effect on the central nervous system (Meyler's Side Effects of Drugs, 2000). Some peripheral effects of ephedrine are transmitted through the release of norepinephrine and some directly via the receptors. The depletion of norepinephrine stores results in tolerance (tachyphylaxis) of ephedrine (WHO, 1999). The toxicity of ephedrine is based on overstimulation of the adrenergic system (CANTOX, 2000). Symptoms of ephedrine intoxication are agitation, anxiety, urge to urinate, arousal of the central nervous system, mental alteration, hand tremors, central and myogenic tachycardia, increase in blood pressure, extrasystole, heart palpitations, insomnia, headache, dizziness, nausea, vomiting, sweating, thirst, difficulty urinating, amyasthenia, fever, delusional hallucination, optical and acoustic hallucination, cramps, hyperthermia, cardiac arrest and circulatory collapse and respiratory paralysis (Rote List, 2003; CANTOX, 2000). Very high doses (>1700 mg/d for years) may induce psychoses (Herridge and a'Brook, 1968). Long-term use may lead to addiction (WHO, 1999).

Table 3: Ephedrine kinetics following administration of products containing Ephedra (- = Ma Huang on its own, + = Ephedra product in combination with other ingredients, E = ephedrine, n = number of subjects investigated)

Ephedrine mg		Ephedrine source	n	C_{max} ng/ml	$t=_{max}$ h	AUC ng*h/ml	$t_{1/2}$ h	CL/F L/h	Reference
19.4	-	Ma Huang	12	81	3.9	798	5.2	24.3	(White et al, 1997)
17.3	+	Ma Huang extract	8	64	2.4	759	6.1		(Haller et al, 2002)
20.2[9]	+	Ma Huang	16	131	8	1 795	5.9	24.3	(Haller et al, 2005)
20[9]	+	Ephedra extract	16	140	8	1 922	6.3	23	(Haller et al, 2005)
27	+	Ma Huang	10	100	2.7	1 134	6.5	25.5	(Gurley et al, 1998)
25.6	+	Ma Huang	10	86	2.6	828	4.9	34	(Gurley et al, 1998)
23.6	+	Ma Huang	10	73	3.1	746	4.9	34	(Gurley et al, 1998)
20	E		12	74	1.7	638	5.7	28.7	(Pickup et al, 1976)
22	E		12	79	1.8	814	6.8	23.3	(Pickup et al, 1976)
25	E		10	87	2.8	909	5.4	28.5	(Gurley et al, 1998)
50	E		6	168	2.1	112	9.4	27.6	(Strömberg et al, 1992)
50	E		16	138	2	778	7.1		(Berlin et al, 2001)

[9] 2 consecutive doses.

The activity of pseudoephedrine is comparable to that of ephedrine, but the hypersensitive and central nervous stimulating effects are weaker (Meyler's Side Effects of Drugs, 2000; WHO, 1999). The other ephedra alkaloids also work on the heart and circulatory system and airways, but differ in the strength of their effects (CANTOX, 2000).

There is no clear correlation between the level of ephedrine in the blood and specific pharmacological effects. This is probably due to tachyphylaxis (pharmacodynamic factors) rather than pharmacokinetic factors (CANTOX, 2000).

Cardiovascular effects

Like epinephrine, ephedrine stimulates the sympathetic nervous system. This causes vasoconstriction and stimulates the heart. The pulse rate, cardiac output and resistance of peripheral vessels rise, resulting in a persistent increase in blood pressure. The cardiovascular effects of ephedrine persist up to 10 times longer than those of epinephrine. Ephedrine also increases both systolic and diastolic blood pressure and the pulse rate. Renal and visceral blood flow are reduced, while the blood flow in the heart, brain and muscles is increased (WHO, 1999). Systolic blood pressure is increased significantly more if a sauna is taken following the administration of ephedrine (Vanakoski et al, 1993), while sporting activities following the administration of ephedrine do not have an additive effect on the blood pressure (Strömberg et al, 1992). The heart rate, which is already significantly increased by taking ephedrine, rises still further as a result of sporting activities (Strömberg et al, 1992).

Cardiovascular effects of ephedrine are described as variable (CANTOX, 2000). This finding is possibly due to methodological differences. Ephedrine increases the blood pressure about 1-2 hours after administration and the pulse rate rises to a maximum after 5-6 hours (Berlin et al, 2001). Similar results are obtained with multiple preparations containing Ma Huang (Haller et al, 2002; Haller et al, 2005). These effects were not measured in studies in which blood pressure was measured over 12 hours or independently of administration (Boozer et al, 2002; Boozer et al, 2001; Coffrey et al, 2004; Hackman et al, 2006; Hioki et al, 2004; White et al, 1997).

Effects on airways

By activating β-adrenoceptors in the lungs, ephedrine expands the bronchia by relaxing the bronchial muscles. This effect is less marked than with epinephrine, but lasts longer (WHO, 1999). Pseudoephedrine is much less effective than ephedrine (Drew et al, 1978).

Effects on central nervous system

Ephedrine stimulates the central nervous system. This effect may last for several hours after oral administration (WHO, 1999). There is slight but significant stimulation of the central nervous system following oral administration of 50 mg of ephedrine (Berlin et al, 2001; CANTOX, 2000). Even Ephedra (60 mg in combination with 300 mg of caffeine) increases alertness and improves the mood (Williams et al, 2008).

Metabolic effects

Products containing Ma Huang or an Ephedra extract significantly increase post-prandial concentrations of glucose (by blocking the absorption of glucose in fat and skeletal muscle cells and boosting endogenous glucose formation) and insulin levels. The concentration of free fatty acids in the plasma increases after the first dose, compared with the placebo. This effect does not apply after the second dose. The plasma potassium level also drops significantly, sometimes bringing concentrations below reference values. It was possible to increase this effect still further by fasting or dieting, thereby enhancing the risk of lethal cardiac arrhythmia, especially in combination with substances with a sympathomimetic effect (Haller et al, 2005).

Other effects

The resistance to urination is increased through activation of the alpha-adrenoceptors of the smooth muscles of the bladder. Ephedra haulm has therefore been used to treat incontinence and nocturnal enuresis (WHO, 1999).

A meta-analysis of the effects of Ephedra (haulm) and ephedrine (20-150 mg) on weight loss and improved athletic performance produced several indications that products containing Ephedra (haulm) or ephedrine promote moderate weight loss in the short term (Shekelle et al, 2003a; Shekelle et al, 2003b). Later studies (12 weeks to 9 months) published on multiple preparations[10] confirm this finding (Coffey et al, 2004; Greenway et al, 2004; Hackman et al, 2006; Hioki et al, 2004). There is insufficient evidence that Ephedra improves athletic performance (Shekelle et al, 2003a; Shekelle et al, 2003b; Williams et al, 2008).

There is no evidence of mutagenic or teratogenic effects (NTP, 2001; WHO, 1999).

Contra-indications/risk groups

Ephedra haulm or ephedrine should not be used for patients with coronary thrombosis, diabetes, glaucoma, heart disease, hypertension, thyroid disease, restricted blood circulation in the brain, autonomic insufficiency, pheochromocytoma, chronic anxiety/mental diseases or an enlarged prostate (Meyler's Side Effects of Drugs, 2000; CANTOX, 2000, WHO, 1999). Persons with reduced kidney elimination are at a higher risk of intoxication. Newborn and breastfed babies (may be exposed via the mother) and the elderly are also risk groups. Persons who are highly responsive to sympathomimetic stimulants should not take products containing ephedra alkaloids (CANTOX, 2000). Even small doses of ephedrine may lead to tremors, sleep disorders and anxiety in sensitive subjects (Meyler's Side Effects of Drugs, 2000). Paradoxically, ephedrine may have a sedative effect in children (Meyler's Side Effects of Drugs, 2000).

Interactions

Simultaneous administration of Ephedra haulm and MAO inhibitors may lead to serious, possibly fatal hypertension. The risk of ventricular arrhythmia (heart rhythm disturbance) and acute pulmonary oedema is enhanced in combination with cardiac glycosides, halothanes and other anaesthetics. Guanethidine (antihypertensive and local anaesthetic) may increase the sympathomimetic effects of Ephedra haulm. Ergot derivatives or oxytocin may also increase the risk of hypertension. Tricyclic antidepressants and beta-blockers increase the cardiovascular effects and the regulation of diabetes with anti-diabetics may be complicated due to its hyperglycaemic effects. Antacids and substances that alter the pH value of the urine may influence the absorption and elimination of ephedra alkaloids. Corticosteroids and theophylline interact with ephedrine (Meyler's Side Effects of Drugs, 2000; CANTOX, 2000; WHO, 1999).

The effects of ephedrine are exacerbated if taken with caffeine (Meyler's Side Effects of Drugs, 2000).

Case reports

Of the 1,173 cases associated with the consumption of food supplements containing ephedra alkaloids and reported in the FDA Special Nutritional Adverse Event Monitoring System (SN/AEMS), 98% lacked important data. Therefore 121 cases which appeared to be adequately documented were selected for more detailed examination (CANTOX, 2000). Approximately 84% of the persons affected consumed less than 150 mg of ephedra alkaloids. The undesirable effects described are in keeping with the advertised effects and the known pharmacological

[10] Containing Ma Huang or Ma Huang concentrate or Ephedra haulm or Ephedra extract.

profile of ephedra alkaloids. 36% of undesirable effects affected the nervous system and 30% the heart and circulatory system. 70% of the 121 persons considered were taking other preparations at the same time (antidepressants, caffeine, nicotine, other food supplements). Serious undesirable effects occurred in 47 cases, of which 15 were seizures or cases with symptoms of seizure, 13 were cases of cramps, 15 were cases of cardiac arrest and two persons collapsed. Serious side effects only occurred with multiple preparations. A total of eight persons died (one road traffic accident, six from cardiovascular causes, one miscarriage). Serious undesirable effects also occurred in persons (n=8) who had no previous medical history or were not taking other products at the same time (CANTOX, 2000).

According to an evaluation of 140 case reports on the undesirable effects of supplements containing ephedra alkaloids sent to the FDA, 43 cases were certainly or probably associated with the consumption of these products. These cases related mainly to the heart and circulatory system and the central nervous system. This resulted in three deaths and seven cases of permanent health damage (Haller and Benowitz, 2000).

Of 926 cases (1995-1997) taken from the FDA Adverse Reaction Monitoring System which might have been associated with the toxic effects of Ma Huang, 37 cases were identified in which serious cardiovascular complications occurred (16 seizures, ten heart attacks, eleven sudden deaths). There is a time (but no causal) link. In 36 out of 37 cases, the products were taken in accordance with the manufacturer's instructions (Samenuk et al, 2002).

Of 1,820 case reports in the FDA's MedWatch files and 15,951 case reports from the manufacturer of food supplements containing Ephedra, a total of 284 cases with serious undesirable effects were identified which provided sufficient evidence for detailed examination. In these, the consumption of Ephedra was linked to two deaths, three heart attacks, nine cases of seizures, three cases of cramps and five psychiatric cases. Consumption of ephedrine was linked to two deaths, two heart attacks, two cases of seizures, one case of cramps and three psychiatric cases. (Shekelle et al, 2003a; Shekelle et al, 2003b).

Twelve out of fourteen firms surveyed which sell food supplements containing ephedra alkaloids included warnings on their packaging, a warning against consumption by children, pregnant women, breastfeeding women, persons with diseases (see contraindications), interactions and recommended doses. They also advised that use should be discontinued and medical advice sought in the event of palpitation, dizziness, serious headache, shortness of breath or similar symptoms (AHPA, 2000).
Nonetheless, approximately two out of one million people who took such products experienced serious undesirable effects (heart attack, seizure, cramps, death or injury requiring medical treatment) linked to their consumption (AHPA, 2000). Less serious undesirable effects were not included in this survey.

Undesirable effects of plant products were entered in the US Toxic Exposure Surveillance System between 1993 and 2002. If cases linked to moderate and serious effects are included, 15% (n=649) are accounted for by single Ephedra preparations, 66% (n=2,855) are accounted for by Ephedra in combination with other ingredients and 3% (n=117) are accounted for by combined products without Ephedra (Woolf et al, 2005).

One study investigated serious side effects (death, heart attack, seizure) in persons prescribed a combined ephedrine/caffeine preparation between 1985 and 2002 (n=257,364). The prescribed preparation contained 20 mg of synthetic ephedrine and 200 mg of caffeine with a recommended dose of 1-3 tablets a day. No enhanced risk of serious cardiovascular side effects

was found. This study only investigated the serious side effects (death, heart attack, seizure) of a product with a defined ephedrine concentration taken under medical supervision. Food supplements contain variable concentrations of ephedra alkaloids, often in combination with other active ingredients. The authors were unable to exclude delayed onset of serious side effects (e.g. caused by the hypertensive effects) (Hallas et al, 2008).

Case reports published on undesirable effects of products containing ephedra alkaloids can be divided into spontaneous undesirable effects not associated with an increased dose and cases in which substantially higher than the recommended quantities were taken over a long period (CANTOX, 2000). Psychoses may be caused by long-term consumption of products containing ephedrine in high doses. High ephedrine doses are linked to cerebrovascular and cardiovascular effects and chronic consumption of ephedrine is linked to kidney stones. Cases of deaths linked to the consumption of ephedra alkaloids have been reported (CANTOX, 2000).

Side effects in clinical studies

A meta-analysis of studies into the safety of Ephedra (haulm) and ephedrine (20-150 mg) taken in order to lose weight and boost athletic performance illustrated a significantly higher risk (x 2.2-3.6) of undesirable effects for psychic symptoms (anxiety, dizziness, euphoria), for autonomic hyperactivity (tremors, sleep disorders, increased sweating), for symptoms in the upper gastrointestinal tract (nausea, vomiting, heartburn) and for palpitations. Approximately 20-30% of participants in the study were affected. The probability of serious undesirable effects which occur with a frequency of less than 1:1000 cannot be estimated from the meta-analysis (Shekelle et al, 2003a; Shekelle et al, 2003b).

In vitro and animal studies provide no evidence of the genotoxic/mutagenic potential of extracts containing ephedra alkaloids (NTP, 2001; WHO, 1999).

11. Risk classification

Ephedra alkaloids have a known and well-described risk potential, due to their pharmacological effect. There is no evidence that matrix effects of the plant material reduce this effect. The different quantities of alkaloids and their varying composition increase the risk of intoxication. The inconsistent composition also applies to numerous food supplements containing ephedra alkaloids. Generally, the Ephedra species used is not given (Ma Huang or Ephedra are listed). Ma Huang is made from the above-ground parts of *Ephedra sinica, Ephedra equisetina and Ephedra intermedia*, although *Ephedra minuta, Ephedra distachya* and *Ephedra gerardinana* are also used as Ma Huang (Abourashed et al, 2003). The relative composition of ephedra alkaloids in these species varies considerably (Table 2). The alkaloid concentrations stated on and measured in the food supplements investigated sometimes come within the range of the quantities used pharmacologically (Baker et al, 2003; Gurley et al, 2000; Commission E of the Federal Health Bureau, 1991). Where recommended doses are given based on the ephedrine content, it is easy to overdose, as this may vary considerably in relation to the total alkaloid content (Mehendale et al, 2004). Sometimes the terms ephedrine and ephedra alkaloid are used interchangeably (Boozer et al, 2002, Shekelle et al, 2003b).

Interactions with caffeine, which is often used in food supplements containing ephedra alkaloids, are known. It is impossible to estimate the effect of caffeine on the risk of undesirable effects caused by ephedra alkaloids, as too few studies have considered ephedra alkaloid-containing Ephedra haulm or ephedrine on their own (Shekelle et al, 2003a; Shekelle et al, 2003b). The work of Woolf et al (2005) indicated the enhanced risk potential of multiple preparations, compared with single preparations, but the data merely reflect the fact that such products are available on the market.

Diet and sporting activities, which are associated with indications for use of products containing ephedra alkaloids, increase certain effects of ephedra alkaloids and thus enhance the risk (Haller et al, 2005; Strömberg et al, 1992). It should be noted that the indication of weight loss on food supplements containing ephedra alkaloids satisfies the definition of a drug in terms of purpose and effect. Tachyphylaxis (development of tolerance to active ingredients) may be expected to result in higher than the recommended dosage. There are known cases in which higher than the recommended dose has been taken due to certain effects (improved mood, increased alertness) (Herridge and a'Brook, 1968). Intake of ephedra alkaloids may be increased by taking various products in combination (food supplements, drugs). Even though many food supplements containing ephedra alkaloids include warnings limiting use to a specific period of time (maximum of twelve weeks) (Baker et al, 2003), these products may be expected to be taken for longer than that, given the indications.

Some people are more sensitive to ephedra alkaloids (Meyler's Side Effects of Drugs, 2000). Case reports illustrate that young people have suffered serious ephedra alkaloid-associated effects at the recommended dose, even with no previous illness. Even the warnings used by some firms have been unable to prevent serious undesirable effects (AHPA, 2000) which, although they have occurred rarely, are life-threatening and therefore unacceptable for a foodstuff.

CANTOX (2000) and some authors have concluded from clinical trials that it is safe to take products containing ephedra alkaloids, because no serious undesirable side effects occurred during the trials (Boozer et al, 2002; CANTOX, 2000; Coffrey et al, 2004; Greenway et al, 2004; Hackman et al, 2006). It should be noted that numerous studies focus solely on the desired effects and disregard or sideline undesirable effects (e.g. hypertension, diabetes, administration of prescribed medication, mental, physical or endocrine illnesses). Furthermore, the products are taken under controlled conditions. In numerous trials, some subjects have left, due to the undesirable effects (e.g. sleep disorders, headaches, jumpiness, dizziness). The significantly more frequent undesirable effects in some studies in the group treated (dry mouth, nausea, sleep disorders, heartburn, headache, palpitations) are disregarded in the safety evaluation (Mehendale et al, 2004). Sometimes the study is not designed to include risk factors (cf. 'The activity of pseudoephedrine is comparable to that of ephedrine, but the hypertensive and central nervous stimulating effects are weaker', Meyler's Side Effects of Drugs, 2000; WHO, 1999). Other ephedra alkaloids also affect the heart and circulatory system and airways, but to a lesser degree (CANTOX, 2000).

There is no clear correlation between the level of ephedrine in the blood and specific pharmacological effects. This is probably due to tachyphylaxis (pharmacodynamic factors) rather than pharmacokinetic factors (CANTOX, 2000).

Cardiovascular effects

According to two studies, these undesirable effects only occur in the first 4 weeks (Astrup et al, 1992; Molnar et al, 2000). One study records withdrawal symptoms following treatment with 20 mg of ephedrine over 24 weeks. Withdrawal from ephedrine in single preparations significantly increases hunger pangs. Withdrawal from ephedrine in combination with caffeine results in significantly more headaches and fatigue (Astrup et al, 1992).

Data evaluating ephedra alkaloid-containing Ephedra haulm are only available for food supplements. These generally contain other active ingredients, meaning that the effects cannot

always be ascribed solely to the ephedra alkaloids in the Ephedra haulm. Effects and undesirable effects also correlate with the pharmacological profile of the ephedra alkaloids.
Evaluations are based mainly on case descriptions. It may also be that cases crop up several times in the various evaluations. The fact that case descriptions admit a time, but not a causal link is not contested, but the effects described are plausible.

Action/measures

Risks from ephedra alkaloid-containing Ephedra haulm are known from medical applications and from the (now banned) use in the USA as a food supplement. Serious undesirable (sometimes life-threatening) effects are associated with the consumption of food supplements containing ephedra alkaloids. Due to the risks described, we recommend that Ephedra haulm containing ephedra alkaloids be classified in List A of Annex III to Regulation (EC) No 1925/2006.

References

For bibliography, please see original.