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United States Pharmacopeia review of the black cohosh case reports of hepatotoxicity

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Abstract

Objective: Black cohosh [*Actaea racemosa* L., formerly *Cimicifuga racemosa* (L.) Nutt.] is a botanical used mainly for the management of menopausal symptoms. Recently, regulatory agencies in Australia, Canada, and the European Union have released statements regarding the "potential association" between black cohosh and hepatotoxicity. In response, the Dietary Supplement Information Expert Committee of the US Pharmacopeia's Council of Experts reviewed safety information for black cohosh products.

Design: The Expert Committee analyzed information from human clinical case reports, adverse event reports, animal pharmacological and toxicological data, historical use, regulatory status, and contemporaneous extent of use. Reports were obtained from diverse sources, including the European Medicines Agency, Health Canada, the Australian Therapeutic Goods Administration, and the US Food and Drug Administration. Case reports pertaining to liver damage were evaluated according to the Naranjo causality algorithm scale.

Results: Thirty nonduplicate reports on use of black cohosh products concerning liver damage were analyzed. All the reports of liver damage were assigned possible causality, and none were probable or certain causality. The clinical pharmacokinetic and animal toxicological information did not reveal unfavorable information about black cohosh.

Conclusions: Based on this safety review, the Dietary Supplement Information Expert Committee determined that black cohosh products should be labeled to include a cautionary statement. This is a change from the Expert Committee's decision of 2002, which required no such statement. With this decision, the US Pharmacopeia's Botanical Expert Committee may develop monographs for black cohosh, and the US Pharmacopeia may offer its verification programs to dietary supplement ingredient and product manufacturers.

Key Words: Black cohosh – *Actaea racemosa* – *Cimicifuga racemosa* – Dietary supplements.

Founded in 1820, the US Pharmacopeia (USP) is a voluntary, science-based, nonprofit, standards-setting organization for foods and drugs. Two of its principal publications, the *USP* and the *National Formulary* (*NF*), are recognized in the US Federal Food, Drug, and Cosmetic Act as official compendia of the United States.[1,2] USP documentary standards and reference materials (also termed official USP reference standards) are recognized not only in the United States but also in approximately 130 nations worldwide. USP's standards-setting body is the Council of Experts, which has five Expert Committees devoted to the creation of official standards for dietary supplements (DSs). These are the DS Information (DSI), Bioavailability, Botanicals, General Chapters, and Nonbotanicals Expert Committees. Beyond USP's documentary standards and reference materials, USP has established DS verification programs that include audit, review, and testing components to assist manufacturers in assuring the public that they are making good-quality DS and DS ingredients.[3]

The US Dietary Supplement Health and Education Act of 1994 (DSHEA) amendments to US Federal Food, Drug, and Cosmetic Act stipulate that if a DS is (1) covered by the specifications (tests, procedures, and acceptance criteria of a monograph) of an official compendium (*USP–NF*), (2) is represented as conforming to the specifications of an official compendium (*USP–NF*), but (3) fails to so conform, then the supplement is considered to be misbranded within the meaning of the US Federal Food, Drug, and Cosmetic Act [§403(s)(2)(D)]. This affords legal recognition to *USP–NF* standards for dietary supplements.

During the 2000 to 2005 cycle, the DSI EC established three classes of DS safety for consumers: (1) safe with no labeling statement; (2) safe only with a suitable labeling statement; or (3) not safe irrespective of label statements (Table 1). Assuming a decision in the first two categories, other USP DS Expect Committees may consider setting

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TABLE 1. *Safety class assignations from Dietary Supplements Information Expert Committee (DSI EC)*

The DSI EC evaluates dietary supplement safety information from diverse sources and categorizes articles into one of the following classes:

Class 1: Articles for which the Committee is unaware of significant safety issues that would prohibit monograph development when the article is used and formulated appropriately.

Class 1a: Articles for which the Committee is aware of limited human scientific data concerning safety of the article but is unaware of significant safety issues that would prohibit monograph development when the article is used and formulated appropriately.

Class 2: Articles for which the Committee is unaware of significant safety issues that would prohibit monograph development when the article is used and formulated appropriately, provided there is a warning statement in the labeling section.

Class 3: Articles for which the Committee is aware of significant safety issues that would prohibit monograph development.

Articles in Class 1, 1a, or 2 would be eligible for a monograph in *US Pharmacopeia* or *National Formulary* and could be admitted into the USP Dietary Supplement Verification Program. However, articles in Class 2 would also require a warning statement in the labeling section. Articles in Class 3 would be admitted neither to *US Pharmacopeia* nor *National Formulary* nor the US Pharmacopeia Dietary Supplement Verification Program because of significant safety issues. However, class assignations are not static and may be revised because of significant adverse event reports. Therefore, the US Pharmacopeia monitors adverse events reported for all dietary supplements for which monographs have been developed. In this manner, adverse event signals can prompt safety re-evaluation and possible reclassification of a supplement.

The following are some examples of the recent safety assessments:

	Class 1	Class 1a	Class 2	Class 3
Asian ginseng	√			
Cat's claw		√		
Chamomile	√			
Chaste tree	√			
Cranberry	√			
Echinacea angustifolia			√	
Echinacea pallida			√	
Echinacea purpurea			√	
Eleuthero		√		
Feverfew	√			
Garlic	√			
Ginger	√			
Ginkgo	√			
Goldenseal		√		
Hawthorn leaf with flower	√			
Horse chestnut	√			
Kava				√
Licorice			√	
Milk thistle	√			
Red clover	√			
Saw palmetto	√			
Spirulina	√			
St. John's wort			√	
Stinging nettle	√			
Valerian	√			

quality standards, and USP may consider verifying a DS and/or its ingredient.

The DSI EC uses the following criteria as they begin a DS safety evaluation: (1) *apparent efficacy* or a presumptive belief in some beneficial activity as evidenced by a long history of use; (2) *demand* or the extent of use by the public sector; (3) *public protection* indicating interest by a regulatory agency; (4) *feasibility* suggesting the likelihood that the ingredient could meet compendial criteria; (5) *compendial presence* demonstrated by the existence of monographs in other official compendia; and (6) *safety* as indicated by a long history of use. If these criteria are met, the DSI EC conducts extensive safety reviews of the selected dietary ingredients, analyzing information from human clinical case reports, adverse event reports (AERs), animal pharmacological and toxicological data, historical use, regulatory status, and global contemporaneous extent of use.

In 2002, black cohosh was assigned a Class 1a rating (Table 1). Numerous case reports after this time suggested possible links between black cohosh and hepatotoxicity, prompting the DSI EC to revisit this initial safety classification. This article summarizes the DSI EC's review and conclusions, working with USP staff.

PRODUCT DESCRIPTION

Black cohosh-based products are among the commonly used dietary supplements in the United States.[4] Black cohosh (*Actaea racemosa* [L.], synonym *Cimicifuga racemosa* [L.] Nutt.) is a perennial woodland plant native to North America. A monograph for black cohosh appeared in the first *USP* in 1820, and the herb was listed in the *US Dispensatory* from 1833 until 1955. Other species of *Actaea*, especially the American species *Actaea podocarpa* (syn. *Cimicifuga americana*; yellow cohosh) have been confused with black cohosh because of the similarity of the ground parts.[5] A number of Asian species of *Actaea* are also marketed, including *A. cimicifuga* (syn. *Cimicifuga foetida*), *A. dahurica* (syn. *C. dahurica*), and *A. heracleifolia* (syn. *C. heracleifolia*).[6] (*C. dahurica* is sold as sheng ma, and many Web sites call it black cohosh). Adulteration or substitution of black cohosh with ingredients of similar binomial name or similar common name (for example, blue cohosh, *Caulophyllum thalictroides*) is a concern. Dose forms contain dried plant material (root or rhizome), hydroalcoholic liquid extracts, and dried extracts of black cohosh. *USP* quality monographs with specifications for these articles became official in the *2nd Supplement* to *USP 30-NF 25* in December 2007. Suitable identification tests are included in the *USP* monograph to facilitate proper identification of black cohosh articles.

METHODS

The focus of the review is AERs for hepatotoxicity from the following sources: (1) European Agency for the Evaluation of Medicinal Products/Herbal Medicinal Products Committee (EMEA/HMPC) report titled "Assessment of Case Reports Connected to Herbal Medicinal Products Containing *Cimicifugae racemosae* Rhizoma (Black Cohosh, Root)," (2) Health Canada Advisory and Canadian Adverse Drug Reaction Monitoring Program (CADRMP)—all available, (3) Australian Therapeutic Goods Administration (TGA)—all available, (4) NIH Workshop on the Safety of Black Cohosh in Clinical Studies, (5) United Kingdom Medicines and Healthcare Products Regulatory Agency (MHRA)—all available, (6) MedWatch of the US Food and Drug Administration (FDA) from 2001 (reports before that time were considered in the DSI EC original evaluation and did not suggest an association between black cohosh and hepatotoxicity), (7) clinical trials and animal pharmacological or toxicological information from PubMed between 1966 and June 2007, and

(8) USP's MEDMARX AER database. For assessable case reports concerning liver damage, the Naranjo causality algorithm was used to assess the likelihood that black cohosh exposure resulted in hepatotoxicity.[7] This scale allows analysis of adverse event reports from different aspects: a patient's previous experience with the substance, evaluation of alternative etiologies, temporal correlation, correlation to intake, and dechallenge/rechallenge information. Taking these factors into account, Naranjo causation is rated as 0– doubtful or unlikely, 1 to 4– possible, 5 to 8– probable, and 9 to 13– definitive or certain.

The Committee debated the merits and limitations of using different causality algorithms, including the Naranjo scale,[7] Jones scale,[8] Kramer scale,[9] World Health Organization (WHO) causality method,[10] and Roussel Uclaf Causality Assessment Method (RUCAM).[11] Each of the methods analyzes the AERs on the basis of different strings: a patient's previous experience with the substance, alternative etiologies, temporal correlation, correlation to dose, and dechallenge/rechallenge information. Each method scores the question strings to assign the likelihood of causation: doubtful/unlikely, possible, probable, and definitive/certain. The objective in choosing a causality scale is to provide a reproducible method of identifying and understanding causality of AERs and to assist in scientific judgment. The algorithms make clear that the more detailed the available information is, the more accurate and reliable the assessment of causality. Some studies have compared the causality scales. Michel and Knodel,[12] for example, suggest that the simpler and less time-consuming Naranjo algorithm compares favorably with the Kramer algorithm in scoring adverse drug reactions. They note that more data are needed to support the use of the Jones algorithm.[8] The Naranjo scale also is adopted by USP's MEDMARX reporting system. The WHO causality method uses the same set of parameters as does Naranjo scale, but it lacks the flexibility to accommodate missing information. Although RUCAM was developed as an instrument to assess causality in drug-induced liver injury, the instrument is marred by seemingly arbitrary selections, the scoring of its components, its relative inflexibility, and its inability to deal well with missing data.[13,14] Recognizing the limitations of the RUCAM and similar causality assessment instruments, many studies rely on the consensus of experts. The DILI Network uses such a process currently for causality assessment in both retrospective and prospective studies.[15] Considering the limitations of dietary supplement AERs, most of which contain incomplete information or confounding variables, the DSI EC recognized the need for consistent evaluation using reliable causality scales. Accordingly, the Committee adopted the Naranjo scale to provide consistency in evaluations and to minimize biases by using a validated causality scale. A bonus is the Naranjo scale's facility in accommodating the limitations of missing data.

RESULTS

From the specified sources the authors found several reports concerning liver damage (five clinical case reports,[16-20] 11 from MedWatch, 2 from CADRMP, 17 from the TGA, and 42 cases from the HMPC report, including duplicate reports). These reports presented a prominent signal of the likely hepatotoxicity. Of these, 30 nonduplicate reports related to liver damage were subjected to Naranjo analysis. The results are shown in Table 2. Although the Committee is aware that the agencies such as the TGA and HMPC and the NIH workshop reviewed more than 30 reports concerning liver damage, all the reports were not available for our analysis. Duplicate reports (such as MedWatch reports 16335, 71405, 78642, and 78707, which were also published as case reports in journals[17,18,20]) were removed during the analysis. USP's MEDMARX medication error reporting system received documentation about three medication error reports that involved prescribing black cohosh. No adverse outcome was noted in any of these MEDMARX reports.

The doses of black cohosh in the AERs ranged from 20 mg (extract) to 1,500 mg of root. The Canadian black cohosh monograph[21] cites the dose range for nontraditional uses as 40 to 200 mg dried root or rhizome per day and for traditional uses at 300 to 3,000 mg dried root or rhizome per day. So the toxicity reported in the AERs occurred within recommended dose ranges.

REVIEW OF REPORTS AND DISCUSSION

Cases in EMEA/HMPC report

EMEA/HMPC issued a statement in July 2006 regarding a "potential connection" between *Cimicifuga racemosa* (black cohosh root/rhizome) and hepatotoxicity.[22] The HMPC evaluated 42 case reports of hepatotoxicity collected from European National Competent Authorities (34 cases), as well as literature case reports. According to the HMPC only 16 of the total 42 cases were considered sufficiently documented to allow assessment of a potential linkage of black cohosh and liver injuries. As a result of the HMPC assessment, five cases were excluded and seven cases were considered unlikely to be related. The HMPC made a temporal association of black cohosh in the remaining four cases (two autoimmune hepatitis, one hepatocellular liver injury, and one fulminant hepatic failure). The EMEA/HMPC issued a public statement concerning the serious hepatic reactions:

Advice to patients

Patients should stop taking *Cimicifugae racemosae rhizoma* (black cohosh, root) and consult their doctor immediately if they develop signs and symptoms suggestive of liver injury (tiredness, loss of appetite, yellowing of the skin and eyes, or severe upper stomach pain with nausea and vomiting or dark urine). Patients using herbal medicinal products should tell their doctor about it.

Advice to healthcare professionals

Healthcare professionals are encouraged to ask patients about use of products containing *Cimicifugae racemosae rhizoma* (black cohosh, root). Suspected hepatic reactions should be reported to the national adverse reaction reporting schemes.

TABLE 2. *Naranjo scores for the black cohosh adverse event reports*[a]

	Did the adverse event appear after the suspected drug was administered?	Did the adverse reaction improve when the drug was discontinued (dechallenge)?	Did the adverse reactions appear when the drug was readministered (rechallenge)?	Could alternative causes on their own have caused the reaction?	Was the adverse event confirmed by any objective evidence?	Naranjo score
HMPC case 28	2	0	0	0	1	3 (possible)
Cohen et al, 2004[16]	2	0	0	−1	1	2 (possible)
Lynch et al, 2006[17]	2	0	0	−1	1	2 (possible)
Levitsky et al, 2005[18]	2	0	0	−1	1	2 (possible)
CADRMP 165497	2	0	0	−1	1	2 (possible)
CADRMP 185112	2	0	0	−1	1	2 (possible)
Lontos et al, 2003[19]	2	0	0	−1	1	2 (possible)
Whiting et al, 2002, case 1[20]	2	0	0	0	1	3 (possible)
Whiting et al, 2002, case 2[20]	2	0	0	−1	1	2 (possible)
TGA 139186	2	0	2	−1	1	4 (possible)
TGA 139544 (repeat of Whiting et al, 2002[20])	2	0	0	0	1	3 (possible)
TGA 166931 (repeat of Whiting et al, 2002[20])	2	0	0	−1	1	2 (possible)
TGA 178294	2	0	0	0	1	3 (possible)
TGA 182984 (repeat of Lontos et al, 2003[19])	2	0	0	−1	1	2 (possible)
TGA 186427	2	0	0	0	1	3 (possible)
TGA 190457	2	0	0	0	1	3 (possible)
TGA 190948	2	0	0	0	1	3 (possible)
TGA 191840	2	0	0	0	1	3 (possible)
TGA 203637	2	0	0	0	0	2 (possible)
TGA 205849	2	0	0	0	1	3 (possible)
TGA 212843	2	0	0	0	0	2 (possible)
TGA 216299	2	0	0	0	1	3 (possible)
TGA 217463	2	0	0	0	1	3 (possible)
TGA 218638	2	0	0	0	1	3 (possible)
TGA 220336	2	0	0	0	1	3 (possible)
TGA 220338	2	0	0	0	1	3 (possible)
MedWatch 16335 (repeat of Whiting et al, 2002[20])	2	0	0	0	1	3 (possible)
MedWatch 66386	2	1	0	−1	1	3 (possible)
MedWatch 66388	2	1	0	−1	1	3 (possible)
MedWatch 71274	2	0	0	0	1	3 (possible)
MedWatch 71405 (repeat of Levitsky et al, 2005[18])	2	0	0	−1	1	2 (possible)
MedWatch 78642 (repeat of Levitsky et al, 2005[18])	2	0	0	−1	1	2 (possible)
MedWatch 78707 (repeat of Lynch et al, 2006[17])	2	0	0	−1	1	2 (possible)
MedWatch 84565	2	0	0	0	1	3 (possible)
MedWatch 84660	2	0	0	0	1	3 (possible)
MedWatch 85756	2	0	0	−1	1	2 (possible)
MedWatch 87056	2	0	0	0	1	3 (possible)

HMPC, Herbal Medicinal Products Committee; CADRMP, Canadian Adverse Drug Reaction Monitoring Program; TGA, Australian Therapeutic Goods Administration.

[a]Information that would allow answers to the following questions on the Naranjo scale was not available in the adverse event reports: Are there previous *conclusive* reports regarding this reaction? Did the reaction reappear when a placebo was administered? Was the drug detected in the blood (or other fluids) in concentrations known to be toxic? Was the reaction more severe when the dose was increased or less severe when the dose was decreased? Did the patient have a similar reaction to the same or similar drugs in any previous exposure? Accordingly, these questions were not listed in the table.

Of the 42 case reports on black cohosh considered by the HMPC, four cases were given a RUCAM score of 3 or more (possible to probable temporal association). Analysis of the four cases follows:

The first case (RUCAM score 4, possible causality) was associated with a report collected from the European National Competent Authorities and was not published in the medical literature. The HMPC report states that the patient used 80 mg/d (no information was reported about whether the product was an extract or whole plant material). No other information is publicly available. Applying the available information to Naranjo scale gives a score of 3 (possible causality).

The second case was a 57-year-old woman with a significant medical history of diabetes, polymyositis, and hypertension (reported by Cohen et al[16]). She had been using labetalol, fosinopril, verapamil, metformin, aspirin, and insulin for more than 2 years. The patient reported use of black cohosh tablets (brand and intake unknown) for 2 weeks. The HMPC report stated that "concomitantly used verapamil may cause allergic hepatotoxic reactions" and that the "onset of hepatocellular damage…could as well be multi-system autoimmune disease." Cohen et al reported positive dechallenge information for this case, but the case was confounded with a concurrent course of steroid treatment.

The patient was not certain about the intake, contents, or the brand of the black cohosh that she used. Excerpts from the NIH workshop[23] recognized this limitation of the case report: "Discussion…revealed that there is no certainty that the product taken by this patient included only black cohosh or any black cohosh. The patient recalled seeing the words 'black cohosh' on the bottle but could not remember any details about the label or the bottle, which she had discarded."[23] In the absence of the product information, it is difficult to assign causality. Applying the available information to the Naranjo scale gives a score of 2 (possible).

The third case was a 54-year-old woman with a history of hypothyroidism, fibromyalgia, osteoarthritis, and depression and was given a RUCAM score of 3 (possible). The patient had reportedly taken 1,000 mg of black cohosh (product not further specified) daily for several months and stated that she drank one or two glasses of wine daily. The case reports included elevated liver enzyme levels. The patient underwent orthotopic liver transplantation but died during the operation because of uncontrollable hemorrhage. Postmortem analysis revealed extensive centrilobular and bridging necrosis and severe canalicular and ductular cholestasis. This case report was first presented by Cohen[23] at the NIH workshop in 2004 and later was published by Lynch et al[17] in 2006. Several inconsistencies and confounding variables were noticed among these reports. Although the Cohen report cites 3 months of black cohosh use, Lynch et al cite 8 months of use. Although the Cohen report cites concomitant treatment with levothyroxine, fluoxetine, and a propoxyphene and acetaminophen combination product, Lynch et al do not cite the latter two medications. The HMPC[22] points out that "known interaction[s] between fluoxetine, propoxyphene, and paracetamol…in combination with contraindicated alcohol use may lead to significant hepatotoxic effect." These reports do not mention the duration and dose of the propoxyphene and acetaminophen combination use. Acetaminophen potentially can cause hepatotoxicity when used at high doses for long durations (as is possible for patients with fibromyalgia and osteoarthritis), especially in combination with alcohol. Further, according to Cohen's report, the patient was positive for hepatitis B surface antibody and herpes simplex virus immunoglobulin M, but Lynch et al[17] reported negative serology. Lynch et al report that the patient used 1,000 mg of black cohosh daily (brand not mentioned), but the product description in the US Food and Drug Administration (FDA) MedWatch report on this case (no. 78707), described in Table 3, does not correlate with the Lynch et al[17] report. Applying the available information to the Naranjo scale gives a score of 2 (possible).

The fourth case was a 50-year-old woman who reportedly used 500 mg of black cohosh daily (product not further characterized) for 5 months before the onset of jaundice (RUCAM score of 6, probable). This case was reported by Levitsky et al[18] in 2005 and also was recorded in FDA MedWatch reports 71405 and 78642. The authors reported that the patient "did not drink alcohol or use illicit drugs and was not taking any medications, including other herbal medications, acetaminophen, or nonsteroidal anti-inflammatory drugs." Provisional diagnosis of autoimmune hepatitis was made, and the patient required a liver transplantation. The patient filed a lawsuit in the US District Court for Nebraska against two manufacturers of black cohosh products. Although Levitsky et al[18] stated that no alternative causes for hepatotoxicity existed, the plaintiff's testimony revealed that the patient regularly consumed wine, used ibuprofen (a nonsteroidal anti-inflammatory drug) on a regular basis, and also used valacyclovir (Valtrex), a drug that is implicated in liver enzyme abnormalities.[24] This case report was originally assigned RUCAM causality rating of probable. With the original information, the Naranjo score is 5 (probable), but with the new information about alternative causality, it results in a score of 2 (possible).

The DSI EC further analyzed the four cases discussed above using other causality algorithms and considering new information regarding alternative causality. For this purpose,

TABLE 3. *Details of MedWatch cases regarding black cohosh and liver damage*

Case no.	Report date	Pathology	Comments
16335	Nov. 19, 2002	Acute drug-induced autoimmune hepatitis requiring liver transplantation	47-y-old patient reported using Remifemin for 1 wk (Whiting et al 2002 report[20])
66386	Feb. 5, 2004	Elevated GGT (>120)	Patient reported 2 mo of black cohosh use and positive dechallenge after 2 mo; product unknown; alcohol use reported
66388	Feb. 5, 2004	Reports elevated liver enzymes	Patient report; elevation of liver enzymes after 3 mo on polyherbal Estrohealth; reported positive dechallenge after 1 mo; alcohol use reported
71274	Aug. 12, 2004	Acute liver failure requiring transplantation	Patient underwent liver transplantation in June 2004; black cohosh product was not characterized
71405	Aug. 4, 2004	Liver transplantation	Pharmavite reported the case cited in Levitsky et al, 2005[18]
78642	June 3, 2005	Fulminant liver failure	Levitsky et al, 2005[18]
78707	June 7, 2005	Fulminant liver failure	Lynch et al, 2006[17]
84565	May 22, 2006	Autoimmune hepatitis	Patient report; Rexall's black cohosh
84660	Mar. 28, 2006	Elevated liver enzymes	Remifemin used
85756	May 22, 2006	Patient developed jaundice	Patient used a polyherbal regimen (Dual Action Cleanse Colon Clear Formula) for at least 30 d; patient increased alcohol to 5 times/wk (5-6 drinks each time); product contains skullcap
87056	July 21, 2006	Liver transplantation	Patient reported taking Spring Valley black cohosh (TID) for 21 d

GGT, γ-glutamyltranspeptidase.

the DSI EC evaluated the cases using the Jones algorithm[8] and the Kramer algorithm[9] in addition to the Naranjo method (Table 4). Multiple analytical tools were used to validate the causality assignment. The causality scores by the Naranjo and Jones algorithms correlated for all four cases. Application of the Kramer algorithm to the reports resulted in a causality level lower than those from the Naranjo and Jones methods. The differences in the causality score results between the RUCAM method and the other three methods in the case of the report by Cohen et al[16] could be attributed to alternative causes discussed above.

The HMPC[22] revised its assessment in May 2007 by including two additional case reports (including one possible causality). The revised assessment retained the advice to patients in view of the potential liver reactions.

CADRMP reports

The Natural Health Products Directorate (NHPD) is the regulating authority for natural health products for sale in Canada. On August 18, 2006, Health Canada issued an advisory to consumers about a possible link between black cohosh and liver damage. Health Canada qualified its advisory by noting that "case reports of liver damage are rare, and the link between black cohosh and liver toxicity is unclear." The NHPD advisory states that "consumers should discontinue the use of products containing black cohosh and consult a physician if they have unusual fatigue, weakness, loss of appetite, or if they develop symptoms suggestive of liver injury such as yellowing of the skin or whites of the eyes, dark urine, or abdominal pain."

Based on information from the Australian TGA, the NHPD estimated that the frequency of AERs for black cohosh is less than 1 in 10 million daily doses. The NHPD updated its black cohosh monograph in March 2007, including a risk statement: "Consult a health care practitioner prior to use if you have a liver disorder or develop symptoms of liver trouble."

Health Canada CADRMP has received two reports dealing with black cohosh and elevated liver enzymes. The details of the two reports are provided in Table 5. In both of these reports, the patients were taking multiple medications or consumed alcohol. Further, the black cohosh products were not characterized, which makes it difficult to ascribe hepatotoxic reactions to black cohosh. When the available information is applied to the Naranjo scale, the result is a possible causality rating for both the reports.

TABLE 4. *Comparative analysis of the HMPC cases (RUCAM score ≥3) by different causality algorithms*

Case report	Naranjo[7] score	Jones[8] score	Kramer et al[9] score
HMPC case no. 28	3 (possible)	Possible	0 (possible)
Cohen et al, 2004[16a]	2 (possible)	Possible	−1 (unlikely)
Lynch et al, 2006[17a]	2 (possible)	Possible	−1 (unlikely)
Levitsky et al, 2005[18a]	2 (possible)	Possible	−1 (unlikely)

HMPC, Herbal Medicinal Products Committee; RUCAM, Roussel Uclaf Causality Assessment Method.

[a]New information about alternative causality was applied to the case reports[16-18] for analysis according to Naranjo, Jones, and Kramer algorithms.

TABLE 5. *Canadian Adverse Drug Reaction Monitoring Program reports regarding black cohosh and liver damage*

Report ID no.	Date received	Pathology	Comments
165497	Dec. 29, 2003	Elevated liver enzymes	46-y-old patient reports concurrent use of acetaminophen with codeine and methocarbamol with acetaminophen
185112	May 11, 2005	Elevated liver enzymes	51-y-old patient reports concomitant alcohol use

Reports from Australian TGA

In February 2006, the TGA reviewed 47 cases of liver reactions from around the world, including nine Australian cases. According to the TGA statement,[25] "In Australia, four patients were hospitalized, including two who required liver transplantation. Although some reports are confounded by multiple ingredients, by more than one medication, or by other medical conditions, there is sufficient evidence of a causal association between black cohosh and serious hepatitis…. However, considering the widespread use of black cohosh, the incidence of liver reaction appears to be very low." Following the safety review, the TGA decided that medicines containing black cohosh should include the following label statement: "Warning: Black cohosh may harm the liver in some individuals. Use under the supervision of a healthcare professional." In May 2007, the TGA expert advisory group concluded that "there appears to be an association between the use of black cohosh and liver damage, but it is very rare."

The cases cited in the TGA review included those of Lontos et al,[19] Whiting et al,[20] Levitsky et al,[18] and Cohen et al.[16] The last two cases were reviewed above as part of the analysis of the HMPC report. The first two cases were also presented by Dr. Paul Kerlin from Australia (coauthor of the paper by Whiting et al[20]) at the NIH workshop in November 2004. The analysis of these two cases follows:

Lontos et al reported (TGA report 182984) that in January 2003 a case of acute liver failure was associated with the use of a pharmacist-prepared herbal mixture containing fluid-extracts of black cohosh (10% by volume), *Nepeta hederacea* (ground ivy; syn. *Glechoma hederacea* L.), *Hydrastis canadensis* (goldenseal), *Ginkgo biloba*, and *Avena sativa* (oat seed). The concentration of black cohosh was 1 g of herb per 1 mL of extract. The patient reported ingesting 7.5 mL of extract BID as needed, with an estimated total consumption of 600 mL for 3 months. The 52-year-old woman stopped taking the preparation 4 weeks before her hospital admission with symptoms of liver failure. She underwent liver transplantation in February 2003 and had an uneventful postoperative course.

Comments: The paper by Lontos et al was criticized in a letter by Thomsen et al,[26] who pointed out that a thorough investigation of the herbal preparation should be made before attributing the adverse event to black cohosh. The TGA response[27] recognized the uncertainties and stated that "on the evidence available it cannot be concluded that black cohosh was a cause." In view of these uncertainties, the application of alternative causality to the Naranjo scale results in a score of 2 (possible).

Whiting et al[20] published two case reports from Australia involving patients who presented with severe hepatitis after reportedly taking black cohosh preparations. The first case involved a 47-year-old patient who developed symptoms of jaundice after she had reportedly taken black cohosh (single ingredient) for 7 days. The patient subsequently required liver transplantation (this case was also recorded in FDA MedWatch 16335 and TGA 139544). The second case involved a 43-year-old patient who developed jaundice after reportedly taking black cohosh with several other herbs (intake or duration unknown), including skullcap (a herb known to be commonly adulterated or substituted with germander [*Teucrium chamaedrys*], which is associated with liver toxicity) and valerian (this case was also recorded in TGA 166931).

Comments: The lack of product information is a serious shortcoming in a number of case reports and is notable in the second case just discussed. Kouzi et al[28] noted that in some formulations germander (*T. chamaedrys*) has been substituted for skullcap. Vitetta et al[29] argue that no efforts were made to verify and analyze the herbal products taken by the patient in the second case just described, and no information was provided regarding the plant and parts of plants included in this preparation. Similarly, information was not provided about the solvent, concentration, manufacturing process, or chemical analysis of the product consumed.[29]

Considering these uncertainties, the HMPC report[22] rejected the first case report in the paper by Whiting et al concluding that "a relation to the intake of *Cimicifugae racemosae rhizoma* (Black Cohosh, root) is improbable because of the short time between intake of drug and transplantation." The HMPC report also rejected the second case report: "because of the combination of different herbs that have not been analyzed for their constituents and the lack of further information, it is not possible to assess the cause of liver failure." The application of available information, including the alternative causality in the second case report leads to a Naranjo score of 3 (possible) for the first case and a score of 2 (possible) for the second case.

TGA adverse drug reactions database reports

As of August 2006, the TGA received 17 reports involving black cohosh and liver toxicity, including the two cases reviewed by Whiting et al,[20] (TGA 139544 and 166931) and one case reviewed by Lontos et al.[19] These 17 reports are reviewed in Table 6.

Comments: The reports from Whiting et al and Lontos et al were analyzed earlier. Three reports included a product named 30 Plus, which contained black cohosh. Five other

TABLE 6. *Australian Therapeutic Goods Administration reports regarding black cohosh and liver damage*

Case no.	Report date	Pathology	Comments
139186	May 3, 1999	Hepatitis, jaundice	39-y-old patient reported using Femone (containing *Dioscoria villosa* and others) for 3 d before onset; rechallenge positive
139544	May 14, 1999	Hepatitis	47-y-old patient reported using Remifemin for 1 wk (repeat of Whiting et al, 2002 [20])
166931	July 1, 2001	Hepatitis, jaundice	43-y-old patient reported using black cohosh for 1 wk; skullcap was concurrently used (repeat of Whiting et al, 2002[20])
178294	Aug. 19, 2002	Hepatic function abnormal	43-y-old patient reported using black cohosh-containing product 30 Plus; concurrent treatment with prednisone, cyclosporine, enalapril maleate, aspirin, and metaprolol
182984	Feb. 17, 2003	Hepatic failure, jaundice	Repeat of Lontos et al, 2003[19]
186427	May 30, 2003	Hepatic steatosis	35-y-old patient reported using a black cohosh-containing product 30 Plus
190457	Sept. 12, 2003	Hepatic function abnormal	44-y-old patient reported using a black cohosh-containing polyherbal product Meno-Eze for 1 mo; symptoms appeared 1 mo after stopping Meno-Eze; minimal alcohol intake reported
190948	Sept. 29, 2003	GGT elevated	39-y-old patient reported using a black cohosh-containing product 30 Plus
191840	Nov.11, 2003	Liver function test abnormal	72-y-old patient reported using a black cohosh-containing product Swiss Women's Ultivite Multi-vitamin, Mineral, and Anti-oxidants; concurrent treatment with levothyroxine and celecoxib was reported
203637	Dec. 17, 2004	Hepatitis	30-y-old patient reported using a black cohosh-containing product Cenovis Libido for Her for 100 d (BID); no lab results provided; concurrent treatment with gabapentin, felodipine, oxycodone, and hydroxychloroquine sulfate was reported
205849	Mar. 8, 2005	Liver function test abnormal	55-y-old patient reported long-term Remifemin usage; prior history of carcinoma of breast
212843	Oct. 26, 2005	Hepatitis	47-y-old patient used Fusion Women's blend black cohosh for 6 mo previously; no lab results provided; patient reported symptoms 20 d after use of the product
216299	Mar. 7, 2006	Hepatic function abnormal	49-y-old patient reported use of Remifemin for >2 y (BID)
217463	Apr. 18, 2006	Cholestatic hepatitis	48-y-old patient reported using a black cohosh-containing product Estrovarin for 6 mo (unknown intake)
218638	May 24, 2006	Hepatic function abnormal	53-y-old patient reported using Remifemin; duration unknown
220336	July 25, 2006	Hepatic failure	50-y-old patient reported using Remifemin for 2 mo (40 mg/d); received liver transplant in July 2006
220338	July 25, 2006	GGT increased to 58	50-y-old patient reported using Remifemin (duration/intake unknown)

GGT, γ-glutamyltranspeptidase.

reports cited multi-ingredient products that contained black cohosh: Femone, Meno-Eze, Swiss Women's Ultivite Multi-Vitamin, Mineral, and Anti-Oxidants, Cenovis Libido for Her, and Estrovarin. The black cohosh products were not characterized, which makes it difficult to ascribe hepatotoxic reactions to black cohosh. The most recent report of liver transplantation (TGA 220336) following use of Remifemin (the isopropanolic extract of black cohosh) is confounded by the patient's regular consumption of significant amounts of alcohol and multivitamin use. When the available information is evaluated according to the Naranjo scale, a possible causality rating attends these 17 reports.

NIH workshop

NIH organized a "Workshop on the Safety of Black Cohosh in Clinical Studies" in November 2004, in the wake of an American case report involving black cohosh.[16] A transcript of the workshop is available at http://nccam.nih.gov/news/pastmeetings/blackcohosh_mtngsumm.pdf (accessed October 5, 2007).

Participants at the workshop reportedly were aware of 51 AERs associated with black cohosh based on reports from FDA, WHO, the Australian Adverse Drug Reactions Advisory Committee, the German Federal Institute for Drugs and Medical Device, and the Committee on Safety of Medicines in the United Kingdom. The DSI EC does not have access to reports from WHO, the German Federal Institute for Drugs and Medical Devices, and the Committee on Safety of Medicines. However, we expect overlap of these cases in the EMEA report. Four case reports of hepatotoxicity with black cohosh were discussed at the NIH workshop.

S. Cohen from Rush University Medical Center, Chicago, IL, described two case reports,[16,23] described above. P. Kerlin from Princess Alexandra Hospital, Australia, presented two published case reports.[19,20] A detailed commentary on these studies was presented above in the TGA statement section.

At the NIH Workshop, N. Farnsworth from the University of Illinois, Chicago, commented on the insufficient quality control of products marketed in the United States and noted that adulteration with related species and with blue cohosh (*Caulophyllum thalictroides*) may occur.[23] Blue cohosh contains quinolizidine alkaloids and has been implicated in myocardial toxicity in infants whose mothers have taken the herb to assist in labor.[30] It has not been associated with liver disease. Farnsworth also reported that more than 2,000 subjects in clinical studies have taken black cohosh extract with no reports of hepatotoxicity.

At the workshop, "participants reiterated that a drug or herb should not be removed from the marketplace without [the presentation of] reasonable evidence of harm. Suspected hepatotoxicity should not be broadcast when toxicity has not been demonstrated." Workshop participants "concluded that a balanced approach [should] be taken with respect to this issue. On the one hand, millions of people have taken black cohosh with very few adverse events reported. On the other hand, those cases of hepatotoxicity associated with products that are known to contain black cohosh and believed to be free from other substances of known toxicity raise concern…. The evidence of risk remains equivocal but certainly warrants continued monitoring."

Reports from the United Kingdom

In July 2006, the MHRA issued a press release stating its concern about links between black cohosh and the risk of liver disorders. The press release stated that this link had been confirmed by the Commission of Human Medicines and the Herbal Medicines Advisory Committee. Following the advice of both committees, the MHRA mandated that a warning must be added to the labels of black cohosh products. The MHRA published its full review, "Black Cohosh, UK Public Assessment Report," on July 31, 2006.

According to the MHRA, "As of 31 May 2006, [the MHRA received] 21 reports of liver reactions—ranging in severity from abnormal liver function (15 people) to various forms of hepatitis (6 people), including 1 case of liver failure. Generally, the individuals recovered or were recovering after stopping black cohosh" (available at www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&useSecondary=true&ssDocName=CON2024131&ssTargetNodeId=663; accessed October 5, 2007). Although the extent of use of black cohosh in the United Kingdom is uncertain, in 2004 an estimated 9 million treatment days were purchased. Thus, the rate of liver reactions is considered to be rare (occurring in between 1/1,000 and 1/10,000) to possibly very rare.

Comments: The DSI EC learned from the MHRA that the 21 reports of liver reactions possibly associated with black cohosh have been passed to the EMEA for their assessment. MHRA reportedly received four new case reports between April 1, 2006 and January 31, 2007.

FDA MedWatch

Eleven MedWatch reports cited liver damage as the outcome after the use of black cohosh products (Table 3). Of the 11 MedWatch reports citing liver damage possibly associated with black cohosh-containing products, four were duplicate reports of published papers that have already been reviewed herein.[17,18,20] Inconsistencies appear in reports 78642 (Levitsky et al[18]) and 78707 (Lynch et al[17]) with respect to the product name. This comparison of the reports is published herein for the first time. Based on the available information, the remaining seven nonduplicate reports were scored as possible black cohosh-mediated liver damage. Diversity is seen in terms of the products reportedly used (some of them polyherbal), duration of use, intake, and outcome. Some of the products were not characterized in terms of identity or quality of the constituents.

PubMed additional information

Clinical trials

Several publications addressed the safety of black cohosh.[31-35] According to the review by Low Dog et al,[31] uncontrolled reports, postmarketing surveillance, and human

clinical trials of more than 2,800 patients demonstrated a low incidence of adverse events (5.4%) with black cohosh use. Of the reported adverse events, 97% were minor and did not result in discontinuation of therapy, and the only severe events were not attributed to black cohosh treatment. In the clinical studies reviewed, a total of 2,140 women received amounts ranging from 20 to 40 drops of ethanolic extract twice daily (corresponding to 48-140 mg root/rhizome) to two to four tablets (corresponding to 39-140 mg root/rhizome) for a period of 8 to 52 weeks. The three severe adverse reactions (thrombophlebitis, hysterectomy, and breast cancer recurrence) were not attributed to the black cohosh therapy. The authors concluded that although the effects of *Cimicifuga racemosa* may depend on the specific extract preparation, their review clearly supported the safety of specific *Cimicifuga* extracts, particularly isopropanolic preparations.[31,32] Gastrointestinal upsets and rashes were the most common complaints. Although more definitive evidence is needed, these authors concluded that black cohosh is a safe herbal preparation.

Postmarketing surveillance

Postmarketing studies support the safety of black cohosh preparations.[36-39] A postmarketing surveillance study was conducted with Remifemin (ethanolic extract—note that the current Remifemin label states that the product is an isopropanolic extract) taken by 629 menopausal women for 8 weeks. In this open, multicenter study, 7% of the women reported mild transitory side effects, predominantly gastrointestinal in nature. None of these side effects required discontinuation of the therapy.[37] A 12-week study conducted with 40 menopausal women given Remifemin reported no adverse events.[36] A recent large study of Remifemin observed no liver dysfunction.[35]

Pharmacokinetics

Few pharmacokinetic studies of black cohosh have been published. Electrophilic quinones that are potentially toxic to the liver were identified in an in vitro model using rat liver microsomes.[40] For this reason, the urine of women (n = 6) undergoing a phase I clinical study with black cohosh was examined for these compounds. The women were given single intakes of 32, 64, or 128 mg of a black cohosh extract (70% ethanol extract). The study concluded that "for moderate doses of a dietary supplement containing black cohosh, this study found no cause for safety concerns over the formation of (toxic) quinoid metabolites in women."[41]

Gurley et al[42] studied the effect of black cohosh on CYP enzymes, the modulation of which may underlie many herb-drug interactions. No clinically relevant effect on CYP 3A (a prominent CYP) activity was observed when 19 young adults (nine women) were given black cohosh extract (standardized to 2.5% triterpene glycosides) at 80 mg/day for 14 days. However, another clinical study involving 12 healthy volunteers (six women) showed that black cohosh extract (1,090 mg BID, standardized to 0.2% triterpene glycosides) weakly inhibited the effect of CYP 2D6 (approximately 7%) but did not appear to be clinically relevant.[32] Studies by the same authors on the modulation of P-glycoprotein drug transporters demonstrated that black cohosh extract (standardized to 2.5% triterpene glycosides, 40 mg/d for 14 d) did not affect P-glycoprotein levels sufficiently to influence the pharmacokinetics of drugs like digoxin.[43]

Animal and in vitro toxicological reports

A long-term (26 wk) study using Remifemin conducted on rats given 250, 1,800, or 5,000 mg/kg body weight/d revealed no evidence of toxicity. The weight of the liver, heart, and ovary were slightly increased in the high-intake group, but this returned to normal 8 weeks after treatment stopped. No mutagenic effects due to the isopropanolic extract of Remifemin were found by the Ames test (literature reviewed in Low Dog et al[31]).

LIMITATIONS OF ANALYSIS

Attributing causality to liver disease is complicated by occurrences of so-called spontaneous hepatotoxicity, which are instances that are not attributed to any particular cause. The pharmacokinetic mechanism or toxicological investigations into black cohosh did not provide evidence of liver damage attributable to black cohosh, as noted from the case studies and evidence presented herein.

In the majority of the AERs, the product was not identified or characterized. Unless a product purporting to cause an AER is analyzed and its identity and quality are confirmed, assigning definitive causality to the product is difficult because contamination of black cohosh with other species (such *as Actaea podocarpa* [yellow cohosh] or *A. cimicifuga* [Asian species]) is a known problem.[5,6,44] Further, the DSI EC believes that safety data should be evaluated with specific reference to the "product," and causality may not be ascribed to the individual ingredient unless ingredient quality is established. Accordingly, assigning any warning label or causality to a dietary ingredient that has not been analyzed calls into question the ingredient's possible association with an AER. During the safety review, the Committee also noted the limitations of the DS adverse event reporting systems. As observed in an FDA-commissioned study, the agency estimates that it receives less than 1% of all AERs associated with dietary supplements.[45] Further, the lack of premarketing and postmarketing safety monitoring of dietary supplements in the United States is a limitation regarding the information about the safety of supplements.

DELIBERATIONS OF THE DSI EC

In developing a new rating statement for black cohosh safety, the DSI EC moved through the following decision-making stages: the DSI EC first unanimously ruled that Class 3 (Table 1) is not the appropriate option for black cohosh. The members then unanimously rejected Class 1a (insufficient information) because AERs suggestive of hepatotoxicity were received from several sources. Further, the DSI EC noticed new reports from several regulatory agencies during

the past year concerning liver damage. Thereafter, the DSI EC deliberations centered on assigning safety Class 1 or 2. The Committee observed that the link between liver damage reports and black cohosh was weak and not of certain causality. The Committee also cited the following weaknesses of the AERs: (1) incomplete case information and unknown products, (2) confounding variables such as use of alcohol, (3) other concurrent medications, and (4) preexisting risk factors. Additionally, neither well-defined animal data nor a clear mechanism of action was available. Despite these limitations of the available data, considering the seriousness of the possible adverse reactions and the increase in recent reports, the DSI EC elected to classify black cohosh as Class 2 with an attendant label statement requirement. This decision reflects a change, based on the current analysis, of a Class 1a rating in 2002.

After reaching a decision on the appropriate label for Class 2, the Committee suggested that *USP* black cohosh monographs carry the following labeling 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.

In finalizing the above labeling statement, the Committee reviewed several comments from interested investigators and organizations. Because the DSI EC constantly monitors current reports concerning the safety of supplements for which *USP–NF* monographs are developed, the safety classification may be reviewed as new information becomes available. In accordance with the USP's open revision policy,[46] the Committee also reviews public comments during periodic safety revisions. The primary purpose in advancing this decision is to alert consumers and healthcare professionals to pay close attention to minimize potential risk.

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REFERENCES

1. Bhattacharyya L, Cecil T, Dabbah R, et al. The value of USP public standards for therapeutic products. *Pharm Res* 2004;21:1725-1731.
2. Schiff PL Jr, Srinivasan VS, Giancaspro GI, Roll DB, Salguero J, Sharaf MH. The development of USP botanical dietary supplement monographs, 1995-2005. *J Nat Prod* 2006;69:464-472.
3. Atwater J, Montgomery-Salguero J, Roll DB. The USP Dietary Supplement Verification Program: helping pharmacists and consumers select dietary supplements. *U.S. Pharmacist* 2005;30:61-64.
4. Nutrition Business Journal. *Top US herbal supplements 2004*. Boulder, CO: Nutrition Business Journal, 2006.
5. Erichsen-Brown C. *Medicinal and Other Uses of North American Plants*. New York: Dover, 1979.
6. McGuffin M, Kartesz J, Leung AY, Tucker AO. *Herbs of Commerce*, 2nd ed. Silver Spring, MD: American Herbal Products Association, 2000.
7. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981;30:239-245.
8. Jones JK. Adverse drug reactions in the community health setting: approaches to recognizing, counseling, and reporting. *Fam Community Health* 1982;5:58-67.
9. Kramer MS, Leventhal JM, Hutchinson TA, Feinstein AR. An algorithm for the operational assessment of adverse drug reactions. I. Background, description, and instructions for use. *JAMA* 1979;242:623-632.
10. World Health Organization. *WHO Guidelines on Safety Monitoring of Herbal Medicines in Pharmacovigilance Systems*. Geneva: World Health Organization, 2004.
11. Danan G, Benichou C. Causality assessment of adverse reactions to drugs—I. A novel method based on the conclusions of international consensus meetings: application to drug-induced liver injuries. *J Clin Epidemiol* 1993;46:1323-1330.
12. Michel DJ, Knodel LC. Comparison of three algorithms used to evaluate adverse drug reactions. *Am J Hosp Pharm* 1986;43:1709-1714.
13. Andrade RJ, Robles M, Fernandez-Castaner A, Lopez-Ortega S, Lopez-Vega MC, Lucena MI. Assessment of drug-induced hepatotoxicity in clinical practice: a challenge for gastroenterologists. *World J Gastroenterol* 2007;13:329-340.
14. Davern T. Can we replace opinion consensus with a Bayesian process? 2006. Available at: http://www.fda.gov/cder/livertox/presentations2006/Davern.pdf. Accessed October 23, 2007.
15. Seeff LB. Causality assessment for drug-induced liver injury. 2006. Available at: http://www.fda.gov/ohrms/dockets/ac/06/slides/2006-4266s1-01-08-FDA-Seeff_files/frame.htm. Accessed October 23, 2007.
16. Cohen SM, O'Connor AM, Hart J, Merel NH, Te HS. Autoimmune hepatitis associated with the use of black cohosh: a case study. *Menopause* 2004;11:575-577.
17. Lynch CR, Folkers ME, Hutson WR. Fulminant hepatic failure associated with the use of black cohosh: a case report. *Liver Transpl* 2006;126:989-992.
18. Levitsky J, Alli TA, Wisecarver J, Sorrell MF. Fulminant liver failure associated with the use of black cohosh. *Dig Dis Sci* 2005;50:538-539.
19. Lontos S, Jones RM, Angus PW, Gow PJ. Acute liver failure associated with the use of herbal preparations containing black cohosh. *Med J Aust* 2003;179:390-391.
20. Whiting PW, Clouston A, Kerlin P. Black cohosh and other herbal remedies associated with acute hepatitis. *Med J Aust* 2002;177:440-443.
21. Natural Health Products Directorate. Black cohosh. 2007. Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodnatur/mono_cohosh-grappes_e.pdf. Accessed October 23, 2007.
22. Herbal Medicinal Products Committee. Assessment of case reports connected to herbal medicinal products containing *Cimicifuga racemosa* rhizome (black cohosh, root). 2007. Available at: http://www.emea.europa.eu/pdfs/human/hmpc/26925806en.pdf. Accessed October 23, 2007.
23. Cohen S. NIH workshop on safety of black cohosh in clinical studies. 2004. Available at: http://nccam.nih.gov/news/pastmeetings/blackcohosh_mtngsumm.pdf. Accessed October 23, 2007.
24. American Herbal Products Association. 2006. Available at: http://ahpa.org/portals/0/pdfs/06_0908_BlackcohoshNebraskaDistrictCt.pdf. Accessed October 23, 2007.
25. Australian Therapeutic Goods Administration Statement. New labeling and consumer information for medicines containing black cohosh (*Cimicifuga racemosa*). 2006. Available at: http://www.tga.gov.au/cm/0705blkcohosh.htm. Accessed August 10, 2006.
26. Thomsen M, Vitetta L, Sali A, Schmidt M. Acute liver failure associated with the use of herbal preparations containing black cohosh. *Med J Aust* 2004;180:598-599.
27. Cumming FJ, Kelly L. Reply to: Acute liver failure associated with the use of herbal preparations containing black cohosh. *Med J Aust* 2004;180:599-600.
28. Kouzi SA, McMurtry RJ, Nelson SD. Hepatotoxicity of germander (*Teucrium chamaedrys* L.) and one of its constituent neoclerodane diterpenes teucrin A in the mouse. *Chem Res Toxicol* 1994;7:850-856.
29. Vitetta L, Thomsen M, Sali A. Black cohosh and other herbal remedies associated with acute hepatitis. *Med J Aust* 2003;178:411-412.
30. Mills S, Bone K. *The Essential Guide to Herbal Safety*. St Louis, MO: Elsevier, 2005.
31. Low Dog T, Powell KL, Weisman SM. Critical evaluation of the safety of *Cimicifuga racemosa* in menopause symptom relief. *Menopause* 2003;10:299-313.
32. Huntley A. The safety of black cohosh (*Actaea racemosa*, *Cimicifuga racemosa*). *Expert Opin Drug Saf* 2004;3:615-623.
33. Lieberman S. A review of the effectiveness of *Cimicifuga racemosa* (black cohosh) for the symptoms of menopause. *J Womens Health* 1998;7:525-529.

34. Osmers R, Friede M, Liske E, Schnitker J, Freudenstein J, Henneicke-von Zepelin HH. Efficacy and safety of isopropanolic black cohosh extract for climacteric symptoms. *Obstet Gynecol* 2005;105: 1074-1083.
35. Briese V, Stammwitz U, Friede M, Henneicke-von Zepelin HH. Black cohosh with or without St. John's wort for symptom-specific climacteric treatment—results of a large-scale, controlled, observational study. *Maturitas* 2007;57:405-414.
36. Nesselhut T, Liske E. Pharmacological measures in postmenopausal women with an isopropanolic aqueous extract of *Cimicifuga racemosae* rhizome. Presented at the 10th Annual Meeting of The North American Menopause Society, 1999.
37. Stolze H. An alternative to treat menopausal complaints. *Gynecology* 1982;1:14-16.
38. Bai W, Henneicke-von Zepelin HH, Wang S, et al. Efficacy and tolerability of a medicinal product containing an isopropanolic black cohosh extract in Chinese women with menopausal symptoms: a randomized, double blind, parallel-controlled study versus tibolone. *Maturitas* 2007;58:31-41.
39. Walji R, Boon H, Guns E, Oneschuk D, Younus J. Black cohosh (*Cimicifuga racemosa* [L.] Nutt.): safety and efficacy for cancer patients. *Support Care Cancer* 2007;15:913-921.
40. Bolton JL, Trush MA, Penning TM, Dryhurst G, Monks TJ. Role of quinones in toxicology. *Chem Res Toxicol* 2000;13:135-160.
41. Johnson BM, van Breemen RB. In vitro formation of quinoid metabolites of the dietary supplement *Cimicifuga racemosa* (black cohosh). *Chem Res Toxicol* 2003;16:838-846.
42. Gurley B, Hubbard MA, Williams DK, et al. Assessing the clinical significance of botanical supplementation on human cytochrome P450 3A activity: comparison of a milk thistle and black cohosh product to rifampin and clarithromycin. *J Clin Pharmacol* 2006;46: 201-213.
43. Gurley BJ, Barone GW, Williams DK, et al. Effect of milk thistle (*Silybum marianum*) and black cohosh (*Cimicifuga racemosa*) supplementation on digoxin pharmacokinetics in humans. *Drug Metab Dispos* 2006;34:69-74.
44. Jiang B, Kronenberg F, Nuntanakorn P, Qiu MH, Kennelly EJ. Evaluation of the botanical authenticity and phytochemical profile of black cohosh products by high-performance liquid chromatography with selected ion monitoring liquid chromatography-mass spectrometry. *J Agric Food Chem* 2006;54:3242-3253.
45. Woo JJ. Adverse event monitoring and multivitamin-multimineral dietary supplements. *Am J Clin Nutr* 2007;85:323S-324S.
46. US Pharmacopeia. USP–NF Development Process. 2007. Available at: http://www.usp.org/USPNF/devProcess/. Accessed October 23, 2007.

