

## Scientific assessment of yohimbe (*Pausinystalia yohimbe*)

### Subject of the assessment

In collaboration with the ALS working Group "Diätetische Lebensmittel, Ernährungs- und Abgrenzungsfragen", the Federal Office of Consumer Protection and Food Safety (BVL) has drafted a "hit list" of 10 substances whose consumption is detrimental to human health. These plants, which include Yohimbe (*Pausinystalia yohimbe* (K. Schum.) Pierre ex Beille), and preparations made from it, contain substances with strong pharmacological and/or psychoactive effects. The European Commission was asked by the Federal Ministry of Food, Agriculture and Consumer Protection to implement the procedure under Article 8 of Regulation (EC) No. 1925/2006 for these plants, and to include them in one of the three Annex III lists. The assessment will affect the bark of the plant, as only this is known to be used. The risk assessment was carried out on the basis of the guidelines published by the EFSA for the assessment of botanicals and botanical preparations for use in food supplements<sup>1</sup> and of the BfR's guidelines on health assessments<sup>2</sup>.

### Results

There are no clinical data available on the effects of yohimbe bark and preparations made from them. Yohimbine hydrochloride (yohimbine HCl), an analogue of the main alkaloid of yohimbe bark, is the only element for which an identification and assessment of dangers can be carried out. The effect of yohimbine HCl varies widely from one individual to another. Matrix effects of the plant material when the bark or preparations from the bark are used cannot be ruled out. These effects could result in the effects of individual substances being strengthened or reduced. An assessment of the risks of yohimbe bark and preparations made from it based on the available data at level A<sup>1</sup> show that the use of yohimbe bark and preparations made from it may be harmful to human health, although there is still scientific uncertainty on this matter.

### Opinion

**1. Identity of the plant** (Kuhlmann, 1999; HagerROM, 2006; Wink et al., 2008; ACS, 2009; USDA, 2009)

- Family: *Rubiaceae* (bedstraw)
- Tribe: *Naucleaeae*
- Genus: *Pausinystalia* L.
- Species: *Pausinystalia yohimbe* (K. Schum.) Pierre ex Beille
- Synonyms: *Pausinystalia johimbe*, *Corynanthe yohimbe*, *Corynanthe johimbi*, *Corynanthe yohimbi*
- common names: Yohimbe, Johimbe, Liebesbaum, Lustholz, Potenzbaum
- Parts of the plant being assessed: Bark (Potenzrinde, Yohimbe cortex, Cortex Yohimbehe)

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<sup>1</sup> 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/cs/BlobServer/Guidance\\_of\\_Panel/sc\\_op\\_ej1249\\_botanicals\\_en.pdf?ssbinary=true](http://www.efsa.europa.eu/cs/BlobServer/Guidance_of_Panel/sc_op_ej1249_botanicals_en.pdf?ssbinary=true)

<sup>2</sup> [http://www.bfr.bund.de/cm/221/bfr\\_leitfaden\\_fuer\\_gesundheitliche\\_bewertungen.pdf](http://www.bfr.bund.de/cm/221/bfr_leitfaden_fuer_gesundheitliche_bewertungen.pdf)

- Geographical origin: tropical West Africa (Cameroon, Congo, Gabon, Equatorial Guinea, Nigeria)
- Growing and harvesting conditions: Gathering from wild plants, as the tree cannot be cultivated.

## **2. Applicable manufacturing methods**

Dried bark from the twigs and stalk of the yohimbe tree are used in their entirety, cut up or ground into powder to use as a drug. Yohimbe is also offered as an extract (CAS: 85117-22-2) (HagerROM, 2006). There is no information on standardisation processes in cultivation. Yohimbine, the main component, can either be obtained from the bark or chemically synthesised (HagerROM, 2006).

## **3. Chemical composition**

Alkaloid content data vary, depending on the method used. The total alkaloid content of the bark is 2–61 mg/g, while the drug should contain  $\geq 15$  mg/g (Brandt, 1922; Madaus, 1938; Betz et al., 1995; HagerROM, 2006). Another source says the drug should contain from 30 to 150 mg/g monoterpene indole alkaloids of the yohimbe bark type (Wink et al., 2008). The alkaloid content increases with the age of the branches (HagerROM, 2006). A preparation made from the extract should contain 95-105 mg/g of total alkaloids, calculated as yohimbine (HagerROM, 2006).

The main alkaloid is yohimbine (Table 1). The other components are primarily yohimbine stereoisomers or derivatives thereof (Table 1) and tannins (Brandt, 1922; Duke, 1992; Tam et al., 2001; HagerROM, 2006; Giftpflanzen - Pflanzengifte, 2008; RÖMPP Online, 2009).

The yohimbine content in the bark is given as 7-115 mg/g<sup>3</sup> and is usually around 10 mg/g (Betz et al., 1995; Zanolari et al., 2003; HagerROM, 2006; Chen et al., 2008). The values depend largely on the method used (Zanolari et al., 2003). Yohimbine is well soluble in alcohol and poorly soluble in water (National Toxicology Program, 1999; HagerROM, 2006)

A variety of yohimbe bark extracts are offered as monopreparations or combined with other substances in liquid, powder, capsule or tablet form. The quantities of yohimbine in these products vary. A study conducted by Betz et al (1995) showed that extracts contain a maximum of 7% of the yohimbine detectable in the bark, with the majority of products having a significantly lower to zero detectable yohimbine content. The authors explain this by the very high rate of dilution of the end-product and by watery extraction methods. The latter methods are poorly suited to transferring the alkaloids, which are poorly soluble in water, to the extract. The highest content was found in liquid products with a high ethanol content ( $\approx 70\%$ ) (0.03% and 0.05% yohimbine). Another study of the yohimbine content of aphrodisiacs shows that the yohimbine concentrations did not always correspond to the quantities detected, some products having more (double) and others less (down to one-tenth) of the stated content (Zanolari et al., 2003).

## **4. Specification**

No specifications are known.

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<sup>3</sup> 11 mg/g with GC-MS (Chen et al., 2008); 7 mg/g with GC (Betz et al., 1995); 8, 12, 22 mg/g (HagerROM, 2006); 13 mg/g with HPLC-UV, 54 mg/g with HPLC-APCI/MS and 115 mg/g with HPLC-ESI/MS (Zanolari et al., 2003)

## 5. Stability of the plants and plant preparations used

### Yohimbe bark

No data are available for yohimbe bark or extracts thereof.

### Yohimbine

When used for medicinal purposes, yohimbine should be kept away from light (HagerROM, 2006).

## 6. Use and quantities suggested as a foodstuff

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

## 7. Other uses

### Yohimbe bark

Yohimbe bark extract was originally used in tropical Africa as a stimulant and a tonic for men. Little is known about the frequency of use, the method of consumption, the amount consumed and length of consumption (Kuhlmann, 1999).

Nowadays it is used to treat sexual dysfunction and erectile problems ([www.biovea-deutschland.com](http://www.biovea-deutschland.com), 2009). It is either taken in the form of tea, or in capsules and tablets (NCCAM, 2009).

### Yohimbine

Yohimbine, the main alkaloid, occurs in drugs in the form of yohimbine-HCl (CAS: 65-19-0) for treating erectile dysfunction and climacterium virile (Fachinformation Yohimbin "Spiegel"<sup>®</sup>, 2008). It is also given to bodybuilders as a weight-loss and performance enhancement drug (National Toxicology Program, 1999; [www.body-academy.com](http://www.body-academy.com), 2009).

## 8. Assessments by other organisations

### Yohimbe bark

In 2007/2008, the *National Center for Complementary and Alternative Medicine* (NCCAM) found that it is unknown whether yohimbe/yohimbe bark can affect health in any way, as no trials have been conducted with yohimbe bark or extracts made from it (NCCAM, 2008).

### Yohimbe bark and yohimbine

Because it is used as a food supplement in the USA, and because of its structural similarity to reserpine (which is carcinogenic), yohimbe bark extract and yohimbine was proposed for assessment by the **National Toxicology Program**. There is no information in the literature on the genotoxicity or carcinogenicity of yohimbe or yohimbine (National Toxicology Program, 1999).

Table 1: Yohimbe bark alkaloids

Name	Synonyms	CAS
Yohimbine	17 $\alpha$ -Hydroxy-yohimban-16 $\alpha$ -carboxylacidmethyl-ester Johimbin Quebrachine Aphrodine Corynine Corymbine Yohimvetol Hydroaerogotocine	146-48-5
$\alpha$ -yohimbine	Rauwolscine Corynanthidine Isoyohimbine Mesoyohimbine	131-03-3
$\beta$ -yohimbine	Amsonine	549-84-8
Pseudoyohimbine		84-37-7
Corynanthine	Rauhimbine	483-10-3
Alloyohimbine		522-94-1
Ajmaline	Rauwolscine Tachmaline	4360-12-7
Ajmalicine	Raubasine d-yohimbine	483-04-5
Corynantheine		
19-Dehydroyohimbine		
Dihydrocorynantheine		
Dihydrosissirikin		
Tetrahydromethylcorynantheine		

### Yohimbine

**Commission E** of the Bundesgesundheitsamt has assessed yohimbe cortex (yohimbe bark consisting of dried bark from the trunk and stems of *Pausinystalia yohimbe* and preparations made from them) as a herbal medicine. Its therapeutic use to treat sexual dysfunction, as an aphrodisiac and for fatigue and exhaustion, has been rejected because of inadequate proof of its efficacy, and the inability to carry out a risk-benefit assessment. The risks in the therapeutic use of the main alkaloid yohimbine are excitation, tremor, insomnia, fear, hypertension, tachycardia, nausea and vomiting. There were also interactions with psychotropic pharmaceuticals. However, it notes that these observations have not been documented for preparations using yohimbe bark (Kommission E, 1987; Kommission E, 1990).

Yohimbinic acid and esters thereof (yohimbine) are prescription-only drugs (**AMVV**, Anlage 1)

Yohimbine and yohimbine salts are prohibited in cosmetics (Regulation (EC) No. 1223/2009, Annex II)

## 9. Exposure data and assessments

Yohimbe bark extract and yohimbine are marketed as food supplements. US studies even speak of "significant human exposure through use as a dietary supplement" (National Toxicology Program, 2008). Depending on the recommended daily dose, users take from 1.3 to 23.2 mg of yohimbe bark extract (Zanolari et al., 2003). There are no data available to for an exposure assessment.

## 10. Identification and characterisation of dangers

### Yohimbe bark

Only uncorroborated individual reports are available on the effect and toxicokinetics of yohimbe bark and extracts made from it (HagerROM, 2006; NCCAM, 2008).

### Yohimbine

#### a) Pharmacokinetic properties

In contrast to yohimbe bark and yohimbe bark extracts, numerous studies on yohimbine-HCl are available. The majority of publications, however, do not distinguish between yohimbine and yohimbine hydrochloride. This means that in this text, a distinction can only be made where precise details have been stated in the sources referred to.

Table 2 summarises the pharmacokinetic data on yohimbine-HCl in various studies. Yohimbine-HCl is rapidly absorbed ( $\approx 11$  min half life) and the maximum plasma concentration is generally achieved in less than one hour (Owen et al., 1987; Tam et al., 2001). The mean bioavailability is low (22–33%) and is subject to very high variation from one individual to another, ranging from 4% to 87% (Guthrie et al., 1990; Le Verge et al., 1992; Le Corre et al., 1999). The simultaneous consumption of fat-rich food reduces the absorption of yohimbine-HCl (Grasing et al., 1996). The plasma concentration of yohimbine appears to correlate only a little with the quantity of yohimbine-HCl administered (Table 2). No concentration was observed after oral intake over 6 days (3x daily 5.4 – 21.6 mg)(Sturgill et al., 1997). The distribution volume of yohimbine is relatively low, although it is a lipophile substance. That is why Le Corre et al (1999) assume that yohimbine is a class II substance in the biopharmaceutical classification of drugs, with a low solubility and high permeability. These substances are subject to a variable absorption, depending on the matrix (Le Corre et al., 1999).

Yohimbine is generally quickly eliminated from the plasma, although here too there are broad differences from one individual to another (Table 2). Clearance generally takes place via the liver metabolism, and less than 1% is excreted in the urine (Tam et al., 2001). Yohimbine is metabolised into the active metabolites 11-hydroxy-yohimbine and the less active 10-hydroxy-yohimbine (Berlan et al., 1993; Le Corre et al., 1999; Fachinformation Yohimbin "Spiegel"<sup>®</sup>, 2008). Metabolisation into 11-hydroxy-yohimbine is subject to a broad variation range ( $> 1000$  times) (Le Corre et al., 2004). Out of 172 persons, no plasma 11-hydroxy-yohimbine was found in 17 persons, mainly of European origin (a significant ethnic difference). In the remaining 155, 12 % of the yohimbine-HCl applied intravenously ( $137 \mu\text{g}/\text{kg}^4$ ) was oxidised into 11-hydroxy-yohimbine. This is achieved above all through cytochrome P450 2D6 (CYP2D6). *In vivo* the extent of the yohimbine metabolism is determined by the CYP2D6 and the CYP3A4 genotypes. Wild types of both genes correspond to an extensive metabolism. The data do not indicate whether this also applies after oral administration or whether further CYPs in the intestines and liver play the decisive role (Le Corre et al., 2004).

After oral administration the AUC values for the active metabolic product of yohimbine, 11-hydroxy-yohimbine, is approximately  $45 \pm 36$  times (0.6–118) higher than for yohimbine. The area below the concentration-time curve of 11-hydroxy-yohimbine (39– 152  $\mu\text{g}/\text{min}/\text{ml}$ ) varies less than for yohimbine (0,5–106  $\mu\text{g}/\text{min}/\text{ml}$ ). Furthermore, 11-hydroxy-yohimbine has a longer elimination half-life (Le Verge et al., 1992; Le Corre et al., 1999). 10-hydroxy-yohimbine is inactive and only detected in the urine, but not in the plasma (Le Corre et al., 1999). It oxidises into 10-hydroxy-

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<sup>4</sup> 70 kg → 9.59 mg yohimbine

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yohimbine primarily through CYP3A4 (Le Corre et al., 2004). Of the yohimbine-HCl taken in,  $0.05\% \pm 0.06\%$  yohimbine,  $0.3\% \pm 0.1\%$  11-hydroxy-yohimbine (more water-soluble and lower plasma protein binding than yohimbine) and  $14.3\% \pm 2.3\%$  of 10-hydroxy-yohimbine were excreted via the liver (Le Corre et al., 1999).

The pharmacokinetics of yohimbine HCl varies widely from one individual to another. Regular administration of yohimbine HCl (three times daily for 6 days) had no effect on the pharmacokinetics. With most individuals, the pharmacokinetics correspond to a single compartment model, but with some to a two compartment model (Sturgill et al., 1997).

Table 2: Pharmacokinetics of yohimbine HCl after single oral intake (MW – mean value, SD – standard variation). The highest and lowest values are given in brackets. Figures with ≈ have been computed (dose) or taken from a figure

Dose	n	C <sub>max</sub> (ng/ml)		t <sub>max</sub> (h)		t <sub>1/2el</sub> (h)		AUC (ng*h/ml)		Clearance (l/h/kg)		Distribution volume (l/kg)		Reference
		MW	SD	MW	SD	MW	SD	MW	SD	MW	SD	MW	SD	
5.4 mg	6	20		0.4			0.5							(Grasing et al., 1996)
5.4 mg	4 <sup>e</sup>	51	46	0.4	0.3	0.3	0.2	31	15					(Sturgill et al., 1997)
5.4 mg	2 <sup>f</sup>	281	250	0.5	0.2	2.2	1.8	580	647					(Sturgill et al., 1997)
8 mg	11	58	85	1.2	0.6	1.5	1.3	211	518					(Le Corre et al., 1999)
		(3-266)		(0.5-2)		(0.4-4.4)		(8-1760)						
10 mg	7	(≈7-300)		(0.2-0.8)				134	231	3.4	3.9	3.2	3.6	(Guthrie et al., 1990)
								(10.7-656)						
10 mg	8					0.6	0.3			2.8	1.2	2.2	1.3	(Owen et al., 1987)
10.8 mg	6	≈130		0.3		0.3		≈100						(Grasing et al., 1996)
		(max. 504)						(max. 550)						
10.8 mg <sup>g</sup>	6	≈100			0.7		0.5	≈70						(Grasing et al., 1996)
10.8 mg	4 <sup>e</sup>	154	107	0.5	0.1	0.2	0.1	119	73					(Sturgill et al., 1997)
10.8 mg	2 <sup>f</sup>	502	493	0.4	0.3	3.7	0.6	2230	2920					(Sturgill et al., 1997)
0.2 mg/kg	6	38	15				0.6	50	42	6.3	1.5	2.7	0.5	(Berlan et al., 1991)
(≈11,2 mg)														
16.2 mg	6	≈80		0.6		0.4		≈120						(Grasing et al., 1996)
16.2 mg	4 <sup>e</sup>	400	314	0.4	0.2	0.3	0.1	376	374					(Sturgill et al., 1997)
16.2 mg	2 <sup>f</sup>	221	49	0.5	0.1	0.9	0.3	250	18.4					(Sturgill et al., 1997)
0.2 mg/kg <sup>h</sup>	10	168	29				0.6	244	147	1.0	0.2	1.0	0.2	(Berlan et al., 1991)
(≈18,8 mg)														
21.6 mg	6	≈150		0.6		0.5		≈220						(Grasing et al., 1996)
21.6 mg	3 <sup>e</sup>	50	19	0.4	0.1	0.2	0.1	72	42					(Sturgill et al., 1997)
21.6 mg	3 <sup>f</sup>	201	70	0.6	0.3	8.3	11.6	1430	1980					(Sturgill et al., 1997)

<sup>e</sup> single compartment model  
<sup>f</sup> double compartment model  
<sup>g</sup> accompanied by a fatty diet  
<sup>h</sup> overweight people, MGI: 36.4±2.1

b) Pharmacological and toxicological properties

Yohimbine HCl (an  $\alpha_2$ -adrenoreceptor antagonist and, less pronouncedly, an  $\alpha_1$ -adrenoreceptor antagonist) is therapeutically used primarily to treat erectile dysfunction. Although 34–86% of patients respond to treatment, because of the pronounced placebo effects, only few studies show significant pharmacological effects compared with the control group (Tam et al., 2001). To treat loss of libido and climacterium virile, 5-10 mg of yohimbine HCl are taken, preferably during meals. The desired effect sometimes occurs with a latency period of 2-3 weeks (Fachinformation Yohimbin "Spiegel"<sup>®</sup>, 2008)

The side effects of yohimbine HCl include high blood pressure and heart rate, palpitations, insomnia, irritability, excitation, shivering, sweating, flushing and headaches. Occasionally (in 0.1–1% of cases) patients have gastrointestinal symptoms such as nausea, vomiting, lack of appetite and diarrhoea. Rarely (0.01–0.1%) there are cases of hypotonic dysregulation (Fachinformation Yohimbin, "Spiegel"<sup>®</sup>, 2008). The increased norepinephrine plasma level and its metabolite 3-Methoxy-4-hydroxyphenylglycol (MHPG) is one of the most common endocrine effects of yohimbine HCl. Depending on the yohimbine plasma level, the plasma catecholamine concentrations can increase. These effects may be accompanied by changes in blood pressure, pulse or mood changes (paranoia) (Grasing et al., 1996; Sturgill et al., 1997). Yohimbine HCl increases heart performance, increasing cardiac output and blood pressure (Le Corre et al., 2004). Although dose-dependent, this effect varies widely from one individual to another. Tam et al (2001) summarised 22 studies in which yohimbine was orally administered and the effects on blood pressure and pulse were investigated. Concentrations of 4–16.2 mg (as a single dose or three times daily) do not generally affect the blood pressure and pulse in patients with normal blood pressure. 20–30 mg of yohimbine either have no significant effect, or result in a moderate increase in blood pressure but without affecting the heart rate. Concentrations of 45.5 mg and above occasionally increase the medium arterial blood pressure, and less commonly, the heart rate. If such haemodynamic effects occur, they reach their maximum level after 60-90 mins and fall again over a few hours. Both young and older people tolerate yohimbine well in these concentrations. The side effects of yohimbine are clearly dose-related. While in therapeutic doses small or mild side-effects occur, they accumulate in higher doses (Tam et al., 2001). Yohimbine can increase the plasma concentration of free fatty acids, although this does not necessarily result in weight loss. The time at which yohimbine is taken compared with food intake plays a role in the effect of yohimbine (Galitzky et al., 1988; Berlan et al., 1991).

In case of overdose, weakness, generalised paraesthesia, loss of coordination and memory problems, as well as severe headaches combined with dizziness, tremor, palpitations and fear occur after 20-30 mins. After 4 h severe chest pain can occur, lasting for several hours. Other side effects include headache, increased blood pressure, tachycardia lasting several hours, nausea, vomiting, mydriasis, increased saliva and tear flow and perspiration. Greatly increased norepinephrine values have been shown (Fachinformation Yohimbin, "Spiegel"<sup>®</sup> 2008). Side effects may persist for 1-2 days (Tam et al., 2001). Instances of intoxication have been described at doses above 200 mg yohimbine HCl (yohimbine drug data sheet, "Spiegel"<sup>®</sup>, 2008). In one 16-year-old girl, 250 mg yohimbine brought about an overdose with dissociative reactions, weakness, paranoia, headache, nausea, chest pains, shivering, increased respiration rate, high blood pressure and tachycardia. The serum epinephrine and norepinephrine concentrations were increased. These symptoms persisted for 36 h (Linden et al., 1985). A dose of 1.8 g is reputed to have resulted in several hours' loss of consciousness (Wink et al., 2008). In a 37-year-old body builder, 5 g of yohimbine resulted in neurotoxic effects after 2 h. These



expressed themselves in nausea, vomiting and repeated episodes, hypertension (259/107 mmHg) and tachycardia. The plasma levels measured 3, 6, 14 and 22 h after intake were 5240, 2250, 1530 and 865 ng/ml (Giampreti et al., 2009).

Interactions of yohimbine HCl with alcohol and medication (antihypertensives, antidepressants and others) are known (McDougle et al., 1995; Fachinformation Yohimbin "Spiegel"<sup>®</sup>, 2008). Taking yohimbine HCl, particularly when combined with alcohol, can impair the ability to drive or operate machinery (Fachinformation Yohimbin "Spiegel"<sup>®</sup>, 2008).

The risk groups among which yohimbine HCl can have a more intense effect are people with cardiac impairment, hypertension, reduced renal and hepatic function, affective or paranoid psychiatric diseases and glaucoma (Fachinformation Yohimbin "Spiegel"<sup>®</sup>, 2008). Even normotensive subjects at risk of high blood pressure respond to yohimbine HCl with higher catecholamine values and increased blood pressure (Dao et al., 1998). Other studies do not give any indication that persons with high blood pressure or a tendency to orthostatic hypotension are particularly sensitive in their response to yohimbine (Tam et al., 2001). In patients with anxiety disorders, yohimbine triggers panic attacks in 50% of cases, while in healthy patients this only occurs in 5% of cases (Charney et al., 1984; Charney et al., 1987). According to the drug data sheet, women should not take yohimbine HCl, as the effect on sexual function disorders has not been subjected to adequate clinical investigation. No foetal effects of yohimbine HCl are known (yohimbine drug data sheet, "Spiegel"<sup>®</sup>, 2008).

#### c) Animal studies

Acute toxicity (oral LD50) in mice arises at less than 50 mg/kg body weight. The LD50 for humans has been calculated as 5 mg/kg body weight (= 350 mg/70 kg body weight). The lethal dose is ten times higher (50 mg/kg). There are no data available for repeated or chronic use (Fachinformation Yocon-Glenwood<sup>®</sup>, 2005).

#### d) in vitro data

*In vitro* studies show that yohimbine is a selective and competitive  $\alpha_2$ -adrenoreceptor antagonist with a low antagonist effect with regard to  $\alpha_1$ -adrenoreceptors (Tam et al., 2001; HagerROM, 2006). Both of the metabolic products of yohimbine also bind to this receptor, but yohimbine has a higher binding affinity. In the presence of 5% albumin, the  $\alpha_2$ -Adrenoreceptor binding affinity reduces 10-fold to that of its active metabolite 11-hydroxy-yohimbine. The plasma protein binding is 82%, 43% and 32% for yohimbine, 11-hydroxy-yohimbine and 10-hydroxy-yohimbine (Berlan et al., 1993). 11-hydroxy-yohimbine is biologically active and has a capacity to block  $\alpha_2$ -Adrenoreceptors in cells similar to that of yohimbine. Although 11-hydroxy-yohimbine has a lower binding affinity to  $\alpha_2$ -adrenoreceptors than yohimbine, this is probably compensated by a significantly lower plasma protein binding (Berlan et al., 1993).

#### Other ingredients

In addition to yohimbine, yohimbe bark contains significant quantities of  $\alpha$ -Yohimbine (rauwolscine). Both alkaloids largely conform in their profile of action. They selectively inhibit  $\alpha$ -adrenoreceptors with equal strength. Raubasine is an alkaloid which is chemically related to reserpine. It does not have a very pronounced anti-hypertensive effect. Raubasine is a selective  $\alpha_1$ -adrenoreceptor antagonist and a prescription drug. Like yohimbine, yohimbinic acid selectively blocks the  $\alpha_2$ -adrenoreceptors. The desirable and undesirable pharmacological effects correspond to those of yohimbine (HagerROM, 2006). Yohimbine is thus not the only pharmacologically relevant substance in yohimbe bark. It is not known to what extent

the effects of the individual substances influence one another. Matrix effects can also be expected from the tannin content of the bark, as these could precipitate the alkaloids (Khanbabaee and van Ree, 2001).

### 11. Characterisation of risk

There are no clinical data available on the **effects of Yohimbe bark** and preparations made from them.

The effects of **yohimbine HCl** vary widely from one individual to another. Huge variations between individuals are known with regard to the pharmacokinetics after oral administration of drugs which, like yohimbine HCl, are primarily metabolised through CYP2D6, and genetic variations for CYP2D6 with varying consequences have been described: defective alleles, alleles leading to a reduced metabolic rate, amplification of alleles with increased metabolic rate and changes to alleles with no functional consequences. The safety factor for substances primarily metabolised through CYP2D6 should accordingly be raised for inter-individual differences in toxicokinetics (Standard: 3.16) to 18, and in children even to 45 (Dorne et al., 2002). So far, it has not been possible to ascribe the high variability of the effect on the blood pressure to differences in the yohimbine metabolism or genetic variations in the  $\alpha_2$ -adrenoreceptor (Le Corre et al., 2004; Etzel et al., 2005). Furthermore, the effects of the drug yohimbine HCl can only be transferred to yohimbe bark or extracts from the bark to a limited extent. Yohimbine HCl is more soluble in water than yohimbine, and the bark contains further pharmacologically active substances as well as tannins which can precipitate the alkaloids. The amount of yohimbine in yohimbe products vary greatly, and the results depend not just on the method of extraction, but also on the analytical method used.

Although yohimbine HCl is a prescription drug in Germany, and yohimbe bark is restricted to pharmacies, because of the claimed aphrodisiac and weight-reducing effect, **it can be assumed** that there is a market for products containing yohimbe bark.

### Framework for action / measures

There are no clinical data available on the effects of Yohimbe bark. On the basis of the available data, the risk assessment of yohimbe bark and preparations made from it which place it at level **A<sup>9</sup>** means that **further data is necessary. To assess it at safety level B, the provision of clinical data on yohimbe bark and the relevant preparations is necessary.**

<sup>9</sup>European Food Safety Authority (2009) Guidance on Safety assessment of botanicals and botanical preparations intended for use as ingredients in food supplements.

## References

- Fachinformation Yocon-Glenwood® (2005)
- HagerROM (2006). Heidelberg
- Fachinformation Yohimbin "Spiegel"® (2008)
- Giftpflanzen - Pflanzengifte (2008). 5. Auflage. Landsberg
- RÖMPP Online (2009). <http://www.roempp.com/prod/index1.html>
- ACS: Yohimbe.  
[http://www.cancer.org/docroot/ETO/content/ETO\\_5\\_3X\\_Yohimbe.asp?sitearea=ETO](http://www.cancer.org/docroot/ETO/content/ETO_5_3X_Yohimbe.asp?sitearea=ETO)  
(15.04.2009)
- Berlan M, Galitzky J, Riviere D, Foureau M, Tran MA, Flores R, Louvet JP, Houin G, Lafontan M (1991). Plasma catecholamine levels and lipid mobilization induced by yohimbine in obese and nonobese women. *Int J Obes.* 15: 305-315
- Berlan M, Le Verge R, Galitzky J, Le Corre P (1993). Alpha 2-adrenoceptor antagonist potencies of two hydroxylated metabolites of yohimbine. *Br J Pharmacol.* 108: 927-932
- Betz JM, White KD, der Marderosian AH (1995). Gas chromatographic determination of yohimbine in commercial yohimbe products. *J AOAC Int.* 78: 1189-1194.
- Brandt W (1922). Monographie der Gattungen Corynanthe Welwitsch und Pausinystalia Pierre, Rubiaceae. (Über die Stammpflanze der Yohimberinde und ihre Verwandten.). *Archiv der Pharmazie* 260: 49-94
- Charney DS, Heninger GR, Breier A (1984). Noradrenergic function in panic anxiety. Effects of yohimbine in healthy subjects and patients with agoraphobia and panic disorder. *Arch Gen Psychiatry* 41: 751-763
- Charney DS, Woods SW, Goodman WK, Heninger GR (1987). Neurobiological mechanisms of panic anxiety: biochemical and behavioral correlates of yohimbine-induced panic attacks. *Am J Psychiatry* 144: 1030-1036
- Chen Q, Li P, Zhang Z, Li K, Liu J, Li Q (2008). Analysis of yohimbine alkaloid from Pausinystalia yohimbe by non-aqueous capillary electrophoresis and gas chromatography-mass spectrometry. *J Sep Sci.* 31: 2211-2218
- Dao TT, Kailasam MT, Parmer RJ, Le HV, Le Verge R, Kennedy BP, Ziegler G, Insel PA, Wright FA, O'Connor DT (1998). Expression of altered alpha2-adrenergic phenotypic traits in normotensive humans at genetic risk of hereditary (essential) hypertension. *J Hypertens.* 16: 779-792
- Dorne JL, Walton K, Slob W, Renwick AG (2002). Human variability in polymorphic CYP2D6 metabolism: is the kinetic default uncertainty factor adequate? *Food Chem Toxicol.* 40: 1633-1656

## Federal Institute for Risk Assessment

Duke JA (1992). Handbook of Phytochemical Constituents of GRAS Herbs and Other Economic Plants.

Etzel JP, Rana BK, Wen G, Parmer RJ, Schork NJ, O'Connor DT, Insel PA (2005). Genetic variation at the human alpha2B-adrenergic receptor locus: role in blood pressure variation and yohimbine response. *Hypertension*. 45: 1207-1213

Farrow S, Mers A, Banta G, Steigerwalt S, Lockette W (1990). Effect of the alpha 2-adrenergic antagonist yohimbine on orthostatic tolerance. *Hypertension*. 15: 877-880.

Galitzky J, Taouis M, Berlan M, Riviere D, Garrigues M, Lafontan M (1988). Alpha 2-antagonist compounds and lipid mobilization: evidence for a lipid mobilizing effect of oral yohimbine in healthy male volunteers. *Eur J Clin Invest*. 18: 587-594.

Giampreti A, Lonati D, Locatelli C, Rocchi L, Campailla MT (2009). Acute neurotoxicity after yohimbine ingestion by a body builder. *Clin Toxicol (Phila)*. 47: 827-829.

Grasing K, Sturgill MG, Rosen RC, Trout JR, Thomas TJ, Kulkarni GD, Maines P, Seibold JR (1996). Effects of yohimbine on autonomic measures are determined by individual values for area under the concentration-time curve. *J Clin Pharmacol*. 36: 814-822.

Guthrie SK, Hariharan M, Grunhaus LJ (1990). Yohimbine bioavailability in humans. *Eur J Clin Pharmacol* 39: 409-411.

Khanbabae K, van Ree T (2001). Tannins: classification and definition. *Nat Prod Rep*. 18: 641-649.

Kommission E (10.15.1987). Yohimbehe cortex. *Bundesanzeiger* 193a.

Kommission E (2.1.1990). Yohimbehe cortex. *Bundesanzeiger* 22a.

Kuhlmann H (1999). Yohimbin. Potenzkraft von Äquator. *Pharmazeutische Zeitung*. 47: 11-16.

Le Corre P, Dollo G, Chevanne F, Le Verge R (1999). Biopharmaceutics and metabolism of yohimbine in humans. *Eur J Pharm Sci*. 9: 79-84.

Le Corre P, Parmer RJ, Kailasam MT, Kennedy BP, Skaar TP, Ho H, Leverage R, Smith DW, Ziegler MG, Insel PA, Schork NJ, Flockhart DA, O'Connor DT (2004). Human sympathetic activation by alpha2- adrenergic blockade with yohimbine: Bimodal, epistatic influence of cytochrome P450-mediated drug metabolism. *Clin Pharmacol Ther*. 76: 139-153.

Le Verge R, Le Corre P, Chevanne F, Doe DM, Royer D, Levy J (1992). Determination of yohimbine and its two hydroxylated metabolites in humans by high-performance liquid chromatography and mass spectral analysis. *J Chromatogr*. 574: 283-292

Linden CH, Vellman WP, Rumack B (1985). Yohimbine: a new street drug. *Ann Emerg Med*. 14: 1002-1004.

Madaus G (1938). *Lehrbuch der Biologischen Heilmittel*. Leipzig.  
<http://212.185.118.226/publlehrbuch/>

McDougle CJ, Krystal JH, Price LH, Heninger GR, Charney DS (1995). Noradrenergic response to acute ethanol administration in healthy subjects: comparison with intravenous yohimbine. *Psychopharmacology (Berl)*. 118: 127-135.

Michel MC, Daul A, Galal O, Wang XL, Brodde OE (1988). Are alpha- and beta-adrenoceptor changes in patients with essential hypertension genetically determined? *J Hypertens Suppl*. 6: S575-S577.

National Toxicology Program (1999). Nomination Background Yohimbe bark extract / Yohimbine. <http://ntp.niehs.nih.gov/?objectid=467AE677-F1F6-975E-757D1311EBE653BE#yohimbe>.

National Toxicology Program (2008). Nominations Reviewed 2000: Yohimbe bark extract/Yohimbine. <http://ntp.niehs.nih.gov/?objectid=467AE677-F1F6-975E-757D1311EBE653BE#yohimbe>.

NCCAM: Yohimbe. [http://nccam.nih.gov/health/yohimbe/D356\\_Herbs.pdf](http://nccam.nih.gov/health/yohimbe/D356_Herbs.pdf) (2008)

NCCAM: Yohimbe - herbs at a glance. <http://nccam.nih.gov/health/yohimbe/> (27.05.2009)

Owen JA, Nakatsu SL, Fenemore J, Condra M, SurrIDGE DH, Morales A (1987). The pharmacokinetics of yohimbine in man. *Eur J Clin Pharmacol*. 32: 577-582

Sturgill MG, Grasing KW, Rosen RC, Thomas TJ, Kulkarni GD, Trout JR, Maines M, Seibold JR (1997). Yohimbine elimination in normal volunteers is characterized by both one- and two-compartment behavior. *J Cardiovasc Pharmacol*. 29: 697-703

Tam SW, Worcel M, Wyllie M (2001). Yohimbine: a clinical review. *Pharmacol Ther*. 91: 215-243.

USDA, ARS National Genetic Resources Program. Germplasm Resources Information Network GRIN National Germplasm Resources Laboratory Beltsville Maryland: *Pausinystalia yohimbe*.

[http://www.ars-grin.gov/cgi-bin/npgs/html/tax\\_search.pl](http://www.ars-grin.gov/cgi-bin/npgs/html/tax_search.pl) (26.05.2009)

Wink M, van Wyk B-E, Wink C (2008). *Handbuch der giftigen und psychoaktiven Pflanzen*. 1. Stuttgart.

[www.biovea-deutschland.com](http://www.biovea-deutschland.com): Yohimbe Produkte. <http://www.biovea-deutschland.com/Biovea/result.aspx?Search=Yes&PageNo=1&key=yohimbe> (27.05.2009)

[www.body-academy.com](http://www.body-academy.com): Yohimbin für Bodybuilder. <http://www.body-academy.com/supplements/yohimbin/> (27.05.2009)

Zanolari B, Ndjoko K, Ioset JR, Marston A, Hostettmann K (2003). Qualitative and quantitative determination of yohimbine in authentic yohimbe bark and in commercial aphrodisiacs by HPLC-UV-API/ MS methods. *Phytochem Anal*. 14: 193-201.