

Editor's Note: Adverse drug reactions experienced by HMC, SCCA, or UWMC patients and reported via Patient Safety Net (PSN) are reviewed quarterly by the UW Pharmacy & Therapeutics Committee. Following the Committee's review, a literature-based companion article regarding some aspect of adverse drug reactions is published in this newsletter. It is hoped that these articles will be useful tools to remind prescribers of the fundamental principle of pharmacology that states, "No drug has only one action." By reminding prescribers to be alert to the appearance of undesired and unintended actions of drugs, therapeutic outcomes may be improved and adverse events minimized. If you have a patient you feel is experiencing an Adverse Drug Reaction, please report it via Patient Safety Net.

ADR Focus by Elizabeth Rudy, DVM, RPh

Do You Know What's Really in Dietary Supplements?

Between 1990 and 1992 approximately 10,000 dieters in Belgium took diet pills containing a combination of Chinese herbs and prescription drugs that were provided by a group of weight-loss clinics. After approximately 70 people experienced renal failure and another 50 suffered renal damage serious enough to require treatment, it was discovered that the clinic pharmacists had been unknowingly using a mislabeled Chinese herb to compound the diet pills. The Chinese herb that was used by accident was Aristolochia fangchi, which contains aristolochic acids, known to be both nephrotoxic and carcinogenic in mammalian species. In 1994, the first cases of urinary tract cancers were reported among the people who had taken these diet pills. Thirty-nine users underwent recommended prophylactic surgery to remove nonfunctioning kidneys and ureters in hope of preventing the development of cancer. Unfortunately, analysis of excised tissues from this group showed histologic evidence of cancer in 18 samples and precancerous lesions in 19 others.^{1,2}

In 2002, it was estimated that Americans spent close to \$19 billion on dietary supplements, approximately half of this amount was spent on minerals and vitamins, and about one quarter on herbal products.³ Currently there are more than 29,000 dietary supplements on the market, with an estimated 1,000 new products being added each year.³ The adulteration of dietary supplements occurs frequently, but the majority of consumers and health care providers are unfamiliar with this under-reported and potentially dangerous problem. The purpose of this *ADR Focus* is to increase practitioner awareness of this worrisome issue and provide an update on some of the efforts underway to rectify it.

In the early 1990s, when the Food and Drug Administration (FDA) considered regulation of dietary supplements, manufacturers of these products and health food stores instituted a massive lobbying effort against regulation.¹ Over the objections of FDA, the Dietary Supplement Health and Education Act (DSHEA) was passed by Congress in 1994, creating a new product class, "the dietary supplement," that was not subject to the strict FDA regulations that applied to drugs. The DSHEA defines dietary supplements as "vitamins, minerals, amino acids, botanicals, and 'other' dietary ingredients."³

Passage of the DSHEA created a dangerous loophole that prevents any effective FDA regulation of the dietary supplement industry. The DSHEA assumes that the dietary supplement industry can self-regulate and prevents FDA from taking action unless it can initially prove that a product is likely to cause "imminent harm" to the user.⁴ FDA was essentially handed the burden of *proving* a dietary supplement is harmful instead of requiring the manufacturer to demonstrate that it is safe.

(Continued on page 2)

A University of Washington Drug Information Center publication
Distributed monthly by authority of the Pharmacy and Therapeutics Committee
Editor: Nelda A. Murri, Pharm.D. (206) 598-6612 – Asst. Editor: Elizabeth Rudy, D.V.M., R.Ph.
Department of Pharmacy Services / School of Pharmacy

Copyright © 2006 by the University of Washington
Also published on the World Wide Web at <http://uw.prnrx.org/therapyTopics.asp>
No material may be reproduced in whole or in part without written permission from the editor.

Do You Know What's Really in Dietary Supplements? (continued)

Passage of the DSHEA created a dangerous loophole that prevents any effective FDA regulation of the dietary supplement industry.

Dietary supplement adulteration can be defined as either "unintentional" or "intentional."

In 1993, FDA launched the Special Nutritionals Adverse Event Monitoring System to monitor adverse reactions involving dietary supplements. This program was replaced in 2002 by the Center for Food Safety and Applied Nutrition (CFSAN) Adverse Events Reporting System (CAERS). A report from the U. S. Office of Inspector General (GAO) has labeled FDA's reporting system for dietary supplements as an "inadequate safety valve" with regard to its ability to collect data and identify potentially harmful products and trends.⁵

Dietary supplement adulteration can be defined as "the addition, (intentional or unintentional) of impurities or inferior products [to the supplement] or the removal of valuable portions" from such a product.⁶ Contamination generally originates from one of four sources: (1) vegetable (plant used by mistake or toxic part of the desired plant retained); (2) biological (insects, bacteria, undesirable parts of animals included); (3) mineral (lead or other heavy metal retained); (4) drug (addition of medications).⁴ Adulteration is often defined as either "unintentional" or "intentional."

The majority of cases of contamination of dietary supplements appear to be unintentional in nature (see Table I). Human error and the processes employed to produce dietary supplements offer a plethora of opportunities for unintentional contamination to occur.⁴ Collection of plants for inclusion in a supplement may require harvesting by persons with specific knowledge as to what parts of the plant are toxic and what parts are medicinal. If mechanical means are used to collect the needed plants, or untrained gatherers are employed, the final product may be contaminated with unwanted, potentially toxic botanicals.

Table I:
Examples of Unintentional Adulteration of Dietary Supplements

(Taken from FDA and Health Canada Advisories issued 2001-2005)

Dietary Supplement	Contaminant
Nature's Way Nettle capsules	Lead
Hashmi Kohl Aswad	Lead
Neo Concept Aller Relief	Aristolochic acid
Lung Tan Xie Gan pills	Aristolochic acid
Yograj Guggul tablets	Lead, mercury, and/or arsenic
Sensa Hair Supplement capsules	Lead, mercury, arsenic
Strauss Lymphatic capsules	Chaparral
Seavite Premium Atlantic Kelp tablets	Iodine
Bejai Bowyantant powder	Borneolum syntheticum
Various dietary supplements	Kava
Various dietary supplements	Comfrey
Various dietary supplements	Star anise

FDA does issue warnings when contaminated dietary supplements are discovered on the market; however, these usually appear after consumers have been exposed and harmful effects reported.

Contamination can also occur if the plants included in a product contain unidentified components that are either toxic or have unwanted physiological effects.⁴ If these unwanted components are unknowingly carried throughout the dietary supplement manufacturing process, they may ultimately end up in the final product. One example would be heavy metal contamination of a dietary supplement due to the inclusion of some plants in the final product that have the ability to effectively extract heavy metals from the soil. To illustrate this point, in a 2001 study, Huggett, et al., analyzed heavy metal levels in select botanical dietary supplements.⁷ They found high cadmium levels in one of the tested supplements that contained St. John's wort. They report that St. John's wort is considered to be a cadmium assimilator.

Another example includes a dietary supplement produced from coumarin-containing plants (such as red clover or fenugreek) from which these potentially dangerous components have not been removed during the manufacturing process.⁴ Botanical coumarins (related to medicinal coumarin derivatives such as the anticoagulant warfarin) have antiplatelet effects. Consumers buying the finished product could unknowingly be put at an increased risk for bleeding, and use of such a product by a consumer on anticoagulant therapy could result in serious adverse effects.

Often, dietary supplement manufacturers in the United States will import raw plant products or animal tissues for inclusion in their products. Current importation regulations for these substances are inadequate to protect consumers.⁴ This presents another

(Continued on page 3)

The USP Dietary Supplement Verification Program was created to inform and safeguard consumers who use dietary supplements.

potential avenue for contamination of dietary supplements. In a Letter to the Editor of the *New England Journal of Medicine*, Norton raised concerns about contamination of dietary supplements with bovine tissue that could be infected with bovine spongiform encephalopathy (BSE).⁸ The U.S. Department of Agriculture ban on importation of bovine tissues from countries where the disease has been reported in cattle extends only if the tissues are to be used in food, medicinal products, and medical devices, and does not cover inclusion in dietary supplements.⁸ The DSHEA only gives FDA the right to *recommend* the exclusion of these high-risk animal tissues from dietary supplements (whether from a national or international source) but does not allow their prohibition.

Intentional contamination of dietary supplements with drugs can occur if a necessary natural component is expensive, in short supply, or if an unscrupulous manufacturer wants

to intensify a specific pharmacological effect.⁴ Drugs, such as corticosteroids, ephedrine, benzodiazepines, caffeine, and non-steroidal anti-inflammatories are sometimes added to dietary supplements in order to make the user feel better.⁴ The reason why a multitude of other prescriptions drugs show up in dietary supplements remains unclear (see Table II). Regardless, intentional contamination of dietary supplements with drugs presents a hidden and serious hazard to users of these products.

Attempts to resolve the problem of adulteration of dietary supplements on both a national and international level have been slow in coming. In 2001, the U.S. Pharmacopeia Convention (USP) launched its

Dietary Supplement Verification Program (DSVP). This independent verification program is open to manufacturers of dietary supplement products recognized under the DSHEA. It was created to inform and safeguard consumers who use dietary supplements. USP will not accept a dietary supplement into the verification program if it contains an ingredient known to present safety concerns (such as ephedra, kava, comfrey, chaparral, or aristolochia).³ When a manufacturer submits their product to the program, it is tested to show that: 1) it has labeling that is accurate; 2) it contains the ingredients stated on the label, in the amount/strength declared on the product label; 3) it passes rigorous standards for product purity and meets federal requirements for limits on potential contaminants (including heavy metals, microbes, and pesticides); and 4) it has been manufactured properly by complying with both USP and proposed FDA standards for "good manufacturing practices" (GMP).^{3,9} If the submitted product passes the USP evaluation, it is awarded the DSVP verification mark that is placed on the product's container. Atwater et al., estimated that by the end of 2004, 20% to 25% of mass-marketed vitamin/mineral supplements displayed the USP verification mark.³ A visit to the USP website shows a total of five companies, to date, participating in the USP-Verified Program for Dietary Supplements (see Table III).

As discussed previously, FDA is unable to effectively police and prevent problems on a national level due to restrictions written into the DSHEA legislation. FDA does issue warnings and recall notices when contaminated dietary supplements are discovered on the market; however, these usually appear *after* consumers have been exposed and harmful

(Continued on page 4)

Table II:
Examples of Intentional Adulteration of Dietary Supplements
(Taken from FDA and Health Canada Advisories issued 2001-2005)

Dietary Supplement	Contaminant
Kartien Slimming Herbs capsules	Sibutramine
Liqiang 4 Dietary Supplement capsules	Glyburide
Actra-Rx	Sildenafil
Viga	Sildenafil
Male Power Plus	Tadalafil
BellMagnum Bullet capsules	Tadalafil-like substance
Ancom Anti-Hypertensive Compound Tablets	Reserpine, diazepam, promethazine, hydrochlorothiazide
RA Spes	Alprazolam, indomethacin
HepaStat	Indomethacin
Osporo	Diethylstilbesterol (DES)
Lipokinetix	Phenylpropanolamine, caffeine, yohimbine, diiodothyroxine, sodium usniate
Shortclean	Gylburide, phenformin



Figure 1: USP-Verified Seal

Table III:
Companies Participating in the USP-Verified Program for Dietary Supplements

Inverness Medical Innovations
Leiner Health Products
Pharmavite LLC
Tishcon Corporation
Weider Nutrition

References

1. Miller HI, Longtin D. Death by dietary supplement. *Policy Review* 2000; Aug/Sept (102):15-26.
2. Nortier JL, et al. Urothelial carcinoma associated with the use of a Chinese herb (aristolochia fangchi). *NEJM* 2000; 342(23):1686-1692.
3. Atwater J, Montgomery-Salguero J, Roll DB. The USP dietary supplement verification program: helping pharmacists and consumers select dietary supplements. *US Pharmacist* 2005; 6:61-64.
4. Cole MR, Fetrow CW. Adulteration of dietary supplements. *Am J Health-Syst Pharm* 2003; 60:1576-1580.
5. Office of Inspector General (Department of Health and Human Services). Adverse event reporting for dietary supplements. OEI-01-00-00180 April 2001:1-110.
6. MacDonald Hocking GM. A dictionary of natural products. Medford, NJ: Plexus Publishing, 1997:18.
7. Huggett, et al. Organochlorine pesticides and metals in select botanical dietary supplements. *Bull Environ Contam Toxicol* 2001;66:150-155.
8. Norton SA. Raw animal tissues and dietary supplements [letter]. *NEJM* 2000;343(4):304-305.
9. United States Pharmacopeia. US Pharmacopeia news release: March 8, 2002.
10. FDA. FDA announces major initiatives for dietary supplements: Nov 4, 2004.
11. Directive 2002/46/EC of the European Parliament and of the Council of 10 June 2002 on the approximation of the laws of the Member States relating to food supplements. *Official Journal of the European Communities* 2002; L183:51-57.
12. Ferner RE, Beard K. Regulating herbal medicines in the UK. *BJM* 2005; 331:62-63.

or toxic effects reported. In November 2004, in an ongoing attempt to better police the dietary supplement industry, FDA announced three major regulatory initiatives designed to further "implement" the DSHEA. The approach includes a regulatory strategy, an open public meeting, and a draft guidance document for industry.¹⁰ Transcripts from the open public meeting that was held on November 15, 2005 can be accessed at the following URL: <http://www.fda.gov/ohrms/dockets/dockets/04n0454/04n-0454-tr00001.htm>.

On the international front, the European Union's Directive on Food (Dietary) Supplements (Directive 2002/46/EC) adopted in June of 2002 went into effect in August 2005.¹¹ This directive specifies which food (dietary) supplements may be sold in countries that are members of the European Union and lists all vitamins and minerals that may be sold as or used in the production of these supplements. Additionally, the directive imposes specific labeling requirements for marketed supplements. In October 2005, another European Union directive, the Traditional Herbal Medicinal Products Directive (Directive 2004/24/EC) went into effect. This directive attempts to place some regulation on which herbal products may be sold in member countries of the European Union.¹²

To date, the ability of FDA to effectively regulate marketed dietary supplements in order to provide adequate consumer protection has been hampered by numerous factors including strong opposition from the dietary supplement industry itself and the DSHEA. Recent ongoing efforts, both in the United States and in Europe to regulate these products are encouraging. However, it probably will be a long time until adequate processes are in place to assure the safety of all dietary supplement products available in the marketplace. Until that time, the best defense for the consumers of dietary supplements is education about the potential dangers lurking within these products.

The editor gratefully acknowledges the assistance of Barak Gaster, M.D., in reviewing this article.

Vol. 35, No. 1

Newsletter: Do You Know What's Really in Dietary Supplements? 1-4

Insert: Complementary & Alternative Medicine: St. John's Wort

Supplement: Contemporary Issues in Drug Therapy



DRUG INFORMATION CENTER
Box 354735
Seattle, WA 98195-4735

drug therapy topics