Health Canada Santé Canada

Your health and safety…our priority. *Votre santé et votre sécurité… notre priorité.*

Canadian Adverse Reaction Newsletter

Volume 20 • Issue 1 • January 2010

www.healthcanada.gc.ca/carn

In this issue

Scope

This quarterly publication alerts health professionals to potential signals detected through the review of case reports submitted to Health Canada. It is a useful mechanism to stimulate adverse reaction reporting as well as to disseminate information on suspected adverse reactions to health products occurring in humans before comprehensive risk–benefit evaluations and regulatory decisions are undertaken. The continuous evaluation of health product safety profiles depends on the quality of your reports.

Reporting Adverse Reactions

Canada Vigilance Program
Phone: 866 234-2345
Fax: 866 678-6789
Online: www.healthcanada.gc.ca/medeffect

Did you know?

To receive the Newsletter and health product advisories free by email, subscribe to the MedEffect™ e-Notice at www.healthcanada.gc.ca/medeffect

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.[1–4] 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* (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

*In the *Natural Health Products Regulations*, a serious adverse reaction means "a noxious and unintended response to a natural health product that occurs at any dose and that requires in-patient hospitalization or prolongation of existing hospitalization, that causes congenital malformation, that results in persistent or significant disability or incapacity, is life-threatening or results in death."

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*

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

*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).
‡At the time of reporting.
§*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/lnhpd-bdpsnh-eng.php.

conducted; updated methods required for unequivocal identity testing were used.[11] This review resulted in the voluntary withdrawal of several products that did not contain authentic black cohosh from the market, including products reported in 4 of the cases in Table 1.

Health Canada continues to monitor the situation, and further recalls by other manufacturers are possible. Health care professionals are encouraged to report any adverse reactions suspected of being associated with the use of products containing black cohosh to Health Canada at www.healthcanada.gc.ca/medeffect.

Danika Painter, PhD; Shahid Perwaiz, PhD; Mano Murty, MD, CCFP, FCFP, Health Canada

Acknowledgement: The authors acknowledge the important contributions of members of the Natural Health Products Program Directorates to this article.

References

1. Medicines and Healthcare products Regulatory Agency. *Black cohosh (*Cimicifuga racemosa*) — risk of liver problems*. London (UK): The Agency; 2006. Available: www.mhra.gov.uk /Howweregulate/Medicines/Herbalmedicines /HerbalSafetyNews/Currentsafetyissues /CON2024131 (accessed 2009 Oct 23).
2. Therapeutic Goods Administration. *Black cohosh (*Cimicifuga racemosa*): new labelling requirements and consumer information for medicines containing black cohosh*. Woden (Australia): The Administration, Department of Health and Ageing; 2007. Available: www.tga.gov.au/cm /0705blkcohosh.htm (accessed 2009 Oct 23).
3. European Medicines Agency. *EMEA public statement on herbal medicinal products containing* Cimicifugae racemosae rhizoma *(black cohosh, root) — serious hepatic reactions*. London (UK): The Agency; 2006. Available: www.emea.europa.eu/pdfs/human/hmpc /26925906en.pdf (accessed 2009 Oct 23).
4. Mahady GB, Low Dog T, Barrett ML, et al. United States Pharmacopeia review of the black cohosh case reports of hepatotoxicity. *Menopause* 2008;15(4):628-38.
5. Sheehy C, Murty M, Pilon K. Black cohosh: international reports of liver toxicity. *Can Advers Reaction Newsl* 2005;15(3):2.
6. *Health Canada is advising consumers about a possible link between black cohosh and liver damage*. Ottawa (ON): Health Canada; 2006. Available: www.hc-sc.gc.ca/ahc-asc/media /advisories-avis/_2006/2006_72-eng.php (accessed 2009 Sept 25).
7. *Black cohosh* [fact sheet]. Ottawa (ON): Health Canada; 2007. Available: www.hc-sc.gc.ca /dhp-mps/prodnatur/applications/licen-prod /monograph/cohosh-grappes_fact-fiche-eng.php (accessed 2009 Sept 25).
8. Jiang B, Kronenberg F, Nuntanakorn P, et al. 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: 3242-53.
9. Jordan S, Murty M, Perwaiz S, et al. Hepatotoxic reaction associated with a product containing "black cohosh": one case of mistaken identity [abstract 709]. The Toxicologist CD — an official Journal of the Society of Toxicology, Number S-1, March 2008.
10. Betz JM, Anderson L, Avigan MI, et al. Black cohosh: considerations of safety and benefit. *Nutrition Today* 2009;44(4):155-62.
11. *Black cohosh* [monograph]. Ottawa (ON): Health Canada; 2009.

Canada Vigilance Adverse Reaction Online Database: redesigned to serve the public better

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.[1] 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.[1] Chronic, excessive ingestion of zinc can result in copper deficiency, which is an established and increasingly recognized cause of neurologic disease.[2] 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.[2]

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.[2,3]

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

1. Grasso JE. Denture adhesives: changing attitudes. *J Am Dent Assoc* 1996;127(1):90-6.
2. Nations SP, Boyer PJ, Love LA, et al. Denture cream: an unusual source of excess zinc, leading to hypocupremia and neurologic disease. *Neurology* 2008;71(9):639-43.
3. Spain RI, Leist TP, De Sousa EA. When metals compete: a case of copper-deficiency myeloneuropathy and anemia. *Nat Clin Pract Neurol* 2009;5(2):106-11.

Quarterly summary of health professional and consumer advisories

(posted on Health Canada's website: Aug. 22, 2009 – Nov. 10, 2009)

Date	Product	Subject
Nov 5	Chaotic beverages	Recall due to health risks to children
Nov 4	H1N1 flu products	Update — fraudulent products online
Nov 3	Relenza (zanamivir) inhalation powder	Association with fatal outcome when administered by nebulization
Oct 30	Medical device clocks	Update — switch to Standard Time
Oct 27	Propofol Injection	Type I product recall
Oct 26	Apo-Lithium Carbonate	Type II product recall — SR 300-mg strength tablets
Oct 23	Tamiflu (oseltamivir)	Update — important information
Oct 21	Rituxan (rituximab)	Association with progressive multifocal leukoencephalopathy
Oct 20 & 21	Cesamet (nabilone) and Trazorel (trazodone)	Type I product recall — mislabelling; potential risk of serious adverse effects
Oct 20	Hospital beds	Risk of entrapment of patients
Oct 15	Ceftriaxone	Updated prescribing information
Oct 15 & 19	Intelence (etravirine)	Severe skin and hypersensitivity reactions
Oct 14	Foreign products	Alerts — Syntrax Fyre, Texiao Fengshi Gutong Ling, Kam Yuen Brand Wan Ying Yang Gan Wan; STEAM lot # 80214 and 90260; Dynasty Worldwide Jinglida So Young Formula; Bao Ling
Oct 13	Tamiflu (oseltamivir) powder for oral suspension	Risk of dosing error
Oct 7	Sleep aid drugs	Risk of complex sleep-related behaviours
Sept 25	Liquid Tamiflu	Potential medication errors
Sept 25	Hospira devices	Medical device recall — defective AC power cords
Sept 17	Apotex health products	Information update — voluntary recall
Sept 15	Portex uncuffed pediatric-sized tracheal tubes	Medical device recall
Sept 11	PediCap Pediatric End-Tidal carbon dioxide detectors	Urgent medical device recall
Sept 10	Cesium chloride	Association with cardiac risks
Sept 4	Foreign products	Alerts — Reduce Weihgt; Dr. Health Series SB Factor and Dr. Health Series GQ Factor
Sept 3	Foreign products	Alerts — Hardcore Energize Bullet; Jin Yuan Pai Xue Guan Qing Dao Fu Jiao Nang and Kam Yuen Brand Xue Guan Qing Dao Fu tablet; Libipower Plus; LibieXtreme, Y-4ever, Powermania, Libimax X and Herbal Disiac; Slim House: Green algae fat-melting agent; One Weight Loss Pill, SlimDemand and Botanical Weight Loss

Advisories are available at www.healthcanada.gc.ca/medeffect.

Canadian Adverse Reaction Newsletter

Health Canada
Marketed Health Products Directorate
AL 0701C
Ottawa ON K1A 0K9
Tel: 613 954-6522
Fax: 613 952-7738

Editorial Team

Ann Sztuke-Fournier, BPharm (Editor-in-Chief)
Jared Cousins, BSP
Alanna Maloney, BHSc
Mary Joy, RPh, BScPhm
Hoa Ly, BSc
Patricia Carruthers-Czyzewski, BScPhm, MSc

Acknowledgement

We thank the following members of the Expert Advisory Committee on the Vigilance of Health Products for their review of material for this issue: Colleen J. Metge, BSc(Pharm), PhD; Dugald Seely, ND, MSc; and Sylvia Hyland, RPh, BScPhm, MHSc.
We also thank Kaitlyn Proulx and Darija Muharemagic, students in Biopharmaceutical Science, for their participation in the production of the newsletter.

Suggestions?

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

Reporting Adverse Reactions

Canada Vigilance Program
Phone: 866 234-2345
Fax: 866 678-6789
Online: www.healthcanada.gc.ca/medeffect

Copyright

ISSN 1499-9447, Cat no H42-4/1-20-1E

Aussi disponible en français

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