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FILE: ▪ Black Cohosh (*Actaea racemosa* syn. *Cimicifuga racemosa*)
▪ Hepatotoxicity
▪ United States Pharmacopeia (USP)

HC 040592-384

Date: September 15, 2009

RE: USP Evaluates Safety of Black Cohosh Due to Possible Association with Liver Toxicity

Mahady GB, Low Dog T, Barrett ML, et al. United States Pharmacopeia review of the black cohosh case reports of hepatotoxicity. *Menopause*. July/August 2008;15(4):628-638.

The United States Pharmacopeia (USP) is a voluntary, nonprofit, science-based organization that sets standards for foods and drugs. USP standards and reference materials are recognized in about 130 countries worldwide. USP standards are established by Expert Committees, which include 5 Expert Committees on dietary supplements. The Dietary Supplements Information Expert Committee evaluates safety information and assigns dietary supplements to one of 4 safety categories.[1] In 2002, the Expert Committee assigned black cohosh (*Actaea racemosa* syn. *Cimicifuga racemosa*) a Class 1a rating, which means there are limited safety data from humans but no significant safety issues. Since 2002, reports of links between black cohosh and hepatotoxicity (liver damage) have surfaced, prompting the Expert Committee to revisit the safety classification. This article summarizes the Expert Committee's review methodology, findings, and conclusions regarding the safety of this popular herb.

The Expert Committee focused on adverse event reports of potential hepatotoxicity from 8 main sources: (1) European Agency for the Evaluation of Medicinal Products/Herbal Medicinal Products Committee, (2) Health Canada Advisory and Canadian Adverse Drug Reaction Monitoring Program, (3) Australian Therapeutic Goods Administration, (4) US National Institutes of Health's report from the Workshop on the Safety of Black Cohosh in Clinical Studies, (5) United Kingdom Medicines and Healthcare Products Regulatory

[1] In February 2009, USP revised Admission Criteria and Safety Classification for dietary supplements - http://www.usp.org/USPNF/notices/USPRevisedAdmissionCriteria.html

Agency, (6) MedWatch reports from the US Food and Drug Administration (FDA), (7) clinical trials, animal studies, and toxicological information available on PubMed, and (8) USP's MEDMARX adverse event report database. The Expert Committee analyzed 30 nonduplicative reports related to liver damage and black cohosh. The Naranjo algorithm was used to assess the probability that hepatotoxicity was caused by black cohosh use. The doses in these adverse event reports ranged from 20 mg of extract to 1,500 mg of root, and these doses fall within typical recommended dose ranges.

The European Agency for the Evaluation of Medicinal Products/Herbal Medicinal Products Committee evaluated 42 reports of hepatotoxicity and in July 2006 issued a statement regarding a potential connection between black cohosh and hepatotoxicity. The public statement included warnings for patients and healthcare professionals to be aware of symptoms of liver damage while taking products containing black cohosh. Four case reports are described in detail in this article.

Health Canada's Canadian Adverse Drug Reaction Monitoring Program received 2 reports of elevated liver enzymes with black cohosh use. In August 2006, Health Canada issued a consumer advisory about a possible link between black cohosh and liver damage and warned consumers to stop using black cohosh if they develop any symptoms suggestive of liver damage.

The Australian Therapeutic Goods Administration reviewed 47 cases of liver reactions worldwide, including nine from Australia, in February 2006. Following this review, products containing black cohosh began carrying label warnings about the possibility of harm to the liver. In May 2007, a Therapeutic Goods Administration advisory group concluded that there appears to be an association between the use of black cohosh and liver damage, but that liver damage is very rare. The UK Medicines and Healthcare Products Regulatory Agency also mandated a label warning in 2006 based on 21 reports of liver reactions in people taking black cohosh.

Since 2001, the FDA MedWatch reporting system received 11 reports of liver damage possibly related to black cohosh use. A review of the safety of black cohosh based on clinical trials cited in PubMed found no reports of liver toxicity, and this review supports the relative safety of black cohosh. The USP Expert Committee found that the link between liver damage and black cohosh is weak and that causality according to the Naranjo scale was possible. Despite the limitations of the available data, considering the seriousness of the possible adverse reactions and the increase in recent reports, the Expert Committee concluded that the appropriate safety category for black cohosh is Class 2. Class 2 indicates greater safety concerns than Class 1a, the safety category established by the Expert Committee in 2002. Class 2 means there are no known significant safety issues when the product is formulated and used properly, but that a cautionary statement is required on the product labeling. The Expert Committee recommended the following cautionary statement:

"Discontinue use and consult a healthcare practitioner if you have a liver disorder or develop symptoms of liver trouble, such as abdominal pain, dark urine, or jaundice."

The authors point out several limitations of this analysis. In the majority of the adverse event reports, the black cohosh product was not identified or analyzed. Contamination of black cohosh with other species is known to occur, and contamination or adulteration with other species may contribute to hepatotoxicity. The FDA estimates that less than 1% of all adverse events associated with dietary supplements are reported to the FDA, and the small number of reports makes causality more difficult to establish. Concurrent use of hepatotoxic drugs and alcohol, pre-existing liver disease, and the occurrence of spontaneous hepatotoxicity all complicate the analysis.

In October 2007, the American Botanical Council sent a letter to USP during its public comment period in which ABC pointed out several problems in the AER (adverse event report) and scientific literature on the alleged association of black cohosh products and hepatotoxicity. In its comments, ABC stated that the available data concerning the possible association between hepatotoxicity and black cohosh ingestion provide insufficient evidence to warrant the proposed caution by USP. ABC further commented that the widespread and historical use of black cohosh products, coupled with the lack of scientific evidence of toxicity, strongly suggest that there is no attributable risk associated with the use of properly manufactured black cohosh preparations. ABC added that case reports suggesting potential hepatotoxicity of black cohosh are not adequately substantiated and the process by which the USP evaluated black cohosh's safety may not meet some of the standards proposed to perform an adequate safety evaluation.

According to two authors of the *Menopause* paper, Tieraona Low Dog MD and Dandapantula Sarma PhD, several new case reports of black cohosh have been reported since the publication of their article: US FDA (ISR #4056698-X; 4087633-X; 4105367-X); Australian TGA (#220336; 227199; 229161; 232304; 235008); Health Canada (#178821; 208967); Vannacci et al, 2009; Pierard et al, 2009; Chow et al, 2008; Dunbar and Solga, 2007; Joy et al, 2008; Nisbet and O'Conner, 2007. [Personal communication to Lori Glenn, Dr. Low Dog (7/27/2009) and Dr. Sarma (7/31/2009)] Dr. Low Dog states the following: While the USP-DSIEC recognizes that the causal association of black cohosh-mediated liver damage is weak, the growing volume of reports cited in the current paper underscores the potential need for a label caution for black cohosh products. Further efforts need to be undertaken to dismiss or to substantiate the likelihood of black cohosh-induced hepatotoxicity through prospective causality evaluation in patients.

The proposed label statements for USP black cohosh monographs became official effective from December 1, 2008 (Second Supplement to USP31-NF26).

—Heather S. Oliff, PhD

The American Botanical Council has chosen not to reprint the original article.