Black cohosh products and liver toxicity: update

**Key points**
- A previous issue of the *Canadian Adverse Reaction Newsletter* highlighted international reports of liver reactions suspected of being associated with the use of black cohosh products.
- In this update, 6 domestic reports of liver toxicity suspected of being associated with black cohosh are discussed.
- Analysis of some of the products identified in these reports revealed that they did not contain authentic black cohosh.

Black cohosh (*Actaea racemosa*, formerly *Cimicifuga racemosa*) is a herbal medicine used mainly to alleviate menopausal symptoms. In recent years, several international regulatory agencies have monitored a possible relationship between black cohosh and liver toxicity.\(^1\)\(^\text{-}^4\) In 2005, an article in the *Canadian Adverse Reaction Newsletter*\(^5\) was published to inform health care professionals of international reports of liver reactions suspected of being associated with the use of this natural health product. At the time of publication, Health Canada had not received domestic reports of such reactions. To alert the public about this risk, Health Canada issued a public advisory\(^6\) and a fact sheet\(^7\) and required cautionary labelling on authorized black cohosh products.

From January 2005 to March 2009, Health Canada received 6 domestic reports of liver adverse reactions suspected of being associated with black cohosh. All 6 cases were reported as being serious\(^8\) (Table 1).

Analysis by Health Canada laboratories of 3 products (one patient was taking 2 Swiss Herbal products) suspected in 2 adverse reactions identified in the reports revealed that these products did not contain authentic black cohosh. Their phytochemical profiles were consistent with the presence of other related herbal species. Although research has shown problems with the herbal identity of some products marketed in the United States as black cohosh,\(^8\) these domestic cases demonstrate that products not containing authentic black cohosh may be associated with liver adverse reactions.\(^9\)\(^,\)\(^10\)

A recent review of the herbal authenticity of all licensed products containing black cohosh in Canada was...
Table 1: Summary of reports of liver toxicity suspected of being associated with black cohosh that were received by Health Canada from Jan. 1, 2005, to Mar. 31, 2009*

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/sex</th>
<th>Product (strength)</th>
<th>Reactions†</th>
<th>Outcome‡</th>
<th>Product analysis</th>
<th>Product status§</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Unknown/F</td>
<td>Swiss Herbal Natural HRT Extra Strength (not specified)</td>
<td>Ocular icterus</td>
<td>Unknown</td>
<td>Not authentic (sponsor analysis)</td>
<td>Voluntarily recalled</td>
</tr>
<tr>
<td>2</td>
<td>47/F</td>
<td>Swiss Herbal Menopause Natural HRT and Natural HRT Nighttime (not specified)</td>
<td>Autoimmune hepatitis, abnormal liver biopsy, elevated bilirubin, fatigue, jaundice</td>
<td>Not yet recovered</td>
<td>Not authentic (Health Canada analysis)</td>
<td>Voluntarily recalled</td>
</tr>
<tr>
<td>3</td>
<td>56/F</td>
<td>Her Balance (not specified)</td>
<td>Upper abdominal pain, fatigue, increased liver enzymes</td>
<td>Not yet recovered</td>
<td>Unknown</td>
<td>Not authorized</td>
</tr>
<tr>
<td>4</td>
<td>64/F</td>
<td>Swiss Herbal Natural HRT Extra Strength (not specified)</td>
<td>Jaundice, upper abdominal pain</td>
<td>Recovered</td>
<td>Not authentic (sponsor analysis)</td>
<td>Voluntarily recalled</td>
</tr>
<tr>
<td>5</td>
<td>51/F</td>
<td>Swiss Herbal Remedies Black Cohosh (100 mg)</td>
<td>Abdominal pain, increased liver enzymes, elevated bilirubin, jaundice</td>
<td>Recovered</td>
<td>Not authentic (Health Canada analysis)</td>
<td>Voluntarily recalled</td>
</tr>
<tr>
<td>6</td>
<td>55/F</td>
<td>Black cohosh Health Balance (80 mg)</td>
<td>Lower abdominal pain, increased liver enzymes, increased bilirubin, fatigue, hepatic cirrhosis, chronic active hepatitis, jaundice</td>
<td>Recovered with sequelae</td>
<td>Unknown</td>
<td>Not authorized</td>
</tr>
</tbody>
</table>

*These data cannot be used to determine the incidence of adverse reactions (ARs) because ARs are underreported and neither patient exposure nor the amount of time the health product was on the market has been taken into consideration.
†Reaction terms are listed according to the Medical Dictionary for Regulatory Activities (MedDRA).
§Voluntarily recalled means that an analysis was conducted and the sponsor voluntarily recalled the product because it did not contain authentic black cohosh. Not authorized means that the suspected product was not authorized for sale by Health Canada, and data on herbal authenticity are not available. Natural health products authorized for sale in Canada have an 8-digit Natural Product Number (NPN) or a Homeopathic Medicine Number (DIN-HM) on the label. These numbers indicate that the products have been assessed by Health Canada’s Natural Health Products Directorate for safety, effectiveness and quality. Authorized natural health products are listed in Health Canada’s searchable Licensed Natural Health Products Database, available at www.hc-sc.gc.ca/dhp-mps/prodnatur/applications/licen-prod/inhpÐ-bdpsinh-eng.php.

References
Health Canada has recently launched a more user-friendly version of the Canada Vigilance Adverse Reaction Online Database.

The online database contains a subset of the information reported to Health Canada about suspected adverse reactions in Canada to health products such as prescription and nonprescription drugs, natural health products, biologics, radiopharmaceuticals, and cells, tissues and organs. Information concerning preventative vaccines, blood, blood components, medical devices and cosmetics is not included in this database.

Enhancements made to the online database include:

- a simplified page layout for search criteria;
- the ability to search brand names, active ingredients, reactions terms and groups of reaction terms;
- the provision of additional help and background information to the user; and
- the ability to print, save or export search results in Adobe PDF and Microsoft Excel file formats.

The data presented in the online database is updated quarterly. The information is a quarter behind; this allows for the complete entry of new reports as well as follow-up to existing information.

For more information about the Canada Vigilance Adverse Reaction Online Database and how to report an adverse reaction, visit the MedEffect™ Canada section of Health Canada’s website at www.healthcanada.gc.ca/medeffect.

Case Presentation

Recent Canadian cases are selected based on their seriousness, frequency of occurrence or the fact that the reactions are unexpected. Case presentations are considered suspicions and are presented to stimulate reporting of similar suspected adverse reactions.

Chronic, excessive use of denture adhesive creams: suspected association with neuropathy

Denture adhesives are used as a means to enhance denture retention, stability and function. In Canada, denture adhesives are regulated as medical devices. Active ingredients in current formulations can include combined polymethyl vinyl ether–maleic anhydride (PVM-MA) zinc and calcium salts with carboxymethylcellulose. Chronic, excessive ingestion of zinc can result in copper deficiency, which is an established and increasingly recognized cause of neurologic disease. This may manifest as weakness and numbness of the extremities. Some marketed denture adhesive creams, including certain Fixodent and Poli-Grip formulations, contain zinc at levels of about 17 to 34 mg/g.

In November 2006, Health Canada received a report of a 52-year-old woman who had used Ultra Poli-Grip Denture Adhesive Cream over a period of years and was reported to have ingested large amounts of the product. The patient experienced numbness in both of her legs (date not reported).

In September 2009, Health Canada received a report of a 56-year-old woman who had used Fixodent Original Denture Adhesive for 7 to 8 years. She recently experienced unexplained pain, numbness and loss of sensitivity in her limbs.

Similar cases have been published of neurologic disease suspected of being associated with the overly liberal use (more than one 68-g tube per week) and chronic, excessive ingestion of denture adhesive creams containing zinc.

Health Canada encourages the reporting of similar suspected adverse incidents involving denture adhesives to the Health Products and Food Branch Inspectorate through the toll-free hotline (1-800-267-9675).

References

### Quarterly summary of health professional and consumer advisories


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<td>Medical device clocks</td>
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<td>Alerts — Syntrex Fyre, Telvano Fengshi, Gutong Ling, Kam Yuen Brand Wan Ying Yang Gan Wan; STEAM lot # 80214 and 90260; Dynasty Worldwide Jingilda So Young Formula; Bao Ling</td>
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<tr>
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</tr>
</tbody>
</table>


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**Medical device recalls**

- **Nov 5**: Chaotic beverages
- **Oct 30**: Medical device clocks
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- **Oct 26**: Apo-Lithium Carbonate
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- **Sept 25**: Hospira devices
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- **Sept 11**: PediCap Pediatric End-Tidal carbon dioxide detectors
- **Sept 10**: Cesium chloride
- **Sept 4**: Foreign products
- **Sept 3**: Foreign products

**Products**

- **Baby’s Breath**: Used in herbal medicine.

**Adverse reactions to health products** are considered to be suspicions, as a definite causal association often cannot be determined. Spontaneous reports of ADRs cannot be used to estimate the incidence of ADRs because ADRs remain underreported and patient exposure is unknown.

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**Suggestions?**
Your comments are important to us. Let us know what you think by reaching us at mhpd_dpse@hc-sc.gc.ca

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