Ephedra

Ephedra sinica Stapf
[Fam. *Ephedraceae*]

Overview

EDITOR'S NOTE: In an attempt to clarify the controversy surrounding the safety of ephedra, the following monograph devotes additional space to some of the safety, legal, and regulatory issues. These comments have been condensed for this clinical overview.

In Asian medicine, ephedra is the chief herbal drug for treatment of asthma and bronchitis. This herb is one of the oldest and most widely used Chinese herbs, having been employed for thousands of years in traditional Chinese medicine (TCM) as a primary component of multi-herb formulas prescribed to treat bronchial asthma, cold and flu, cough and wheezing, fever, chills, lack of perspiration, headache, and nasal congestion. Ephedra became controversial in the 1980s and 1990s due to its potential adverse effects and its increasing popularity as a major ingredient in herbal dietary supplements in the United States. As a result, in June 1997, the FDA issued proposed regulations on ephedra-containing dietary supplements that would limit the level of total ephedra alkaloids in herbal preparations to no more than 8 mg per dose, and no more than 24 mg total ingestion per day. However, the U.S. General Accounting Office (GAO) questioned the reliability of many of the adverse event reports (AER's) and criticized the apparent lack of science employed in formulating the proposed dosage limits of alkaloids. In February 2000, the FDA responded to GAO by announcing that it would withdraw portions of its proposed rules on duration of use and dosage levels. In August 2000, the Office of Women's Health (OWH) of the U.S. Department of Health and Human Services (HHS) held a two-day public hearing on the safety of ephedra in which testimony was presented by various scientific and medical experts who had conducted extensive reviews of the scientific and clinical literature on ephedra, as well as some who had conducted clinical investigations into the potential risks and benefits of ephedra for weight loss. That same panel also conducted the first comparison of incident rates of the adverse events at issue (e.g., stroke, heart attack, and seizure) in the general population and incident rates of the same events in ephedra consumers. The conclusion of the expert panel was that the analysis suggests that there was no evidence of increased risk, even using the most conservative of assumptions. In September 2000, the OWH issued a report recommending that additional research be conducted. Additionally, recent clinical research suggests that ephedra, in combination with other herbs, can be used safely in persons with normal blood pressure levels. Peer-reviewed scientific literature suggests that the risks of caffeine combined with ephedrine are outweighed by the benefits of achieving and maintaining a healthy weight. Further confirmation of that conclusion for herbal products containing caffeine and ephedrine awaits additional controlled clinical trials. Additional research into the use of ephedra as a weight loss aid appears to be warranted. In June 2002, the Secretary of HHS called for more research on ephedra to determine its safety and efficacy. Various athletic organizations have banned the use of ephedra supplements and ephedrine alkaloid-containing over-the-counter (OTC) drugs. Medical groups have stated that these items should be available by prescription only.

Primary Uses

- Mild bronchospasms in adults and children over the age of six (per approval in Germany)
- Bronchodilator in treatment of bronchial asthma
- Nasal congestion due to hay fever, allergic rhinitis, acute coryza (rhinitis), common cold, sinusitis
- Weight loss and thermogenesis

Pharmacological Actions

Ephedrine and related alkaloids produce sympathomimetic effects, including vasoconstriction; increased heart rate; and stimulation of central nervous system. Ephedrine decreases gastric emptying, possibly contributing to reduction of food intake. Ephedra herb preparations are shown to produce dilated bronchi, and induce perspiration (diaphoretic), and diuresis (diuretic). Ephedra-caffeine herb combinations are shown to increase thermogenesis and weight loss in obese patients.

Dosage and Administration

According to the German Commission E, ephedra preparations should only be used short-term because of tachyphylaxis and potential addiction. However, a recent analysis of available U.S. health and safety data showed no evidence of significant abuse or addiction to ephedra, despite decades of widespread use.

Crude Preparations

NOTE: According to U.S. herb industry labeling policy, the maximum adult daily dose for ephedra and ephedra-containing products is 100 mg total alkaloids.

DECOCTION: 1–6 g dried herb daily.

CHINESE PHARMACOPEIA DOSAGE: 1.5–9 g dried herb daily.

DRIED COMMINUTED HERB (for Commission E approved bronchial indications):

ADULT SINGLE DOSE: 15–30 mg total alkaloid, calculated as ephedrine.

DRIED COMMINUTED HERB (for Commission E approved bronchial indications) (cont.):

ADULT MAXIMUM DAILY DOSE: corresponding to 300 mg total alkaloid calculated as ephedrine.

CHILD SINGLE DOSE (over age 6): corresponding to 0.5 mg total alkaloid per kg of body weight.

CHILD MAXIMUM DAILY DOSE (over age 6): 2 mg total alkaloid per kg of body weight.

[NOTE: These children's dosages are based on the recommendations for licensed preparations for the approved bronchial indication in Germany only. Ephedra supplements in the U.S. are not recommended for children under the age of 18, according to industry labeling policy.]

FLUID EXTRACT: 1:1 (*g/ml*), 45% alcohol, 1–3 ml daily.

TINCTURE: 1:4 (*g/ml*), 45% alcohol, 6–8 ml daily. Maximum weekly dose: 48 ml.

NO OBSERVED ADVERSE EFFECT LEVEL BASED ON THE CANTOX TOXICOLOGICAL REVIEW: ephedra preparations equivalent to 30 mg total alkaloids per dose; 90 mg per day.

Purified alkaloids (i.e., OTC drugs)

For bronchodilation the maximum adult daily dose of ephedrine (or ephedrine hydrochloride) is 150 mg per day, and the maximum adult daily dose of pseudoephedrine (or pseudoephedrine hydrochloride) is 240 mg per day.

CONTRAINDICATIONS

Anxiety and restlessness, hypertension, glaucoma, impaired cerebral circulation, adenoma of prostate with residual urine accumulation, pheochromocytoma, thyrotoxicosis, pregnancy, anorexia, diabetes, heart disease, insomnia, stomach ulcers, children, renal failure. Patients with the following conditions or symptoms should consult a healthcare provider before using ephedra: difficulty urinating, prostate enlargement, thyroid disease, depression or other psychiatric condition, or if using a monoamine oxidase (MAO) inhibitor, any other prescription drug, or an OTC drug containing ephedrine, pseudoephedrine or phenylpropanolamine (PPA) (ingredients found in certain allergy, asthma, cough/cold, and weight control products). (PPA has been removed from the OTC market, but consumers might still possess older PPA-containing drug products.) Exceeding recommended dosage will not improve therapeutic benefits and may cause serious adverse health effects. Patients should discontinue use and call a health care professional immediately if they experience rapid heartbeat, dizziness, severe headache, shortness of breath, or other similar symptoms.

PREGNANCY AND LACTATION: Ephedra is not recommended for use during pregnancy or lactation.

ADVERSE EFFECTS

Insomnia, motor restlessness, irritability, headaches, nausea, vomiting, disturbances of urination, tachycardia; higher dosages (greater than the equivalent of 300 mg ephedra alkaloids per day) may produce a drastic increase in blood pressure, cardiac arrhythmia, and development of dependency. Isolated reports of adverse events, some serious, including stroke and death, have been received by the FDA. One highly publicized review of selected events reported to the FDA concluded that the adverse event reports (AERs) do not establish causality and cannot be used to quantify risk. Recent evidence submitted to the FDA shows no association between clinically significant adverse events and doses of under 100 mg of ephedra alkaloids per day.

An epidemiological analysis of the AERs showed no greater incidence of seizures, strokes, and myocardial infarctions (MIs) in persons consuming dietary supplements containing ephedrine alkaloids than that expected in the general U.S. population. In addition, the FDA advises that AERs alone do not provide a scientific basis for assessing the safety of dietary supplements containing ephedrine alkaloids.

DRUG INTERACTIONS

Actual or potential interactions may occur between orally ingested ephedrine alkaloids (mainly ephedrine and/or pseudoephedrine and not necessarily the herb ephedra itself) and:

ANTIHYPERTENSIVES (including ACE inhibitors and beta-blockers): May result in severe hypertension.

CARDIAC GLYCOSIDES OR HALOTHANE: Disturbs heart rhythm.

CORTICOSTEROIDS: Increase the clearance of dexamethasone, therefore decreasing its activity.

GUANETHIDINE: Antagonizes the hypotensive effect.

MAO-INHIBITORS (including tranylcypromine, pargyline, procarbazine, selegiline, phenelzine, and moclobemide): Significantly raise the sympathomimetic action of ephedrine.

METHYL XANTHINES (e.g., caffeine, theophylline): Increase thermogenesis and weight loss due to reduction in body fat when ephedrine is combined with xanthines, plus causes excessive nervous stimulation.

SECALE ALKALOID DERIVATIVES OR OXYTOCIN: May lead to hypertension.

URINARY ALKALIZERS (e.g., acetazolamide, sodium bicarbonate): Excrete more slowly (than with urinary acidifiers, e.g., ammonium chloride), due to effects of reabsorption from tubules in the kidneys.

CLINICAL REVIEW

There is one published clinical trial based on ephedra as a single ingredient. Most ephedra trials tested multi-ingredient formulations that include a caffeine-containing herb such as cola nut or guarana. At least 3 such trials on ephedra combination preparations suggest safe and effective use for weight loss. Several unpublished trials employed 4 different ephedra products (ephedra only, not combinations) on 300 subjects over a period of 6 weeks and 6 months to monitor weight loss and adverse effects, respectively. The studies concluded that ephedra appears to be safe, effective, and cost effective, and compares favorably with pharmaceutical weight loss agents, with a relatively low side effect profile. Ephedrine and caffeine combinations and a much-publicized Danish formula of ephedrine combined with caffeine and aspirin have demonstrated relative safety and efficacy in weight loss in clinical trials.

Ephedra

Ephedra sinica Stapf
[Fam. *Ephedraceae*]

Description

For thousands of years in Traditional Chinese Medicine, ephedra (*ma huang* in Chinese) has been a primary ingredient in formulas used to treat bronchial asthma, cold, flu, wheezing, fever, and chills. In the 1980s and 1990s ephedra became controversial because of its possible adverse effects and its growing popularity as a major ingredient in herbal dietary supplements in the U.S. The FDA has attempted to amend regulations since that time in an effort to reduce potential risk and misuse of this herb. Recent research and expert reviews have raised questions about how to evaluate the potential risks of ephedra use. Nevertheless, further research is warranted to assess the use of ephedra as a weight loss aid. In June 2002, the U.S. Department of Health and Human Services announced it would sponsor more research on ephedra's safety and efficacy.

Uses

Mild bronchospasms in adults; asthma (bronchodilator); nasal congestion due to hay fever, allergic nasal inflammation, common cold, or sinusitis; weight loss; thermogenesis (burning of fatty tissue).

Dosage

NOTE: According to U.S. herb industry labeling policy, the maximum adult daily dose for ephedra and ephedra-containing products is 100 mg total alkaloids, while a safety review recommended a slightly lower dose of 90 mg total alkaloids per day.

Crude Preparations

DECOCTION (TEA): 1–9 g daily.

Purified alkaloids (i.e., OTC drugs)

For bronchodilation the maximum adult daily dose: 150 mg/day ephedrine; 240 mg/day pseudoephedrine

Contraindications

Ephedra and products containing it should be avoided in cases of anxiety and restlessness, high blood pressure, glaucoma, reduced circulation to the brain, benign tumor of the prostate with residual urine accumulation, pheochromocytoma (a usually benign tumor that frequently produces high blood pressure), hyperthyroidism (over-active thyroid), pregnancy, anorexia, diabetes, heart disease, insomnia, stomach ulcers, kidney failure, and in children. Patients with the following should consult a healthcare provider before using ephedra: difficulty urinating, prostate enlargement, thyroid disease, depression or other psychiatric condition, or if using a monoamine oxidase (MAO) inhibitor drug, any other prescription or over-the-counter (OTC) drug containing ephedrine, pseudoephedrine, or phenylpropanolamine (PPA) (ingredients found in certain allergy, asthma, cough/cold, and weight control products). (PPA has been removed from the OTC market.) Exceeding recommended dosage will not improve therapeutic benefits and may cause serious adverse health effects. Patients should discontinue use and call a health professional immediately if they experience rapid heartbeat, dizziness, severe headache, shortness of breath, or other similar symptoms.

PREGNANCY AND LACTATION: Not recommended for use during pregnancy or lactation.

Adverse Effects

Adverse effects include insomnia, motor restlessness, irritability, headaches, nausea, vomiting, disturbances of urination, rapid heart beat. Higher dosages (more than 300 mg of ephedra alkaloids per day) may produce drastic increase in blood pressure and cardiac arrhythmia. There are reports of serious adverse events, including stroke and death. However, FDA advises that adverse events reports cannot be used alone to scientifically determine the overall safety of ephedra.

Drug Interactions

The herb ephedra and/or its alkaloids (e.g., ephedrine, pseudoephedrine) may cause a disturbance of heart rhythm when combined with cardiac glycoside drugs, or halothane; may increase stimulation of the nervous system when combined with MAO inhibitors; may reduce the blood pressure-lowering effect of guanethidine; may lead to hypertension when combined with secale alkaloid derivatives, or oxytocin; when combined with corticosteroids, may increase their effects. Patients should discuss the potential use of ephedra or ephedrine-containing alkaloid OTC drugs with their healthcare provider or pharmacist before using these products with any medicines.

Comments

When using a dietary supplement, purchase it from a reliable source. For best results, use the same brand of product throughout the period of use. As with all medications and dietary supplements, please inform your healthcare provider of all herbs and medications you are taking. Interactions may occur between medications and herbs or even among different herbs when taken at the same time. Treat your herbal supplement with care by taking it as directed, storing it as advised on the label, and keeping it out of the reach of children and pets. Consult your healthcare provider with any questions.

Ephedra

***Ephedra sinica* Stapf**

[Fam. *Ephedraceae*]

Overview

EDITORS' NOTE: In an attempt to clarify the controversy surrounding the safety of ephedra, this monograph devotes additional space to some of the safety, legal, and regulatory issues. Thus, the "Overview" section is longer for ephedra than for other monographs in this publication.

In Asian medicine, ephedra (known in Chinese as *ma huang*) is the primary herbal drug for treatment of asthma and bronchitis. This herb is one of the oldest and most widely used Chinese herbs, having been employed for thousands of years in traditional Chinese medicine (TCM) as a primary component of multi-herb formulas prescribed to treat bronchial asthma, cold and flu, cough and wheezing, fever, chills, lack of perspiration, headache, and nasal congestion. Listed in the oldest comprehensive materia medica, *Shen Nong Ben Cao Jing* (ca. 100 C.E.), among the "middle class" herbs, ephedra is used to induce perspiration, and as an anti-allergy agent (Blumenthal and King, 1995; Bruneton, 1995; Der Marderosian, 1999; Huang, 1999; Leung and Foster, 1996; Weiss, 1988). Presently, ephedra is official in the national pharmacopeias of China, Germany, and Japan, while the isolated or synthesized alkaloids from the plant, primarily ephedrine and pseudoephedrine, are official in most countries.

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Ephedra-containing dietary supplements have become increasingly popular in the past two decades as agents to help promote weight loss and athletic performance. A recent survey has suggested that 7% of the American adult population uses nonprescription drugs for weight loss, 2% using phenylpropanolamine (PPA) (no longer sold over-the-counter), and 1% using products containing ephedra (Blanck *et al.*, 2001). In a survey on herb use in the Minneapolis metro area, 230 people (61.2% of responders) said they had used herbs in the past 12 months; with 13.6% responding that they had used herbs for weight loss. Forty-four (12.0%) said they used ephedra for a variety of reasons: 23 to boost energy; 20 for weight loss; 10 as a decongestant; 7 for asthma. Over half rated the ephedra effective or very effective (Harnack *et al.,* 2001).

Discussions of the safety and effectiveness of the herb ephedra are usually based on scientific research conducted on the isolated (sometimes synthesized) alkaloids in the herb (i.e., ephedrine and pseudoephedrine or their related isomers; see Chemistry section below). Both are approved by the U.S. Food and Drug Administration (FDA) as safe and effective over-the-counter (OTC) drug ingredients. Most of the scientific literature to date focuses on these alkaloids. Due to the popularity of the herb there is an increasing number of clinical studies being conducted on the herb itself, often in combination with other herbs. This review focuses on the herb itself, with reference to research on ephedrine and pseudoephedrine in the Pharmacology and Mechanisms sections, and others, as necessary.

The safety and the appropriate regulation of ephedra arose as controversial issues in the U. S. during the 1980–90's when the herb began to be used as a major ingredient in herbal dietary supplements intended to aid weight loss and exercise. Some products that were subsequently determined to be adulterated with synthetic ephedrine (e.g., Formula One®) or marketed as purportedly legal substitutes for the illicit drug Ecstasy (e.g., Herbal Ecstacy® and Ultimate Xphoria®) raised significant concerns among various state health authorities, health professionals, and responsible members of the herb and dietary supplement industry (Blumenthal and King, 1996). In 1994, increasing concerns about potential risks associated with the use of ephedra herbal products prompted the American Herbal Products Association (AHPA) and the National Nutritional Foods Association (NNFA) to issue a labeling policy for its member companies to set serving and daily intake limits as well as list contraindications for the herb on labels of ephedra-containing products (see Contraindications section below) (AHPA, 1994).

Health professionals also became increasingly concerned about the public health implications of ephedra and ephedra alkaloid-containing products, and several groups passed resolutions supporting the restriction of ephedra alkaloid-containing products. In May 1995 the Texas Medical Association (TMA) adopted a policy that ephedrine and ephedrine alkaloids should be prohibited from non-prescription foods, dietary supplements, or other OTC commercial products intended for public consumption, and that such products be made available by prescription only. In November 1998, TMA also proposed that such products be labeled to declare the amount of active ingredients of the substances with pharmacologic properties and that the products have accurate warning labels (TMA, n.d.). The American Medical Association (AMA) has adopted a similar policy (AMA, 2002, 2000).

In 1996, the Ohio legislature passed a law, supported by industry dietary supplement organizations, to appropriately regulate

these products. Since that time, laws regulating ephedra that incorporate the AHPA and NNFA standards for formulation and labeling have been passed in Hawaii, Michigan, Washington, Oklahoma, and Nebraska.

In June 1997, the FDA issued proposed regulations on ephedra-containing dietary supplements that would limit the level of total ephedra alkaloids in herbal preparations to no more than 8 mg per dose, with no more than 24 mg per day (FDA, 1997). The proposal would have banned the combination of ephedra with other stimulants like caffeine or caffeine-containing herbs (including cola [*Cola nitida*], guarana [*Paullinia cupana* var. *sorbilis*], maté [*Ilex paraguariensis*]) in herbal products; would have prohibited the sale of ephedra products for use in weight loss or for athletic performance; would have restricted use of ephedra-containing herbal products to no more than seven days duration; and would have required warnings on all labels for products containing ephedra. The proposal also called for the ban of so called "street drug knockoffs" containing the herb ephedra or ephedrine alkaloids, to be used as replacements for illicit drugs; such copies of drugs are illegal under federal law. The proposed rule was based primarily on approximately 800 adverse event reports (AERs) submitted to FDA. Industry, scientific and medical experts, and many consumers criticized the proposed rule, often noting that the AERs were not a valid scientific basis for rulemaking, as was established by the FDA's own policies.

As a result of this criticism, Congress requested that the U.S. General Accounting Office (GAO), the government agency that monitors accountability of all federal agencies, conduct an audit of the scientific basis for FDA's proposed serving and daily intake limits, the proposed duration of use limit (seven days), including the ban on claims for weight loss and exercise, and FDA's cost/benefit analysis for the proposed rule. In August 1999, the GAO issued a 68-page report, *Dietary Supplements: Uncertainties in Analyses Underlying FDA's Proposed Rule on Ephedrine Alkaloids* (GAO, 1999). The report reveals deficiencies in the FDA's proposed rule on ephedra. GAO acknowledged that the AERs the FDA had received for ephedra raised concerns that warranted examination. At the same time, GAO questioned the reliability of many of the AERs and criticized the apparent lack of science employed in formulating the proposed dosage limits of alkaloids, the proposed duration limits, and ban on weight loss and exercise claims. As a result of this and other significant deficiencies, including a failure to establish that the proposed rule would have a public health benefit, the GAO recommended that the FDA not finalize the proposed rule unless it could develop a valid scientific basis and meet other requirements applicable to federal rulemaking.

In March 2000, the FDA responded to the GAO by withdrawing portions of its proposed rule on duration of use (including prohibitions against marketing ephedra for weight loss and exercise) and dosage levels. FDA simultaneously made public additional AERs on ephedra received since the publication of the June 1997 proposed rule, as well as reviews of those AERs by the FDA and outside consultants (FDA, 2000).

In August, the Office of Women's Health (OWH) of the U.S. Department of Health and Human Services (HHS) held a two-day public hearing on the safety of ephedra in which testimony was presented by various scientific and medical experts who had conducted extensive reviews of the scientific and clinical literature on ephedra, as well as some who had conducted clinical investigations into the safety and benefits of ephedra for weight loss. At the OWH hearing, the Ephedra Education Council (EEC, an industry group) presented the consensus views of a seven-member panel comprised of experts from various medical and scientific disciplines who concluded, based on reviews of both the published literature and the entire public record of more than 1,000 AERs submitted to the FDA, that there was no evidence of an association between ephedra and significant adverse events at the intake levels established by the AHPA's 1994 standards and subsequently adopted as law by several states. The panel's multi-disciplinary review of the AERs, which was subsequently submitted to the FDA as public comment, was critical of reviews performed by FDA consultants, one of which was subsequently published (Haller and Benowitz, 2000). One member of the EEC panel also conducted the first comparison of incident rates of the adverse events at issue (e.g., stroke, heart attack, and seizure) in the general population and incident rates of the same events in ephedra consumers. His conclusion was that the analysis suggests that there was no evidence of increased risk, even using the most conservative of assumptions (Kimmel, 2000). In September 2000 the OWH issued a report recommending that additional research be conducted (OWH, 2000).

The FDA's review of 140 AERs, reportedly associated with the ingestion of ephedra-containing dietary supplements, from the FDA's MedWatch program concluded that 43 (31%) of the AERs were "definitely" or "probably" associated with ephedra use (Haller and Benowitz, 2000). In response to a critical letter to the editor (Hutchins, 2001) the authors cautioned that their report "does not prove causation, nor does it provide quantitative information with regard to risk" (Hutchins, 2001). A subsequent evaluation concluded: "These reports, while possibly associating the use of herbal dietary supplements containing ephedra with side effects, do not in any way prove a causative relationship between herbal use and these problems. On the other hand, controlled studies of supplements containing ephedra provide considerable evidence of efficacy in weight loss and weight maintenance." (Heber and Greenway, 2002).

There have been several attempts to put the number of ephedra-related AERs and ephedra-using consumers into perspective, but there are no accurate or reliable data on how many consumers are using ephedra, how many doses have been consumed, or how many AERs are directly related to ephedra consumption. According to a survey by AHPA of 14 companies that manufactured and marketed ephedra-containing supplements there was a 700% increase in sales in ephedra-containing supplements in five years from 1995 to 1999, representing 425 million "servings" sold in 1995 rising to an estimated 3 billion servings in 1999, with total estimated sales of ephedra supplements equaling 6.8 billion servings (McGuffin, 2000). (Technically, dietary supplements are considered foods, not drugs, under federal law, and thus what would normally be considered a "unit dose" by a pharmacist or physician must be referred to in food language by members of the herb and supplement industries, hence the term "serving.") A total of 66 serious adverse events were reported to these 14 responding companies over the 5-year period from 1995 to 1999. Based on the estimate of more than 6.8 billion servings sold in the same 5-year period, these AERs represent a reporting rate of less than 10 such reports per billion servings sold. According to the survey, these sales statistics, based on a large but not total segment of ephedra manufacturers, show that although the reported sales of supplements containing ephedrine alkaloids has increased more than seven-fold in the past 5 years, there has been no commensurate increase of adverse events gathered by FDA (McGuffin, 2000).

In October 2000, a group of industry trade associations petitioned the FDA to accept proposed limits of 100 mg ephedra alkaloids per day and a proposed warning label (AHPA *et al.,* 2000). In December 2000, Cantox Health Sciences International (CHSI), an independent Canadian research organization, concluded, on the basis of a quantitative method developed by the National Academy of Sciences, that 90 mg per day is a safe upper limit for the ingestion of ephedra alkaloids in normal, healthy individuals and that the lowest observed adverse effect level (LOAEL) is 150 mg per day (CHSI, 2000; Hathcock, 2001). The safety assessment was based on a review of all available clinical studies on the alkaloid ephedrine and the herb ephedra, plus pharmacological and other relevant studies. CHSI also reviewed the FDA's AER database but concluded that due to insufficient and inconsistent clinical data, these reports were not useful for assessing product safety. (The Council for Responsible Nutrition, a Washington, D.C.-based trade association of dietary supplement manufacturers and suppliers, commissioned the review.)

Some experts have suggested that the relative safety and potential benefits of ephedra-containing dietary supplements should be viewed within the broader public health context of the prevalence of obesity in America. In December 2001, the U.S. Surgeon General David Satcher, M.D. estimated that 300,000 Americans die each year from illnesses caused or exacerbated by obesity (Anon., 2001b). Satcher said that 62% of Americans are either overweight or obese, compared to 48% in 1980 (Anon., 2001a). A comprehensive review article of the scientific and medical literature of caffeine and ephedrine combinations in the treatment of obesity (Greenway, 2001) summed up the situation:

> Overweight and obesity are common problems affecting more than half the population, yet obesity is stigmatized by society. Therefore, it is not surprising that an effective weight loss product containing compounds with a long history of safe non-prescription use would be embraced enthusiastically by the public. When large numbers of the public are using any product, adverse events will inevitably occur, but the cause and effect relationship of these adverse events to the product use are usually unclear. Obesity is a disease that predisposes to diabetes, hypertension, and cardiovascular disease. These increased risks are reversed with weight loss. The peer-reviewed scientific literature suggests that the risks of caffeine and ephedrine are outweighed by the benefits of achieving and maintaining a healthy weight. Confirmation of that conclusion for herbal products containing caffeine and ephedrine awaits controlled clinical trials.

Recent clinical research, published after the Greenway (2001) review, suggests that ephedra, in combination with other herbs, produces significant weight loss with no clinically significant adverse effects in the study participants, and with small impact on blood pressure or heart rate (Boozer *et al.,* 2002; de Jonge *et al.*, 2001) and safety (Belfie *et al.*, 2001). Based on these findings, additional research into the use of ephedra as a weight loss aid appears to be warranted. In June 2002, the Secretary of HHS called for more research on ephedra to determine its safety and efficacy (HHS, 2002). Supporters and some prominent critics of ephedra agree that scientific reviews of the cases of the AERs on ephedra do not establish causality, thereby making additional clinical research the key to developing regulatory policy.

Description

Ephedra consists of the dried, young branchlets, harvested in the fall, of *Ephedra sinica* Stapf [Fam. *Ephedraceae*] or other equivalent *Ephedra* species (Blumenthal *et al.,* 1998; DAB, 1999), including *E. intermedia* Schrenk ex C.A. Mey. and *E. equisetina* Bunge (syn. *E. shennungiana* Tang) (PPRC, 1997). The Japanese Pharmacopeia requires that it contain not less than 0.6% total alkaloids, calculated as ephedrine (JSHM, 1993). The *Pharmacopoeia of the People's Republic of China* requires not less than 0.8% (PPRC, 1997), and the *German Pharmacopoeia* requires not less than 1% (DAB, 1999).

Primary Uses

Respiratory System

- Mild bronchospasms in adults and children over the age of six (Blumenthal *et al.,*1998)
- Bronchodilator in treatment of bronchial asthma (WHO, 1999)

Ear Nose and Throat

- Nasal congestion due to hay fever, allergic rhinitis, acute coryza (rhinitis), common cold, sinusitis (WHO, 1999)

Obesity/Weight Management

- Increased weight loss and thermogenesis (Boozer *et al.,* 2002, 2001; Belfie *et al.*, 2001; de Jonge *et al.*, 2001; Greenway, 2001; Liu *et al.,* 1995; Astrup *et al.,* 1986; Pasquali *et al.,* 1985)

Other Potential Uses

- Uses in Traditional Chinese Medicine (TCM) include common cold marked by chilliness and mild fever, headache, stuffed and running nose, general aching, but no sweating; edema in acute nephritis; bronchial asthma (PPRC, 1997).
- Ephedra dietary supplements are frequently used by athletes as performance enhancing agents (This use is highly controversial and has been the subject of numerous athletic groups' attempts to ban or restrict dietary supplements containing ephedra for this application.) (IOC, 2001; Anon., 2001c; NCAA, 2001)

Dosage

Internal

Crude Preparations

NOTE: According to U.S. herb industry labeling policy, the maximum adult daily dose for ephedra and ephedra-containing products is 100 mg total alkaloids (AHPA, 2002).

DECOCTION: 1–6 g dried herb daily (WHO, 1999), 1.5–9 g dried herb daily (PPRC, 1997). NOTE: The yield of alkaloids is higher with hot water decoction than with extraction with ethanol and/or methanol (Noguchi *et al.,* 1978). In a decoction made with ephedra containing a range of a minimum of 0.8% alkaloids (according to the *Pharmacopoeia of the People's Republic of China*, PPRC) to 1.0% (according to the *German Pharmacopoeia*), the estimated range of alkaloids based on the WHO daily dosage range would be 8–60 mg and the range based on the PPRC dosage would be 12–90 mg.

DRIED COMMINUTED HERB (According to the German Commission E for approved bronchial indications): the adult single dose corresponds to 15–30 mg total alkaloid, calculated as ephedrine. The adult maximum daily dose corresponds to 300 mg total alkaloid calculated as ephedrine. For a child (over

age 6) a single dose corresponds to 0.5 mg total alkaloid per kg of body weight. A child's maximum daily dose is 2 mg total alkaloid per kg of body weight (Blumenthal *et al.,* 1998). [NOTE: This children's dosage is based on the recommendation for licensed preparations for the approved bronchial indication in Germany only. Ephedra supplements in the U.S. are not recommended for children under the age of 18, according to industry labeling policy.]

FLUID EXTRACT: 1:1 (*g/ml*), 45% alcohol, 1–3 ml daily (WHO, 1999).

TINCTURE: 1:4 (*g/ml*), 45% alcohol, 6–8 ml daily (WHO, 1999). Maximum weekly dose: 48 ml (Denham, 1998).

NO OBSERVED ADVERSE EFFECT LEVEL BASED ON THE CANTOX TOXICOLOGICAL REVIEW: ephedra preparations equivalent to 30 mg total alkaloids per dose; 90 mg per day (CHSI, 2000).

Purified Ephedra Derivatives (i.e., OTC drugs):
For bronchodilation the maximum adult daily dose of ephedrine (or usually its salt form, ephedrine hydrochloride) is 150 mg per day (21 CFRa), and the maximum adult daily dose of pseudoephedrine (or its salt form pseudoephedrine hydrocholoride) is 240mg per day (21 CFRb). [NOTE: for comparison purposes, the maximum daily nonprescription oral dose of caffeine is 1,600 mg (Heber and Greenway, 2002).]

DURATION OF ADMINISTRATION

The Commission E monograph, published in 1991, recommended that ephedra preparations should be used only short-term because of tachyphylaxis and potential addiction. NOTE: A more recent analysis of the available U.S. health and safety data compiled by Edgar H. Adams, M.S., Sc.D., former director of the Division of Epidemiology and Statistical Analysis at the U.S. National Institute on Drug Abuse, indicates that there is no evidence of significant abuse of, or addiction to, ephedra despite decades of widespread use, concluding that any potential for addiction is low and does not rise to the level of regulatory concern that warrants scheduling (as is done with addictive narcotic drugs) (Adams, 2000). Nevertheless, as with other stimulant products that enhance athletic performance, products containing ephedra alkaloids are still banned by the International Olympic Committee for use by athletes competing in the Olympic games (IOC, 2001).

CHEMISTRY

The herb ephedra contains approximately 1.3% alkaloids composed mainly of ephedrine (up to 90%), pseudoephedrine, norephedrine, nor-pseudoephedrine, methylephedrine, and methylpseudoephedrine (Huang, 1999; Tang and Eisenbrand, 1992). These alkaloids are the primary active constituents. Other components include flavonoid glycosides; glycans (ephedrans); citric, malic, and oxalic acids; proanthocyanidins (condensed tannins); tannins and volatile oils (l-*a*-terpineol, limonene, and linalool) (Bruneton, 1995) but these compounds are not believed to exert much influence on the well established pharmacological effects of this herb.

PHARMACOLOGICAL ACTIONS

The pharmacological data cited below pertain to research conducted on the whole ephedra herb or its extracts, as well as to the isolated alkaloids ephedrine and pseudoephedrine, plus (as noted below) combinations of ephedrine and caffeine, or ephedrine and aspirin. Extensive clinical and pharmacological research has been conducted on ephedrine, usually its salt form, e.g. ephedrine hydrochloride (Astrup *et al.*, 1986; Tang and Eisenbrand, 1992), ephedrine and caffeine (Astrup *et al.*, 1991; Astrup *et al.*, 1992; Astrup and Toubro, 1993), and an ephedrine-caffeine-aspirin combination (Daly *et al.*, 1993). These results are probably directly relevant to the actions of the herb ephedra or its combinations with caffeine-containing herbs. One review on thermogenic agents states that the effects of ephedra and ephedrine are the same, except that ephedra is gentler and less likely to cause adverse effects, with the large body of scientific data on ephedrine being applicable to ephedra (Jones, 2001). A small clinical trial suggests similar pharmacokinetics between the ephedrine in ephedra and synthetic ephedrine (Gurley *et al.*, 1998). Research shows that ephedra alkaloids (e.g., ephedrine) from supplements containing ephedra *extracts* are absorbed more quickly than the alkaloids from preparations containing powdered ephedra herb, and thus products containing extracts probably exhibit absorption and disposition characteristics indistinguishable from those products containing isolated ephedra alkaloids (e.g., OTC drugs) (Gurley, 2000). For a detailed review of the clinical pharmacology of ephedrine, see Tang and Eisenbrand (1992), and for ephedrine combined with caffeine and/or aspirin, see Heber and Greenway (2002).

Human

- Ephedrine and related alkaloids produce sympathomimetic effects, including vasoconstriction, increased heart rate, and stimulation of central nervous system (Weiner, 1985).
- Ephedra herb preparations are shown to produce dilated bronchi (WHO, 1999), and induce perspiration (diaphoretic), and diuresis (diuretic) (PPRC, 1997).
- Increased thermogenesis and weight loss in obese patients (ephedra-caffeine herb combination) (Boozer *et al.*, 2002, 2001).
- Ephedrine stimulates brown adipose tissue (BAT) in rodents, but since humans possess relatively little BAT, ephedrine-induced thermogenesis happens mainly in skeletal muscle (Astrup, 1986).
- Ephedrine decreases gastric emptying, possibly contributing to reduction of food intake (Jonderko and Kucio, 1991).

An ephedrine-caffeine combination was found safe and effective in a pilot study on 32 obese adolescents, reducing weight more than 5% in 81% of the treatment group, compared to 31% in the placebo group (Molnar *et al.*, 2000).

An acute dose of a combination of ephedrine (30 mg) and aspirin (300 mg) produced greater post-prandial thermogenesis in 10 obese women for 160 minutes following a liquid meal than an acute dose of ephedrine (30 mg) alone. Aspirin alone did not produce this additional effect on thermogenesis in 10 lean women (Horton and Geissler, 1991) while ephedrine and aspirin normalized the post-prandial thermogenesis in obese women to levels equal to the lean (Geissler, 1993).

- Stimulation of central nervous system and cardiovascular parameters (i.e., increases in pulse rate, blood pressure, and serum glucose levels) have been documented when ephedrine and/or caffeine are given acutely either separately or together. According to a recent review of the peer reviewed literature, these side effects disappear with chronic use and are no longer present after 4 to 12 weeks, depending on the trial (Heber and Greenway, 2002).

There has been concern about the potential hypertensive effects of ephedra and its alkaloids. However, in one trial a proprietary ephedrine (20 mg) and caffeine (200 mg) preparation tested for its weight loss effects on 136 overweight normotensive or drug-controlled subjects with controlled hypertension, three doses of the product showed blood pressure-lowering effects over 6 weeks (Svendsen *et al.*, 1998). Systolic blood pressure was reduced 5.5 mm HG more in the controlled hypertensive subjects treated with the preparation than placebo in subjects treated with medication other than beta-blockers. The anti-hypertensive effect of the beta-blocker drug was not reduced by the caffeine-ephedrine combination. The normotensive patients treated with caffeine and ephedrine had a 4.4/3.9 mm HG greater drop in blood pressure than those treated with placebo. The mean loss of weight of 4 kg (8.8 lbs.) was significant for all groups.

- A recent review of ephedrine cites literature proposing it as an adjunct to cognitive restructuring and notes that ephedrine has been considered in reviews about non-prescription weight loss supplements, obesity management, energy balance, and obesity treatment (Heber and Greenway, 2002).

There has been recent concern about the use of dietary supplements containing the herb ephedra when used as performance enhancers in athletic activities. Although no studies are available on the herb ephedra in athletic performance, numerous clinical trials conducted at the Canadian Defence and Civil Institute of Environmental Medicine have measured the effects of ephedrine and caffeine combinations on exercise and related performance activities. These pilot studies have concluded that the combination of ephedrine (E) and caffeine (C), or ephedrine alone, produces the following effects in athletes or soldiers: (1) an improvement in anaerobic exercise performance is likely a result of both stimulation of the CNS by E and skeletal muscle by C (Bell *et al.* 2001); (2) although the metabolic rate in subjects was slightly increased with C+E treatment, it was sufficiently offset by increased heat loss mechanisms so that internal body temperature was not increased during moderate exercise in a hot, dry environment (Bell *et al.*, 1999a); (3) C+E improved performance of the Canadian Forces Warrior Test, a 3.2 km run wearing about 11 kg of battlefield uniform and equipment (Bell, Jacobs, 1999b); (4) C+E significantly prolonged exercise time to exhaustion compared to placebo, while neither C nor E treatments alone significantly changed time to exhaustion, the improved performance being attributed to increased CNS stimulation (Bell *et al.*, 1998); (5) the previously observed additive effects of C+E was not evident, with the primary ergogenic effect being attributed to E (Bell *et al.*, 2002); and (6) a lower dose (approx. 20% lower) of C+E than used previously resulted in an ergogenic effect similar in magnitude to that reported previously with a higher dose, and with a reduced incidence of negative side effects (vomiting and nausea) (Bell *et al.*, 2000).

Animal

- Ephedra herb prevents or relieves coughing and inhibits growth of bacteria in animal experiments, according to the Commission E (Blumenthal *et al.,* 1998);
- Ephedra stimulates the sympathetic nervous system in dogs (Huang, 1999), analogues of feruloyl-histamine, an alkaloid in ephedra *roots*, inhibit hypotension and histidine decarboxylase, is anti-ulcerous and anti-hepatoxic (Hikino *et al.,* 1984);
- Ephenadrines block ganglions (Hikino *et al.,* 1983);
- Pseudoephedrine relieves inflammation (Hikino *et al.,* 1980).

Mechanism of Action

All mechanistic data cited below pertain to isolated ephedra alkaloids.

- Ephedrine indirectly stimulates the sympathomimetic and central nervous systems (Blumenthal *et al.,* 1998). It has been shown to produce sympathomimetic effects (e.g., vasoconstriction and cardiac stimulation) by combining with α- and β-adrenergic receptors (WHO, 1999; Hardman *et al.,* 1996; Chang and But, 1986);
- The chemical structure of ephedrine resembles epinephrine (adrenaline) (Chang and But, 1986), though unlike epinephrine, it is completely absorbed from the intestine and has a much longer duration of action (Huang, 1999);
- Ephedrine triggers the release of endogenous catecholamines from post-ganglionic sympathetic fibers (Bruneton, 1995);
- Ephedrine relaxes bronchial muscles and acts as a bronchodilator by activating the β-adrenoceptors in the lungs (Weiner, 1985; Hardman *et al.,* 1996);
- Both ephedrine and pseudoephedrine inhibit norepinephrine uptake by nervous and nonnervous tissues (Chang and But, 1986);
- Ephedrine (i.v.) stimulates beta-1 receptors (stimulating heart rate), beta-2, and beta-3 receptors (stimulating glucose and oxygen consumption), insulin, and c-peptide (Jaedig and Henningsen, 1991).

Contraindications

The Commission E noted the following contraindications: anxiety and restlessness, hypertension, glaucoma, impaired circulation of the cerebrum, adenoma of the prostate with residual urine accumulation, pheochromocytoma, and thyrotoxicosis (Blumenthal *et al.,* 1998). Additional contraindications include pregnancy, anorexia, diabetes, heart disease, insomnia, stomach ulcers, renal failure, and in children (Brinker, 2001).

The industry label warning for ephedra, currently being suggested as an official national standard by a group of dietary supplement industry trade organizations in a petition to the FDA, is as follows: "WARNING: Not intended for use by anyone under the age of 18. Do not use this product if you are pregnant or nursing. Consult a health care professional before using this product if you have heart disease, thyroid disease, diabetes, high blood pressure, depression or other psychiatric condition, glaucoma, difficulty in urinating, prostate enlargement, or seizure disorder, if you are using a monoamine oxidase inhibitor (MAO), or any other prescription drug, or you are using an over-the-counter drug containing ephedrine, pseudoephedrine or phenylpropanolamine (PPA) (ingredients found in certain allergy, asthma, cough/cold and weight control products). [PPA has been removed from the OTC market, but consumers might still possess older PPA-containing drug products.] Exceeding recommended serving will not improve results and may cause serious adverse health effects. Discontinue use and call a health care professional immediately if you experience rapid heartbeat, dizziness, severe headache, shortness of breath, or other similar symptoms." (AHPA *et al.,* 2000).

Pregnancy and Lactation: Not recommended for use during pregnancy or lactation (Brinker, 2001; McGuffin *et al.,* 1997).

Adverse Effects

According to the Commission E, the adverse effects of the herb ephedra include insomnia, motor restlessness, irritability, headaches, nausea, vomiting, disturbances of urination, and tachycardia. The commission also noted that higher dosages (presumably higher than the Commission E's recommended daily limit, equivalent to 300 mg ephedra alkaloids) may produce a drastic increase in blood pressure, cardiac arrhythmia, and development of dependency (Blumenthal *et al.,* 1998). (See "Note" about dependency in "Duration of Administration" above.)

There have been isolated reports of adverse events, some serious, including stroke and death, in the published literature. Some are related to overdosing; others (e.g., possible myocarditis in a few case reports) are attributed to the consumption of relatively normal levels (Leikin and Klein, 2000; Zaacks *et al.,* 1999).

In a recent review of FDA's AERs (926 cases reported to FDA between 1995 to 1997) focusing on 37 patients, ephedra use was temporarily related to stroke (16 patients, 3 deaths), myocardial infarction (10), or sudden death (11), noting that cardiovascular adverse effects were not limited to large doses (Samenuk *et al.*, 2002). (This review relied on the same FDA database of AERs that had been previously analyzed and questioned for accuracy by the GAO.)

One highly publicized review of selected events reported to the FDA concluded that the AERs do not establish causality and cannot be used to quantify risk (Haller and Benowitz, 2000). This paper reviewed 140 reports of adverse events associated with the use of dietary supplements containing ephedra alkaloids submitted to the FDA between June 1, 1997, and March 31, 1999. The authors employed a standardized rating system for evaluating causation. They concluded that 43 (31%) cases were *definitely* or *probably* related to the use of ephedra-containing supplements, 44 cases (31%) deemed *possibly* related to the use of ephedra supplements, and 24 cases (17%) were considered unrelated. Of the adverse events that were assessed to be definitely, probably, or possibly related to the use of ephedra supplements, 47% involved cardiovascular symptoms and 18% involved the central nervous system. The most frequently reported adverse event was hypertension (17 reports), followed by palpitations, tachycardia, or both (13); stroke (10); and seizures (7). Ten events were associated with deaths, and 13 associated events resulted in permanent disability; these represent 26% of the definite, probable, and possible cases. In response to a critical letter to the editor (Hutchins, 2001) the authors cautioned that their report "does not prove causation, nor does it provide quantitative information with regard to risk" (Hutchins, 2001). A recent review concluded, "These reports, while possibly associating the use of herbal dietary supplements containing ephedra with side effects, do not in any way prove a causative relationship between herbal use and these problems." (Heber and Greenway, 2002).

More extensive evaluations of the entire FDA database of AERs have been submitted to the FDA, suggesting no association between clinically significant adverse events at doses of up to 100 mg per day (EEC, 2000; CHSI, 2000).

The AERs associated with ephedra have been analyzed from an epidemiological perspective suggesting no greater incidence of seizures, strokes, and myocardial infarctions (MIs) in persons consuming dietary supplements containing ephedrine alkaloids than that expected in the general U.S. population (Kimmel, 2000).

The Secretary of HHS, in a press release announcing plans to study ephedra, stated as follows:

> Adverse event reports regarding the use of dietary supplements containing ephedrine alkaloids have been received by the Food and Drug Administration (FDA) and have raised questions regarding the safety of these products. However, the FDA has advised that adverse event reports alone regarding dietary supplements containing ephedrine alkaloids do not provide a scientific basis for assessing the safety of these products and that there is need for further scientific research. (HHS, 2002).

Isolated ephedrine has been reported to cause urinary difficulty in men with benign prostatic hyperplasia and is believed to exacerbate angle-closure glaucoma (Dvorak *et al.*, 1997), forming the basis for the contraindications for these conditions noted above. Other adverse effects documented for ephedrine in controlled conditions include agitation, insomnia, headache, weakness, palpitations, giddiness, tremors, and constipation; these effects were noted only with 50 mg dose given three times daily (total 150 mg per day), with amelioration during the duration of use, with no significant changes in pulse rate or blood pressure (Pasquali and Casimirri, 1993). The German phytomedicine authority R.F. Weiss, claims that the natural ephedrine found in ephedra is "better tolerated, causing fewer heart symptoms such as palpitation" than synthetic ephedrine (Weiss, 1988), although a revision of his book by another author suggests that patients use synthetic beta-sympathomimetics for bronchodilation due to the potential toxicity of ephedra (Weiss and Fintelmann, 2000).

Drug Interactions

The following are actual or potential interactions of orally ingested ephedrine alkaloids (mainly ephedrine and/or pseudoephedrine, not necessarily the herb ephedra itself), with other substances. Documented interactions are derived mainly from human case studies or clinical trials, based on the alkaloid intake at various dosages.

ANTIHYPERTENSIVES, INCLUDING ACE INHIBITORS AND BETA-BLOCKERS: May be antagonized with resulting severe hypertension (speculative) (Brinker, 2001).

BROMOCRIPTINE: Dopaminergic activity may become increasingly toxic due to ephedra's sympathomimetic actions (speculative) (Brinker, 2001).

CARDIAC GLYCOSIDES OR HALOTHANE: Can cause arrhythmia (Brinker, 2001).

CORTICOSTEROIDS: Increases the clearance of dexamethasone, decreasing its activity (Brinker, 2001; Jubiz and Meikle, 1979).

GUANETHIDINE: Antagonizes the hypotensive effect (Brinker, 2001).

MAO-INHIBITORS (including tranylcypromine, pargyline, procarbazine, selegiline, phenelzine, and moclobemide) Significantly raise the sympathomimetic action of ephedrine (Brinker, 2001).

METHYL XANTHINES (e.g., caffeine, theophylline): Increase thermogenesis and weight loss with reduction in body fat when ephedrine is combined with xanthines, plus excessive nervous stimulation (noted in some case reports) (Brinker, 2001).

CAFFEINE: The alkaloids in ephedra combined with methylxanthines have been demonstrated to be synergistic on oxygen consumption in animals. A recent review noted both the caffeine and the catechins in various types of tea (*Camellia sinensis*), e.g., oolong tea, may interact with respect to respiration of brown

adipose tissue, based on *in vitro* evidence. Catechins in green tea are synergistic with respect to oxygen consumption with caffeine, ephedrine, and the combination of caffeine and ephedrine; catechins inhibit catechol-*O*-methyl transferase, the enzyme that breaks down norepinephrine (Heber and Greenway, 2002).

SECALE ALKALOID DERIVATIVES OR OXYTOCIN: Develop hypertension (listed by German Commission E) (Blumenthal *et al.,* 1998).

SYMPATHOMIMETICS: May be potentiated when used with ephedra or ephedra alkaloids (speculative) (Brinker, 2001).

URINARY ALKALIZERS e.g., acetazolamide (Wilkinson and Beckett, 1968); sodium bicarbonate: Excrete more slowly than with urinary acidifiers (e.g., ammonium chloride), due to effects of reabsorption from tubules in the kidneys (Brinker, 2001).

American Herbal Products Association (AHPA) Safety Rating

CLASS 2B: Not for use during pregnancy.

CLASS 2C: Not for use during nursing.

CLASS 2D: Contraindicated with anorexia, bulimia, and glaucoma; thyroid stimulant; not recommended for excessive or long-term use; may potentiate pharmaceutical MAO-inhibitors (McGuffin *et al.,*1997).

Regulatory Status

AUSTRALIA: Ephedra, and products containing ephedra, are controlled substances listed in the Customs Prohibited Imports Regulations. Import permit required (TGA, 2001).

CANADA: Included in Drugs Directorate "List of Herbs Unacceptable as Non-medicinal Ingredients in Oral Use Products" (Health Canada, 1995). Ephedra Labeling Standard: Approved Schedule OTC drug with specific indications: (1) Traditional Herbal Medicine (THM) for relief of nasal congestion (cold, hayfever); (2) Traditional Herbal Nasal Decongestant. Dried young stem contains no less than 1.25% total alkaloids calculated as l-ephedrine (Health Canada, 1996). Also, permitted as a homeopathic drug. In either case requires premarket authorization and assignment of a Drug Identification Number (DIN) (Health Canada, 2001). In January, 2002 Health Canada issued a "voluntary recall" for ephedra- and ephedrine-containing products that are marketed for unapproved uses, e.g., appetite suppression, promoting weight loss, or increasing energy; or that contain over 8 mg ephedrine or a total dose of ephedrine alkaloids exceeding 32 mg per day (Lawlor, 2002).

CHINA: Dried herbaceous stem containing no less than 0.80% total alkaloids, calculated as ephedrine, official drug of the *Pharmacopoeia of the People's Republic of China* (PPRC, 1997).

FRANCE: Ephedra removed from *French Pharmacopoeia*. Isolated ephedrine is official (Bruneton, 1995).

GERMANY: Dried young whole or cut branchlet collected in autumn containing no less than 1.0% total alkaloids (as ephedrine) official in *German Pharmacopoeia* (DAB, 1999). Dried young branchlet is approved drug of the German Commission E (Blumenthal *et al.,* 1998).

JAPAN: Traditional Kampo medicine (Tsumura, 1996). Dried terrestrial stem containing no less than 0.15% total alkaloids (as ephedrine) official in *Japanese Pharmacopoeia* (JSHM, 1993).

SWEDEN: No products containing ephedra are presently registered in the Medical Products Agency's (MPA) "Authorized Natural Remedies," "Homeopathic Remedies" or "Drugs" listings (MPA, 2001a and 2001b).

SWITZERLAND: No monograph in the Swiss pharmacopeia. No ephedra-containing products are listed in the *Swiss Codex 2000/01* (Ruppanner and Schaefer, 2000). Since 1992, traditional Chinese medicine (TCM) has been made available as a primary health care option in the national HMO. Patients who choose TCM for their primary health care plan may receive traditional Chinese herbal medicines (which may contain ephedra) by prescription (Grüninger, 1992).

U.K.: Schedule III herb recommended to be limited for use by medical herbalists only (Denham, 1998).

U.S.: Dietary supplement (USC, 1994) and approved OTC drug ingredient, for bronchodilation (25 mg/dose orally up to 6 times per day, no limit on duration of use) and as a nasal decongestant (nasal spray) (21 CFR a-d).

Clinical Review

Seven studies conducted on the herb ephedra (327 total participants) are summarized in the Table of Clinical Studies on Ephedra. One study on a preparation containing only powdered ephedra measured cardiovascular effects and pharmacokinetics (White *et al.*, 1997). However, few clinical trials are based on ephedra as a single ingredient. Most ephedra trials tested multi-ingredient formulations that include a caffeine-containing herb like cola nut (*Cola nitida*) (Boozer *et al.,* 2002; DeJong *et al.*, 2001; Greenway *et al.*, 2000) or guarana (*Paullinia cupana*) (Belfie *et al.*, 2001; Boozer *et al.* 2001). The Boozer *et al.*, 2002 and 2001 trials focused on weight loss and safety. One small randomized, crossover trial concluded that the pharmacokinetic properties of ephedrine in ephedra in dietary supplements were similar to those of synthetic ephedrine hydrochloride (Gurley *et al.*, 1998). At least three clinical studies have been conducted on the isolated alkaloid ephedrine for its use in weight loss (Liu *et al.,* 1995; Astrup *et al.,* 1986; Pasquali *et al.,* 1985), as summarized in the Table of Clinical Studies on Ephedra.

[EDITORS' NOTE: the following studies are not listed in the Table of Clinical Studies on Ephedra or the Table of Clinical Studies on Ephedrine.] Several unpublished trials employed four different ephedra products (ephedra only, not combinations) on 300 subjects over a period of six weeks and six months, to monitor weight loss and adverse effects respectively. The studies concluded that ephedra appears to be safe, effective, and cost-effective; and compares favorably with pharmaceutical weight loss agents, with a relatively low side effect profile (Huber, 2001). Clinical trials have been successfully conducted for weight loss using ephedrine and caffeine combinations (Astrup and Toubro, 1993; Astrup *et al.*, 1992, 1991) and a much-publicized Danish formula of ephedrine in combination with caffeine and aspirin demonstrated the relative safety and efficacy of this combination for weight loss (Daly *et al.*, 1993).

Branded Products

DietMax®: NaturalMax Co./ Kal Inc., Div. Nutraceutical Corp., 1400 Kearns Blvd. / Park City, Utah 84060 / U.S.A. / Tel: (800) 669-8877 / www.nutraceutical.com. Each tablet contains 110 mg extract standardized to 8% ephedra alkaloids, equivalent to 5 mg ephedrine, 50 mg standardized kola nut extract (equivalent to 10 mg caffeine), 50 mg mustard seed powder, 50 mg spirulina, 50 mg ascorbic acid (vitamin C), potassium citrate 25 mg, magnesium aspartate 25 mg.

Escalation™: Enzymatic Therapy / 825 Challenger Drive / Green Bay, WI 54311 / U.S.A. / Tel: 920-469-1313 / www.enzy.com. Each capsule contains 250 mg cola (*Cola nitida)* nut extract containing 35 mg of caffeine alkaloids; 250 mg ephedra aerial part extract containing 15mg concentrated ephedrine group alkaloids in the form of herbal extracts; and 110 mg green tea (*Camellia sinensis*) leaf extract containing 15 mg of caffeine alkaloids.

Excel: Excel Corporation / Salt Lake City, UT: no information available.

Metabolife 356®: Metabolife International, 5070 Santa Fe Street / San Diego, CA 92109 / U.S.A. / Tel: (858) 490-5222 / www.metabolife.com. Each tablet contains 12 mg of ephedrine group alkaloids and 40 mg of caffeine alkaloids, combined with the following ingredients: Ma huang, Siberian ginseng (Eleuthero), lecithin, ginger root, damiana, sarsaparilla root, goldenseal, gotu kola, spirulina, algae, bee pollen, nettle leaf, royal jelly, bovine complex, 6 I.U. vitamin E, 75 mg magnesium chelate, 5 mg zinc chelate, and 75 mcg chromium picolinate.

Solaray® Ephedra: Nutraceutical Corp. Each capsule contains 375 mg powdered ephedra herb calculated at 4.8 mg ephedrine, 1.2 mg pseudoephedrine, 0.3 mg methyl-ephedrine per capsule.

Up Your Gas: National Health Products / 731 South Kirkman Road / Orlando, FL 32811 / U.S.A. / Tel: (407) 297-7671. Each capsule contains: 30 IU Vitamin E (as dl-alpha-tocopherol acetate); 255 mg calcium (as dicalcium phosphate and calcium carbonate); 4.5 mg magnesium (as magnesium carbonate); 5 mg potassium (as potassium bicarbonate); and 695 mg Up Your Gas Blend consisting of: guarana concentrate (seed), mahuang extract (*Ephedra sinica*) (stem) (285 mg of 6% alkaloid extract), ginseng extract (root), bee pollen, spirulina blue green algae, gotu kola (leaf), inosine monophosphate, pyridoxal-alpha-ketoglutarate, wheat grass, cayenne pepper (fruit), lipoic acid, co-enzyme Q-10, and octacosanol.

References

21 CFRa [Code of Federal Regulations] Sect. 341.76 Food and Drug Administration, Department of Health and Human Services. Labeling of Bronchodilator Drug Products.

21 CFRb [Code of Federal Regulations] Sect. 341.80. Food and Drug Administration, Department of Health and Human Services. Labeling of Nasal Decongestant Drug Products.

21 CFRc [Code of Federal Regulations] Sect. 341.16 Food and Drug Administration, Department of Health and Human Services. Bronchodilator Active Ingredients.

21 CFRd [Code of Federal Regulations] Sect. 341.20. Food and Drug Administration, Department of Health and Human Services. Nasal Decongestant Active Ingredients.

Adams E. Statement of Edgar H. Adams, M.S., Sc.D. Submitted to FDA; Docket No. 98N–0148, cmt. 28, tab A: February 10, 1999.

AHPA. See: American Herbal Products Association.

American Herbal Products Association (AHPA). Policy Statement on *Ephedra sinica* (Ma huang). Austin, TX, 1994 Mar. 30.

American Herbal Products Association (AHPA), Consumer Healthcare Products Association, National Nutritional Foods Association, and Utah Natural Products Alliance. Citizens Petition to FDA on Ephedra Labeling. Oct. 25, 2000.

American Herbal Products Association (AHPA). Code of Ethics and Business Conduct. Silver Spring (MD): AHPA; 2002 Jul [cited 2002 Nov 13]. Available at: URL: http://www.ahpa.org/CodeJuly02.pdf.

Anonymous. NFL bans ephedrine, other stimulants. NFL News 2001c Sept 27. Available from:URL: http://www.nfl.com/news/2001/ephedrine092701.html.

Anonymous. Obesity becoming top threat to health. *Los Angeles Times* article published in *Austin American-Statesman*, Dec. 14, 2001a.

Anonymous. U.S. warning of death toll from obesity. Associated Press in *New York Times*. Dec. 14, 2001b.

Astrup A. Thermogenesis in human brown adipose tissue and skeletal muscle induced by sympathomimetic stimulation. *Acta Endocrinol* 1986(suppl.);278:1-32.

Astrup A, Breum L, Toubro S *et al*. The effect and safety of an ephedrine/caffeine compound compared to ephedrine, caffeine and placebo in obese subjects on an energy restricted diet. A double-blind trial. *Int J Obesity* 1992;16:269–77.

Astrup A, Madsen J, Holst JJ, Christensen NJ. The effect of chronic ephedrine treatment on substrate utilization, the sympathoadrenal activity, and energy expenditure during glucose-induced thermogenesis in man. *Metabolism* 1986;35(3):260–5.

Astrup A, Toubro S. Thermogenic, metabolic, and cardiovascular responses to ephedrine and caffeine in man. *Int J Obesity* 1993;17 (suppl):S41–3.

Astrup A, Toubro S, Cannon S *et al*. Thermogenic synergism between ephedrine and caffeine in healthy volunteers: A double-blind, placebo-controlled study. *Metabolism* 1991;40(3):323–9.

BAnz. See: *Bundesanzeiger*.

Belfie L, Petrie H, Chown S *et al.* Safety and effectiveness of an herbal dietary supplement containing ephedra (ma huang) and caffeine (guarana extract) when used in combination with a supervised diet and exercise intervention [presentation abstract]. *Obesity Research* 2001;9(S3):26.

Bell DG, McLellan TM, Sabiston CM. Effect of ingesting caffeine and ephedrine on 10-km run performance. *Med Sci Sports Exerc* 2002;34(2):344–9.

Bell DG, Jacobs I, Ellerington K. Effect of caffeine and ephedrine ingestion on anaerobic exercise performance. *Med Sci Sports Exerc* 2001;33(8):1399–403.

Bell DG, Jacobs I, McLellan TM, Zamecnik J. Reducing the dose of combined caffeine and ephedrine preserves the ergogenic effect. *Aviat Space Environ Med* 2000;71(4):415–9.

Bell DG, Jacobs I, McLellan TM, Miyazaki M, Sabiston CM. Thermal regulation in the heat during exercise after caffeine and ephedrine ingestion. *Aviat Space Environ Med* 1999a;70(6):583–8.

Bell DG, Jacobs I. Combined caffeine and ephedrine ingestion improves run times of Canadian forces warrior test. *Aviat Space Environ Med* 1999b Apr;70(4):325-9.

Bell DG, Jacobs I, Zamecnik J. Effects of caffeine, ephedrine and their combination on time exhaustion during high intensity exercise, *Eur J Appl Physiol* 1998:77:427-33.

Bensky D, Gamble A. *Chinese Herbal Medicine Materia Medica.* Revised (ed.). Seattle, WA: Eastland Press;1993.

Blanck HM, Khan LK, Serdula MK. Use of nonprescription weight loss products: results from a multistate survey. *JAMA* 2001;286(8):930-5.

Blumenthal M, Busse WR, Goldberg A, Gruenwald J, Hall T, Riggins CW, Rister RS (eds.). Klein S, Rister RS (trans.). *The Complete German Commission E Monographs—Therapeutic Guide to Herbal Medicines*. Austin, TX: American Botanical Council; Boston: Integrative Medicine Communication; 1998.

Blumenthal M, Goldberg A, Brinckmann J. *Herbal Medicine—Expanded Commission E Monographs.* Austin: American Botanical Council; Boston, MA: Integrative Medicine Communication; 2000.

Blumenthal M, King P. The agony of the ecstasy: Herbal high products get media attention. *HerbalGram* 1996; 37:20-24,32,49.

Blumenthal M, King P. Ma Huang: Ancient herb, modern medicine, regulatory dilemma. *HerbalGram* 1995;34:22–27,42–3,56–7.

Boozer CN, Daly PA, Homel P, Solomon JL, Blanchard D, Sanner JA, *et al.* Herbal ephedra/caffeine for weight loss: a 6-month randomized safety and efficacy trial. *Int J Obes* 2002;26:593-604.

Boozer C, Nasser J, Heymsfield S, Wang V, Chen G, Solomon J. An herbal supplement containing ma huang-guarana for weight loss: a randomized, double-blind trial. *Intl J Obesity* 2001 Mar;25(3):316–24.

Brinker F. *Herb Contraindications and Drug Interactions*, 3d ed. Sandy, OR: Eclectic Medical Publications; 2001:87–90.

Bruneton J. *Pharmacognosy, Phytochemistry, Medicinal Plants.* Paris, France: Lavoisier Publishing; 1995;711–4.

Bundesanzeiger (BAnz). *Monographien der Kommission E* (Zulassungs- und Aufbereitungskommission am BGA für den humanmed. Bereich, phytotherapeutische Therapierichtung und Stoffgruppe). Köln: Bundesgesundheitsamt (BGA); 1998.

Cantox Health Sciences International (CHSI). Safety assessment and determination of a tolerable upper limit for ephedra. December 2000. http://www.crnusa.org/CRNCantoxreportindex.html.

Chang H, But P (eds.). *Pharmacology and Applications of Chinese Materia Medica*, Vol. 1. Philadelphia, PA: World Scientific;1986:1119–24.

CHSI. See: Cantox Health Sciences International.

Code of Federal Regulations. See: 21 CFR.

DAB. See: *Deutsches Arzneibuch*.

Daly PA, Krieger DR, Dulloo AG *et al*. Ephedrine, caffeine, and aspirin: safety and efficacy for treatment of human obesity. *Int J Obesity* 1993;17 (suppl):S73–8.

De Jonge L, Frisard M, Blanchard D, Greenway F. Safety and efficacy of an herbal dietary supplement containing caffeine and ephedra for obesity treatment. *Obesity Research* 2001;9(S3):20.

Denham A. The 1968 Medicines Act - Schedule 3 herbs, and their use by practi-

tioners. *Eur J Herbal Med* 1998;4(3):19–28.
Der Marderosian A (ed.). *The Review of Natural Products.* St. Louis: Facts and Comparisons; 1999.
Deutsches Arzneibuch (DAB 1999). Stuttgart, Germany: Deutscher Apotheker Verlag;1999.
Dvorak R, Starling RD, Calles-Escandon J *et al.* Drug therapy for obesity in the elderly. *Drugs Aging* 1997;11:338-51.
EEC. See: Ephedra Education Council.
Ephedra Education Council (EEC). Comments of the Expert Panel of the Ephedra Education Council on the Safety of Dietary Supplements Containing Ephedrine Alkaloids and on the Adverse Event Reports (AERs) and Health Assessments Released by the Food and Drug Administration (FDA) on April 3, 2000. Submitted to FDA; Docket No. 00N-1200: September 29, 2000.
FDA. See: Food and Drug Administration.
Fleming T. *PDR for Herbal Medicines*. Montvale, NJ: Medical Economics Co.; 1998.
Food and Drug Administration (FDA). Dietary Supplements Containing Ephedrine Alkaloids: Proposed Rule. *Federal Register* 1997;62(107):30678–717.
Food and Drug Administration (FDA). FDA announces the availability of new ephedrine and "street drug alternative" documents. *FDA Talk Paper*; 2000 Mar 31 [cited 2002 Jul 3]. Available from: URL: http://www.cfsan.fda.gov/~lrd/tpephedr.html.
GAO. See: General Accounting Office.
Geissler CA. Effects of weight loss, ephedrine and aspirin on energy expenditure in obese women. *Int J Obes Relat Metab Disord* 1993;17 (suppl. 1):S45-8.
General Accounting Office (GAO). Dietary Supplements: Uncertainties in Analyses Underlying FDA's Proposed Rule on Ephedrine Alkaloids. Washington, DC: United States General Accounting Office; 1999 July.
Greenway F. The safety and efficacy of pharmaceutical and herbal caffeine and ephedrine use as a weight loss agent. *Obesity Rev* 2001;2:199-211.
Greenway F, Raum W, DeLany J. The effect of an herbal dietary supplement containing ephedrine and caffeine on oxygen consumption in human. *J Alt Compl Med* 2000;6(6):553–5.
Grüninger T. Traditional Chinese Medicine in ENT. [in German]. *HMO Aktuell* 1992;3:3.
Gurley B. Extract versus herb: effect of formulation on the absorption rate of botanical ephedrine from dietary supplements containing Ephedra (ma huang). *Ther Drug Monitoring* 2000;22(4):497.
Gurley B, Gardner S, White L, Wang P. Ephedrine pharmacokinetics after the ingestion of nutritional supplements containing *Ephedra sinica* (ma huang). *Ther Drug Monit* 1998 Aug;20(4):439–45.
Haller C, Benowitz N. Adverse cardiovascular and central nervous system events associated with dietary supplements containing ephedra alkaloids. *N Engl J Med* 2000 Dec 21;343(25):1833–8.
Hardman J, Limbird L, Molinoff P, Ruddon R, Gilman A (eds.). *Goodman and Gilman's The Pharmacological Basis of Therapeutics,* 9th ed. New York: MacMillan Publishing;1996:221.
Harnack LJ, Rydell SA, Stang J. Prevalence of use of herbal products by adults in the Minneapolis/St. Paul, Minn, metropolitan area. *Mayo Clin Proc* 2001;76(7):688–94.
Hathcock JN. CRN's Cantox Report on the Quantitative Risk Assessment of Ephedra. *HerbalGram* 2001;53:31–3.
Health & Human Services (HHS). HHS announces plans to study ephedra: steps up enforcement of illegal ephedrine marketing [press release]. HHS; 2002 Jun 14 [cited 2002 Jul 3]. Available from: URL: http://www.hhs.gov/news/press/2002pres/20020614.html.
Health Canada. Ephedra. In: *Drug Product Database (DPD).* Ottawa, Ontario: Health Canada Therapeutic Products Programme; 2001.
Health Canada. Ephedra. In: *Herbs Used as Non-medicinal Ingredients in Non-prescription Drugs for Human Use. Appendix II: List of Herbs Unacceptable as Non-medicinal Ingredients in Oral Use Products Subject to Part B.* Ottawa, Ontario: Health Canada Therapeutic Products Programme; 1995 Sept 22:6–15.
Health Canada. *Labelling Standard: Ephedra*. Ottawa, Canada: Health Canada Drugs Directorate; 1996:1–4.
Heber D, Greenway F. Herbal and Alternative Approaches to Obesity. In: Bray GA, Bouchard C (eds.). *Handbook of Obesity* 2d ed. New York: Marcel Dekker, 2002. (in press).
HHS. See: Health & Human Services.
Hikino H, Kiso Y, Ogata M, Konno C, *et al*. Pharmacological actions of analogues of feruloyl-histamine, an imidazole alkaloid of ephedra roots. *Planta Med* 1984;50(6):478–80.
Hikino H, Ogata K, Konno C, Sato S. Hypotensive actions of ephenadrines, macrocyclic spermine alkaloids of ephedra roots. *J Med Plant Res* 1983;48:290–3.
Hikino H, Konno C, Takata H, Tamada M. Anti-inflammatory principle of ephedra herbs. *Chem Pharm Bull* 1980;28:2900–4.
Horton TJ, Geissler CA. Aspirin potentiates the effect of ephedrine on the thermogenic response to a meal in obese but not lean women. *Int J Obes* 1991;15:359-66.
Hsu H. *Oriental Materia Medica*. Oriental Healing Arts Institute; 1986.
Huang K. *The Pharmacology of Chinese Herbs*, 2nd edition. Boca Raton, FL: CRC Press LLC; 1999:291–300.
Huber G. Preliminary results from clinical trials on ephedra dietary supplements (unpublished). Personal communication to M Blumenthal, Dec 18, 2001.
Hutchins GM. Dietary supplements containing ephedra alkaloids [letter]. *N Engl J Med* 2001 Apr 5;344(14):1095–6;discussion 1096–7.
Indian Pharmacopoeia (IP, 1996), Vol. I (A-O). Delhi, India: Controller of Publications Government of India Ministry of Health & Family Welfare; 1996:282–5.
International Olympic Committee (IOC). Prohibited classes of substances and prohibited methods 2001–2002. September, 2001. Available from: URL: http://www.wada-ama.org/asiakas/003/wada_english.nsf/Home?/OpenPage.
IOC. See: International Olympic Committee
IP. See: *Indian Pharmacopoeia.*
Jaedig S, Henningsen NC. Increased metabolic rate in obese women after ingestion of potassium, magnesium- and phosphate-enriched orange juice or injection of ephedrine. *Int J Obes* 1991;15:429-36.
Japanese Pharmacopoeia (JP XII). Tokyo, Japan: The Society of Japanese Pharmacopoeia; 1991.
Japanese Standards for Herbal Medicines (JSHM). Tokyo, Japan: Yakuji Nippo, Ltd.; 1993:107–8.
Jonderko K, Kucio C. Effect of anti-obesity drugs promoting energy expenditure, yohimbine and ephedrine, on gastric emptying in obese patients. *Aliment Pharmacol Ther* 1991;5:413-8.
Jones D. Thermogenesis: Theoretical and practical implications of thermogenic agents as aids to weight loss. Unpublished, 2001.
JP. See: *Japanese Pharmacopoeia.*
JSHM. See: Japanese Standards for Herbal Medicines.
Jubiz W, Meikle A. Alterations of glucocorticoid actions by other drugs and disease states. *Drugs* 1979;18:113–21.
Kimmel S. Summary of incidence of seizures, strokes, and myocardial infarctions in the population and estimations of risk in the population from ephedra products. Submitted to FDA; 2000 Aug [cited 2002 Jul 3]. Available from: URL: http://ephedrafacts.com/2.html.
Lawlor A. Health Canada recalls certain Ephedra products. *Globe and Mail*, Jan. 9, 2002.
Leikin J, Klein L . Ephedra causes myocarditis. *J Toxicol Clin Toxicol* 2000;38 (3):353–4
Leung A. Personal communication to M. Blumenthal. 1999, July 7th.
Leung A, Foster S. *Encyclopedia of Common Natural Ingredients Used in Food, Drugs and Cosmetics*, 2nd ed. New York, NY: John Wiley & Sons, Inc.; 1996.
Ling M, Piddlesden SJ, Morgan BP. A component of the medicinal herb ephedra blocks activation in the classical and alternative pathways of complement. *Clin Exp Immunol* 1995 Dec;102(3):582–8.
Liu Y, Toubro S, Astrup A, Stock M. Contribution of Beta-3-adrenoceptor activation to ephedrine-induced thermogenesis in humans. *Intl J Obesity* 1995;19:678–85.
McGuffin M. Statement before Department of Health & Human Services Office of Public Health & Sciences, Public Meeting on the Safety of Dietary Supplements Containing Ephedrine Alkaloids; 2000 Aug 8; Washington DC.
McGuffin M, Hobbs C, Upton R, Goldberg A. (eds.). *American Herbal Products Association's Botanical Safety Handbook* Boca Raton, FL: CRC Press; 1997.
Medical Products Agency (MPA). *Läkemedel: Läkemedelsnära Produkter* (registrerade homeopatiska produkter). Uppsala, Sweden: Medical Products Agency; 2001b.
Medical Products Agency (MPA). *Naturläkemedel: Authorised Natural Remedies* (as of January 24, 2001). Uppsala, Sweden: Medical Products Agency; 2001a.
Molnar D, Torok K, Erhardt E, Jeges S. Safety and efficacy of treatment with an ephedrine/caffeine mixture. The first double-blind placebo-controlled pilot study in adolescents. *In J Obes Relat Metab Disord* 2000;24(12):1573-8.
Morton J. *Major Medicinal Plants: Botany, Culture and Uses.* Springfield, IL: Charles C. Thomas; 1977.
MPA. See: Medical Products Agency.
Nasser J, *et al.* Efficacy trial for weight loss of an herbal supplement of ma huang and guarana. *FASEB J* 1999;13(5).
National Collegiate Athletic Association (NCAA) 2001–2002 NCAA banned-drug classes. Updated 2001 Aug 9. Available from: URL: http://www.ncaa.org/sports_sciences/drugtesting/banned_list.html.
NCAA. See: National Collegiate Athletic Association.
Noguchi M, Kubo M, Naka Y. Studies on the pharmaceutical quality evaluation of crude drug preparations used in the Oriental Medicine "Kampo". IV. Behavior of alkaloids in ephedra herb mixed with other crude drugs under decoction processes. [in Japanese]. *Yakugaku Zasshi* 1978;98(7):923–8.
Office on Women's Health. Safety of dietary supplements containing ephedrine alkaloids [report on public meeting of 8-9 Aug 2000]. The National Women's Health

Information Center; 2000 Sep [cited 14 Nov 2002]. Available at: http://www.4woman.gov/owh/public/report.htm.
OWH. See: Office on Women's Health.
Pasquali R, Casimirri F. Clinical aspects of ephedrine in the treatment of obesity. *Int J Obes Relat Metab Disord* 1993;17 (suppl 1):S65-8.
Pasquali R, Baraldi G, Cesari M *et al.* A controlled study using ephedrine in the treatment of obesity. *Intl J Obesity* 1985;9(2):93–8.
Pharmacopoeia of the People's Republic of China (PPRC 1997 English Edition). Beijing, China: Chemical Industry Press. 1997;92–93.
PPRC. See: *Pharmacopoeia of the People's Republic of China.*
Robbers J, Tyler V. *Tyler's Herbs of Choice: The Therapeutic Use of Phytomedicinals.* New York: Haworth Herbal Press; 1999;112–6.
Ruppanner H, Schaefer U (eds.). *Codex 2000/01 — Die Schweizer Arzneimittel in einem Griff.* Basel, Switzerland: Documed AG; 2000.
Samenuk D, Link MS, Homoud MK *et al.* Adverse cardiovascular events temporarily associated with ma huang, an herbal source of ephedrine. *Mayo Clin Proc* 2002;77:12-6.
Svendsen TL, Ingerslev J, Mork A. Is Letigen contraindicated in hypertension? A double-blind, placebo controlled multipractice study of Letigen administered to normotensive and adequately treated patients with hypersensitivity. *Ugeskr Laeger* 1998;160:4073-5, cited in Heber D, Greenway F. Herbal and Alternative Approaches to Obesity. In: Bray GA, Bouchard C (eds.) *Handbook of Obesity* 2d ed. NewYork: Marcel Dekker, 2002. (in press).
Tang W, Eisenbrand G. *Chinese Drugs of Plant Origin*. New York: Springer-Verlag; 1992;481–90.
Texas Medical Association. TMA Policy Compendium 260.057 Regulation of Ephedrine Products; 260.058 Labeling of Ephedrine Products. Austin, TX.
TGA. See: Therapeutic Goods Administration.
TMA. See: Texas Medical Association.
Therapeutic Goods Administration (TGA). *Commonly Asked Questions: Why are some substances available without a prescription overseas but are controlled substances in Australia?* Woden, Australia: TGA; 2001.
Tsumura Co., Ltd. Science and expert know how join forces to maintain the quality of raw herbs. *Kampo Today* 1996;1(3):1–2.
United States Congress (USC). Public Law 103–417: *Dietary Supplement Health and Education Act of 1994*. Washington, DC: 103rd Congress of the United States; 1994.
USC. See: United States Congress.
Weiner N. Norepinephrine, Epinephrine and the Sympathomimetic Amines. In: Goodman A *et al*. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 8th edition. New York, NY: MacMillan; 1985;169–70.
Weiss R. *Herbal Medicine*. Beaconsfield, England: Beaconsfield Publishers; 1988.
Weiss R, Fintelmann V. *Herbal Medicine* 2nd ed. New York: Thieme; 2000:209.
White L,M, Gardner SF, Gurley BJ *et al*. Pharmacokinetics and cardiovascular effects of ma huang *(Ephedra sinica)* in normotensive adults. *J Clin Pharmacol* 1997;37:116–22.
WHO. See: World Health Organization.
Wilkinson GR, Beckett AH. Absorption, metabolism and excretion of the epinedrines in man. II. Pharmacokinetics. *J Pharm Sci* 1968 Nov;57(11):1933–8.
World Health Organization (WHO). Herba Ephedrae. In: *WHO Monographs on Selected Medicinal Plants,* Vol. 1. Geneva: World Health Organization; 1999:145–53.
Zaacks S, Klein L, Tan C, Rodriguez E, Leikin J. Hypersensitivity myocarditis associated with ephedra use. *J Toxicol Clin Toxicol* 1999;37(4):485–9.
Zhu Y. *Chinese Materia Medica*. Australia: Harwood Academic Publishers; 1998.

Clinical Studies on Ephedra (*Ephedra sinica* Stapf)

Metabolism and Weight Loss

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Boozer *et al.*, 2002	Weight loss and long-term safety: changes in blood pressure, heart function and body weight	R, DB, PC n=167 (BMI 31.8±4.1 kg/m^2). Subjects were carefully selected by medical evaluation, excluding those consuming more than 500 mg caffeine/day and numerous other parameters.	6 months	2 tablets, 3x/day (equivalent to 90 mg/day ephedrine; 192 mg/day caffeine)	Tablets containing ephedra (15 mg ephedrine alkaloids) and kola nut (32 mg caffeine) (Custom made preparation)	The ephedra/caffeine combination versus placebo significantly increased weight loss (–5.3 vs –2.6 kg, p<0.001), and reduced body fat (–4.3 vs. –2.7 kg, p=0.02). LDL-cholesterol was lowered (–8 vs. 0 mg/dl, p=0.013) while HDL-cholesterol was raised (+2.7 vs. –0.3 mg/dl, p=0.004). These results occurred without significant adverse events and with minimal side effects in a carefully selected patient population.
Boozer *et al.*, 2001	Weight loss and short-term safety	R, DB, PC n=48 overweight, weight-stable men and women (BMI>29 and <35 kg/m^2)	8 weeks	2 tablets, 3x/day (equivalent to 72 mg/day ephedrine alkaloids; 240 mg/day caffeine)	Metabolife 356®	Herbal supplement versus placebo significantly increased loss of body weight (–4 vs. –0.8 kg) and fat (–2.1% vs. 0.2%). Greater reductions in hip circumference and serum triglyceride levels were also seen with the herbal supplement versus placebo. Authors concluded this herbal supplement effectively promoted short-term weight and fat loss.
de Jonge *et al.*, 2001	Weight loss	R, DB, PC n=40	3 months	70 mg of caffeine and 24 mg of ephedra, 3x /day	Brand not stated	After 3 months, the treatment group showed an 8% ± 0.4% (SD) rise in resting metabolic rate (RMR) compared to placebo (p<0.01). Weight loss with the treatment was 4 kg ± 4.2 kg compared to 0.7 kg ± 2.6 kg with placebo (p<0.05). An insignificant drop in pulse and blood pressure (4/1 mm Hg and 0.5 bpm) was observed with treatment. The study concluded that the caffeine and ephedra combination provided safe weight loss and increase in metabolic rate.
Greenway *et al.*, 2000	Metabolism, oxygen consumption	DB, PC, CO n=10 obese females 41 ±4 years. Mean BMI 33kg/m^2	45 minutes	2 capsules (10 mg caffeine; 5 mg ephedrine) or 2 placebo capsules	DietMax®	Herbal supplement increased peak oxygen consumption 0.178 ±0.03 (SEM) kcal/minutes (8.01 ±1.35 kcal minimum over 45 minutes) above baseline (p<0.0001); 2.0 ±0.56 kcal/min over 45 minutes compared to placebo (p<0.006). The significance of this result in weight loss requires more research.

Safety

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Belfie *et al.*, 2001	Weight loss and safety (changes in heart rate and blood pressure)	DB, PC n=21 obese men (BMI ≥ 30 kg/m^2) (ages 19–34 years)	12 weeks	Ephedra alkaloids (20 mg) and guarana (200 mg caffeine) 3x/day vs. placebo	Herbal supplement containing ephedra alkaloids (20 mg) and guarana (200 mg caffeine); brand not stated	When taken in a controlled manner, the herbal supplement had only mild side effects, and did not influence the improvement in serum lipids. There was no impact on amount of adipose mass lost when diet and exercise were controlled. The authors suggest that any benefits of ephedra and caffeine supplements are likely the result of the anorectic effects.
Gurley *et al.*, 1998	Pharmacokinetics	R, CO n=10 healthy volunteers (5 men, 5 women; 22–40 years; weight range 47–103 kg)	1 day for each of 4 phases with 1 week washout between phases	2 capsules of one of the commercial preparations or 25 mg ephedrine	Escalation™ or Excel or Up Your Gas or 25 mg ephedrine	Pharmacokinetic parameters were similar for botanical ephedrine and synthetic ephedrine hydrochloride. The authors suggest that the increased incidence of ephedra toxicity stems from accidental overdose often prompted by exaggerated off-label claims and a belief that "natural" medicinal agents are inherently safe, and not from differences in the absorption of botanical ephedrine compared with synthetic ephedrine.
White *et al.*, 1997	Adverse effects, changes in blood pressure and heart rate and pharmacokinetics	Unstated n=12 normotensive non-smokers (ages 23–40 years)	20 hours	2 capsules (375 mg ea.) 4x/day	Solaray® capsules (375 mg *E. sinica* powdered herb each)	None of the 12 subjects experienced adverse effects. 6 patients showed an increased heart rate (78 bpm vs. 86 bpm). Results suggest that the use of ephedra herb powder is benign in a normotensive, young population in short-term use.

KEY: C – controlled, **CC** – case-control, **CH** – cohort, **CI** – confidence interval, **Cm** – comparison, **CO** – crossover, **CS** – cross-sectional, **DB** – double-blind, **E** – epidemiological, **LC** – longitudinal cohort, **MA** – meta-analysis, **MC** – multi-center, **n** – number of patients, **O** – open, **OB** – observational, **OL** – open label, **OR** – odds ratio, **P** – prospective, **PB** – patient-blind, **PC** – placebo-controlled, **PG** – parallel group, **PS** – pilot study, **R** – randomized, **RC** – reference-controlled, **RCS** – retrospective cross-sectional, **RS** - retrospective, **S** – surveillance, **SB** – single-blind, **SC** – single-center, **U** – uncontrolled, **UP** – unpublished, **VC** – vehicle-controlled.

Clinical Studies on Ephedrine

Thermogenesis and Weight loss

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Liu *et al.*, 1995	Thermogenesis	SB, PC, CO n=9	5 days	30 mg ephedrine chloride with 0, 2.5, 5, or 10 mg nadolol/day, or placebo	Ephedrine chloride	Significant increase was found in thermogenesis, heart rate, systolic blood pressure, and plasma glucose. Ephedrine combined with nadolol maintained 43% thermogenesis without affecting heart rate and plasma glucose.
Astrup *et al.*, 1986	Glucose-induced thermo-genesis	C n=5	3 months	20 mg ephedrine hydrochloride, 3x/day	Ephedrine hydrochloride	Chronic treatment was found to enhance thermogenic response compared to acute treatment. Chronic ephedrine treatment sustained 10% elevation of meta-bolic rate. Plasma epinephrine levels were increased 87% during treatment.
Pasquali *et al.*, 1985	Weight loss	DB, PC n=46	3 months	25 mg or 50 mg ephedrine hydrochloride, 3x/day, or placebo	Ephedrine hydrochloride tablets	The study did not find significant weight loss benefit in unselected obese patients. The authors concluded ephedrine HCL might be useful in obese patients with defective thermogenesis.

KEY: C – controlled, **CC** – case-control, **CH** – cohort, **CI** – confidence interval, **Cm** – comparison, **CO** – crossover, **CS** – cross-sectional, **DB** – double-blind, **E** – epidemiological, **LC** – longitudinal cohort, **MA** – meta-analysis, **MC** – multi-center, **n** – number of patients, **O** – open, **OB** – observational, **OL** – open label, **OR** – odds ratio, **P** – prospective, **PB** – patient-blind, **PC** – placebo-controlled, **PG** – parallel group, **PS** – pilot study, **R** – randomized, **RC** – reference-controlled, **RCS** – retrospective cross-sectional, **RS** - retrospective, **S** – surveillance, **SB** – single-blind, **SC** – single-center, **U** – uncontrolled, **UP** – unpublished, **VC** – vehicle-controlled.