SUMMARY OF DATA FOR CHEMICAL SELECTION

Yohimbe bark extract / Yohimbine
85117-22-2 / 146-48-5

BASIS OF NOMINATION TO THE CSWG

Yohimbe bark extract and its active ingredient, yohimbine, are presented to the CSWG as part of a review of botanicals being used as dietary supplements in the United States.

Yohimbe has a history of use as an aphrodisiac although it is increasingly used to enhance athletic performance. Yohimbine and yohimbe extracts are used to treat impotence by dilating the blood vessels, resulting in vasocongestion.

No information on the genotoxicity or carcinogenicity of yohimbe or yohimbine was found in the available literature. The structurally related compound reserpine was carcinogenic in both mice and rats, raising concerns about the potential carcinogenicity of yohimbe bark extract and yohimbine.

INPUT FROM GOVERNMENT AGENCIES/INDUSTRY

Dr. John Walker, Executive Director of the TSCA Interagency Testing Committee (ITC), Environmental Protection Agency (EPA), indicated that the ITC has deferred action on yohimbine and yohimbine hydrochloride.

Don Stanek, director of sales, at Nuova Linnea, Inc., provided technical documentation on their yohimbine hydrochloride product.

SELECTION STATUS

ACTION BY CSWG: 12/16/99

Studies requested:

Recommended for testing in Ames *Salmonella* and micronucleus assays

Followup: Based on the results of the battery of genotoxicity tests, reconsider for additional testing

Priority: The CSWG does not assign a priority for genotoxicity tests

Rationale/Remarks:

An α-2 adrenergic antagonist used as an aphrodisiac

Yohimbine is a prescription drug that can cause substantial rise in blood pressure; yohimbe bark extract, which contains yohimbine as the active ingredient, is a widely available dietary supplement

A structurally related compound, reserpine, was carcinogenic when administered orally to mice and rats

NCI is conducting Ames and mouse lymphoma assays on yohimbe bark extract and yohimbine

CHEMICAL IDENTIFICATION

Yohimbe Bark Extract

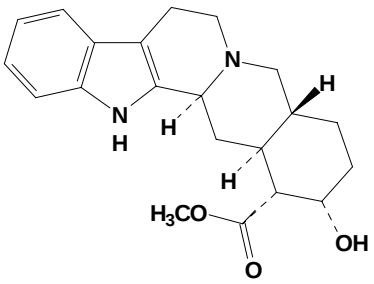
CAS Registry Number:	85117-22-2
Chemical Abstracts Service Name:	Corynanthe yohimbe extract
Structural Class:	Botanical

Yohimbine[a]

CAS Registry Numbers:	146-48-5 65-19-0 [hydrochloride]
Chemical Abstracts Service Names:	Yohimban-16-carboxylic acid, 17-hydroxy-, methyl ester, (16α, 17α)- (9CI) Yohimban-16-carboxylic acid, 17-hydroxy-, methyl ester, monohydrochloride, (16α, 17α)- (9CI)
Synonyms and Trade Names:	Aphrodyne; corynine; quebrachine
Structural Class:	Indolealkylamine alkaloid

[a]In the published literature, yohimbine is often used interchangeably with yohimbine hydrochloride

Structure, Molecular Formula and Molecular Weight:



Yohimbine

$C_{21}H_{26}N_2O_3$ Mol. wt.: 354.45

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Chemical and Physical Properties (Yohimbine):

Description:	Orthorhombic needles (Budavari, 1997; PDR Herbal, 1998)
Melting Point:	234°C (Budavari, 1997)
Solubility:	Sparingly soluble in water; soluble in alcohol, chloroform, hot benzene; moderately soluble in ether (Budavari, 1997)

Chemical and Physical Properties (Yohimbe extract):

Yohimbe (*Corynanthe yohimbe*), a member of the Rubiaceae family, is a tall evergreen tree with grey-brown bark and leaves that are oblong and elliptical. The bark of the tree is used for medicinal purposes. Yohimbe extract contains indole alkaloids (2.7-5.9%) including, among others, yohimbine and its stereoisomers (α-yohimbine, β-yohimbine, allo-yohimbine), ajamalicin, dihydroyohimbine, corynanthein, dihydrocorynanthein, corynanthin (rauhinbin). The most thoroughly studied is the major active constituent, yohimbine. Yohimbe extract is odorless with a bitter taste (Betz *et al.*, 1995; PDR Herbal, 1998; PDR, 1999; Yohimbe, 1999).

Technical Products and Impurities: Yohimbe bark extracts, standardized to varying amounts of yohimbine, are widely available in health food stores and through direct-mail companies. Extracts are supplied as capsules, tablets, and liquids. Some of these yohimbe preparations are sold in combination formulas with other herbs. Yohimbine hydrochloride is a Food and Drug Administration (FDA) approved prescription drug for the treatment of impotence (Betz *et al.*, 1995; Dialog Information Services, 1999a; PDR, 1999; Yohimbe, 1999).

Betz and coworkers (1995) investigated yohimbine in commercial yohimbe products. Gas chromatograph determinations were done on liquids and powders (from capsules and caplets). Virtually all the products tested did not specify on their labels that the product contained yohimbe bark extract. Concentrations of yohimbine in the commercial products

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ranged from >0.1 to 489 ppm, compared with 7089 ppm in the authentic bark material. Of the 26 products examined, nine contained no quantifiable amount of yohimbine; eight contained only trace amounts (0.1-1 ppm). The authors suggest that the absence of alkaloids in the products indicated that the original extraction was aqueous (because the alkaloids are not particularly water soluble), the extract was extremely diluted in the final dosage form, or no yohimbe bark was used to make the product.

Yohimbine is available in research quantities at 98% purity from Aldrich Chemical Company. Yohimbine hydrochloride is available from Aldrich and Sigma at 99 and 80% purity, respectively (Aldrich Chemical Co., 1999; Sigma, 1999).

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EXPOSURE INFORMATION

Production and Producers: Yohimbe grows in the jungles of West Africa (Cameroon, Congo, and Gabon). Yohimbe bark consists of the dried bark of the trunk and/or branches of *Corynanthe yohimbe* (syn. *Pausinystalia yohimbe*). Yohimbine, which constitutes about six percent of yohimbe bark, is also present in the related species *P. macroceras*, *P. paniculata*, and *P. trillesii*. Although yohimbe has been used medicinally since ancient times, yohimbine was first isolated in 1896 and its correct constitution was not identified until 1943 (Mekkawi & Al-Badr, 1972; PDR Herbal, 1998).

The total synthesis of yohimbine has been reported (vanTamelen *et al.*, 1958; Florey, 1972; Goodman, 1988; Shi, 1989; Budavari, 1997). vanTamelen and coworkers (1958) achieved synthesis of yohimbine through a 23-step process.

Yohimbe bark and extract are available from Charles Bowman & Co., Mini Star International, Inc., Motherland Herb-Pharm, Inc., QBI (Quality Botanicals Ingredients, Inc.), and Stryka Botanics Co., Inc. (McCoy, 1998).

Yohimbine is available from The Graymor Chemical Co., Inc., Pharmline, Inc., SPS Alfachem, Paul Schueller International, Inc., and B.I. Chemicals, Inc. (Kuney, 1997; McCoy, 1998).

Yohimbine hydrochloride is available from BCN Chemicals, Inc., B.I. Chemicals, Inc., Boehringer Ingelheim KG, CPB International, Inc., Flavine International, Inc., Maypro Industries, Inc., Mini Star International, Inc., Monomer-Polymer & Dajac Labs, Inc., Motherland Herb-Pharm, Inc., Nuova Linnea, Inc., Ria International, SST Corp., Schweizerhall, Inc., Spectrum Bulk Chemicals, Division of Spectrum Quality Products, Inc., Synkem Div. de Plasto S.A., and Westco Chemicals, Inc. (Kuney, 1997; Hunter, 1998; McCoy, 1998; Nuova Linnea, 1999).

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In the 8-month period from September 1998 to May 1999, the Port Import/Export Reporting Service (PIERS) reported yohimbine and yohimbine hydrochloride imports of 547 and 52 pounds, respectively (Dialog Information Services, 1999b).

Yohimbine hydrochloride is listed in the EPA's Toxic Substances Control Act (TSCA) Inventory (NLM, 1999).

Use Pattern: Health food stores in the US have carried yohimbe for many years. Both the crude bark and its purified compounds have a history of popular use for supposed aphrodisiac properties. Pharmacologists have generally disparaged the use of yohimbine as an aphrodisiac that produces a true stimulation of libido (Clark *et al.*, 1984). In recent years, the market has shifted from aphrodisiacs to enhancers of athletic performance (Clark *et al.*, 1984; Kowalchik & Hylton, 1987; Owen *et al.*, 1987; Betz *et al.*, 1995; Africanfly, 1999; Angelfire, 1999; Bodybuild, 1999; Dialog Information Services, 1999b).

Yohimbine and yohimbe extracts are used to treat impotence, a disorder that occurs in 1.2 to 2 percent of the male population. Yohimbe has also been used extensively in veterinary medicine for treatment of impotent breeding stallions (Clark *et al.*, 1984; Kowalchik & Hylton, 1987; Owen *et al.*, 1987; Sandler & Aronson, 1993; Betz *et al.*, 1995; Africanfly, 1999; Angelfire, 1999; Aphrodisiacal Drugs, 1999; PDR, 1999).

Yohimbine is an α-2 adrenergic antagonist that inhibits norepinephrine release, decreasing sympathetic overflow from the central nervous system (Buffum, 1985). Its peripheral nervous system effect is to increase cholinergic and decrease adrenergic activity. In male sexual performance, erection is linked to cholinergic activity and to α-2 adrenergic blockade (Mekkawi & Al-Badr, 1972; PDR, 1999).

Yohimbine affects impotence by dilating the blood vessels of the skin and mucous

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membranes, thus bringing the blood closer to the surface of the sex organs, resulting in increased peripheral genital vasocongestion. It also increases the reflex excitability of the lower region of the spinal cord. For the treatment of erectile impotence, the recommended dose of yohimbine is 16.2 mg (yohimbine hydrochloride) a day taken in three divided doses. The suggested treatment period is no more than 10 weeks. The yohimbe bark is taken as a sweet tea, smoked, or sniffed (Clark *et al.*, 1984; Kowalchik & Hylton, 1987; Lacomblez *et al.*, 1989; Betz *et al.*, 1995; PDR, 1999).

Yohimbe has been as an antidiuretic, for angina pectoris, as a hallucinogen, and for treatment of atherosclerosis. Yohimbine also exerts a stimulating action on the mood and may increase anxiety. It has a mild anti-diuretic action and reportedly does not significantly influence cardiac stimulation and other effects mediated by β-adrenergic receptors (Clark *et al.*, 1984; Kowalchik & Hylton, 1987; Lacomblez *et al.*, 1989; Atala & Amin, 1991; Betz *et al.*, 1995; PDR, 1999).

Between 1979 and 1999, the US Patent and Trademark Office issued 5 patents involving yohimbe and 420 involving yohimbine (US Patent and Trademark Office, 1999a,b).

Human Exposure: The primary exposure of humans to yohimbe occurs through its use as an herbal supplement. Approximately one third of the US adult population or approximately 60 million consumers, have increasingly used alternative pharmaceutical preparations to prevent or treat illnesses (Tanaka, 1997).

There is potential for worker exposure to yohimbe during the growing, harvesting and processing of the plants. For the purposes of quantifying the costs of food labeling regulations, the FDA (1997) estimated that there were 250 herbal/botanical firms; the number of firms producing yohimbe products was not identified

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No listing was found for yohimbe or yohimbine in the National Occupational Exposure Survey (NOES), which was conducted by the National Institute for Occupational Safety and Health (NIOSH) between 1981 and 1983.

Environmental Occurrence: Yohimbe (*Corynanthe yohimbe*), a member of the Rubiaceae family, is a tall evergreen tree that grows in the jungles of west Africa (Cameroon, Congo, and Gabon) (Betz *et al.*, 1995; PDR Herbal, 1998). Information on controlled cultivation was not found in the available literature.

Regulatory Status: Since 1994, dietary supplements have been regulated under the Dietary Supplement Health and Education Act (DSHEA). For dietary supplements on the market prior to October 15, 1994, the DSHEA requires no proof of safety in order for them to remain on the market. The labeling requirements for supplements allow warnings and dosage recommendations as well as substantiated "structure or function" claims. All claims must prominently note that they have not been evaluated by the FDA, and they must bear the statement "This product is not intended to diagnose, treat, cure, or prevent any disease" (Croom & Walker, 1995).

The FDA classifies yohimbe as an unsafe herb, containing "the toxic alkaloid, yohimbine, and other alkaloids" (Duke, 1985). In Germany, Commission E, an expert panel that evaluates the uses of herbal medicines, did not recommend the therapeutic administration of yohimbe bark and its preparations because of insufficient proof of efficacy and the unforeseeable correlation between risk and benefit (Blumenthal, 1998).

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EVIDENCE FOR POSSIBLE CARCINOGENIC ACTIVITY

Human Data: No epidemiological studies or case reports investigating the association of exposure to yohimbe bark extract or yohimbine and cancer risks in humans were identified in the available literature.

Yohimbine readily penetrates the central nervous system and produces a complex pattern of responses in lower doses than required to produce peripheral α-2 adrenergic blockade. These include anti-diuresis, elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea, and vomiting are common after parenteral administration of yohimbine; dizziness, headache, and skin flushing have been reported when yohimbine is used orally. Yohimbine has also caused bronchospasms (Landis & Shore, 1989; Betz *et al.*, 1995; Gilman *et al.*, 1998; PDR, 1999).

Doses of 20 to 30 mg yohimbine increase blood pressure and heart rate, piloerection, and rhinorhea. Paresthesia, incoordination, tremulousness, and dissociation states were reported in the most severe cases (Kowalchik & Hylton, 1987; Betz et al., 1995).

Lethargic debility of the limbs, restlessness, chills and shivers, nausea, and vertigo may be caused by consuming tea prepared by adding 6 to 10 teaspoons of shaved yohimbe bark to 1 pint boiling water (Duke, 1985).

A number of precautions have been suggested regarding the use of yohimbine. It should never be taken at the same time as foods or substances containing the amino acid tyramine. Liver, cheese, and red wine are rich in tyramine, as are certain diet aids and decongestants. Yohimbine is contraindicated for anyone with hypotension; diabetes; heart, liver, or kidney disease, and nervous disorders, especially schizophrenia (Kowalchik & Hylton, 1987).

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Animal Data: No 2-year carcinogenicity studies of yohimbe bark extract and yohimbine were identified in the available literature.

LD_{50} values for yohimbine and yohimbine hydrochloride are listed in Table 1. No further information on the toxicity of yohimbe bark extract or yohimbine was found in the available literature (Kowalchik & Hylton, 1987).

Table 1. LD_{50} (mg/kg) values for yohimbine and yohimbine hydrochloride (NLM, 1999)

Species (route)	Yohimbine / Yohimbine hydrochloride (mg/kg)
Mouse	
(intraperitoneal)	16 / 45
(subcutaneous)	37 / 44
(oral)	43 / 40
Rat	
(intraperitoneal)	- / 55
Frog	
(subcutaneous)	- / 34
(parenteral)	- / 26
Guinea pig	
(intraperitoneal)	- / 42

Short-Term Tests: No information on mutagenicity was found in the available literature.

Metabolism: Owen and coworkers (1987) examined the distribution of yohimbine in eight young male subjects following a single oral dose of 10 mg yohimbine hydrochloride. The drug was rapidly absorbed (absorption half-time 0.17±0.11 h) and rapidly eliminated from the plasma (elimination half-life 0.60±0.26 h). Plasma concentrations were monitored over 2-3

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orders of magnitude and a elimination profile characteristic of a slowly equilibrating peripheral compartment was not observed, suggesting that distribution into a second pharmacokinetically distinct compartment was not responsible for the rapid decline in plasma yohimbine levels. In the 24 hours following administration, virtually no yohimbine was eliminated in the urine (0.35±0.50% of the administrated dose). Furthermore, only 20 percent of the yohimbine in the blood was located in red blood cells. The authors suggested that yohimbine is eliminated primarily through metabolism since rapid plasma clearance of yohimbine was not the result of renal elimination or sequestration by red blood cells.

Ho and coworkers (1971) investigated the distribution and metabolism of tritiated yohimbine in Swiss-Webster mice following intraperitoneal injections. Yohimbine was readily absorbed, widely distributed, and retained in tissue for some time before being metabolized and excreted. At both 10-minute and 45-minute periods, between 54 and 95 percent of the total radioactive material present in the central nervous system (CNS), heart, liver, and spleen was accounted for by tritiated yohimbine. Yohimbine rapidly penetrated the blood-brain barrier and a substantial quantity (17%) was retained in the CNS six hours after administration. The authors estimated the half life of yohimbine in the brain to be 3 hours.

The metabolic breakdown of yohimbine was found to be very rapid. Ten minutes after administration, no yohimbine but large amounts of metabolites including yohimbinic acid were found in the intestine. In the liver and kidney, 40 and 60 percent of the total tritated material was in the form of metabolites. The authors suggested that the major metabolic pathway for yohimbine was hydrolysis of the ester linkage by non-specific esterases present in the intestine. Furthermore, the reappearance of yohimbine in the intestine at 45 minutes (63%) and 90 minutes (73%) probably reflected the release of the drug from other tissues, whereas its relative absence thereafter reflected the observed presence during this period of drug metabolites. The liver had the highest count of total radioactivity at 30 minutes

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and 90 minutes, and was the only organ that retained yohimbine (6%) after 24 hours (Ho *et al.*, 1971).

Other Biological Effects: *Human studies*. Several studies have examined the effectiveness of yohimbine as a treatment for male impotence.

Kunelius and coworkers (1997) conducted a prospective, double blind, randomized, placebo-controlled study to determine the effectiveness and safety of yohimbine for treatment of patients with mixed-type impotence. Twenty-nine patients received either a placebo or yohimbine hydrochloride (36 mg per day orally). The treatment consisted of two 25 day courses; after a 14 day washout period, the patients who initially received the placebo for 25 days were switched to yohimbine hydrochloride for 25 days. Erectile function, ejaculation, interest in sex, physical examination findings, blood pressure, pulse rate, weight, and audiovisual sexual stimulation test were investigated before treatment and at the end of each drug period. Twenty seven patients (93%) completed the entire schedule. Positive clinical results were obtained in 12 cases (44%) at the end of the yohimbine phase and in 13 (48%) after the placebo period. No statistical difference was indicated. Drug-related adverse effects occurred in 2 patients in the yohimbine group (7%). The authors concluded that yohimbine was no better than the placebo as a first-line treatment for mixed-type impotence.

Animal studies. Clark and coworkers (1984) injected thirty sexually vigorous male Long-Evans rats intraperitoneally with yohimbine or vehicle (2 mg/kg body weight). Twenty minutes later they were anesthetized in the genital area and subjected to mounting tests. The rats injected with yohimbine exhibited about twice as much mounting behavior in the 15 minute test period as did the controls. No evidence of seminal emission was observed. The authors noted that yohimbine appeared to be a potent stimulator of sexual arousal in the intact, sexually vigorous male rat in the absence of feedback from the genitalia.

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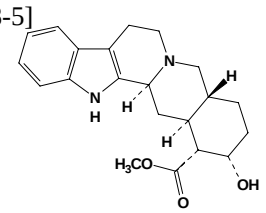
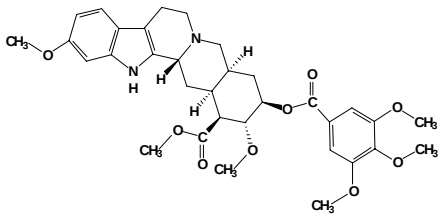
Structure Activity Relationships: Reserpine, a chemical structurally similar to yohimbine was screened for relevant information on mutagenicity, genotoxicity, and carcinogenicity. A summary of the information found in the available literature is presented in Table 2. Reserpine, administered orally, increased the incidence of adrenal medullary pheochromocytomas in male rats, mammary adenocarcinomas in female mice and undifferentiated carcinomas of the seminal vesicles in male mice. When administered by subcutaneous injection, reserpine slightly increased adrenal pheochromocytomas in rats and mammary neoplasms in mice. An International Agency for Research on Cancer (IARC) Working Group reported that there were no adequate data available to evaluate the carcinogenicity of reserpine in humans (Bhat *et al.*, 1995; IARC, 1987; NTP, 1999a).

Table 2. Summary of information on yohimbine and related compounds

Chemical Name	Carcinogenicity data	Mutagenicity Data
Yohimbine [146-48-5] 	NDF	NDF
Reserpine  [50-55-5]	Positive in 2-year oral study in male and female B6C3F1 mice and male F344 rats (NTP, 1980; NTP, 1999b)	Positive for CA (NTP, 1999b) Sex chromosome loss and non-disjunction in *S. cerevisiae* (NTP, 1999b) Negative for CA and SCEs in Chinese hamster ovary cells (NTP, 1999b) Negative in mouse lymphoma (NTP, 1999b) Negative in micronucleus test (NTP, 1999b) Negative in *S. typhimurium* (NTP, 1999b)

NDF = No data found; CA = chromosome aberrations; SCE = sister chromatid exchanges

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