



**Health
Canada**

Health Products
and Food Branch

**Santé
Canada**

Direction générale des produits
de santé et des aliments

Marketed Health Products Directorate
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Ms Bev Gray
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Dear Ms Gray:

Re: evidence for the Public Advisory on comfrey

This is in response to your enquiry dated 2003-12-30 concerning Health Canada's recent Public Advisory on comfrey containing products. We would like to clarify some of the issues you raised concerning comfrey, in order to explain why Health Canada has taken regulatory action on these products.

Health Canada strives to improve the health of all Canadian, while respecting individual choices and circumstances. Concern regarding comfrey (*Symphytum* spp) has been raised a number of times in the last few decades due to the presence of unsaturated pyrrolizidine alkaloids (PAs) such as echimidine. Some of these alkaloids are able to damage the veins within the liver, causing a condition known as hepatic veno-occlusive disease (VOD). As you are aware, two species of comfrey (prickly [*Symphytum asperum*] and Russian [*Symphytum x uplandicum*]) are prohibited pursuant to section 8 of the *Food and Drugs Act* and section C.01.038 of the *Food and Drug Regulations*. These particular species have been prohibited since 1988. Also prohibited is a specific PA, echimidine, which is toxic to the liver and is a constituent of prickly and Russian comfrey. Other comfrey species, including common comfrey (*Symphytum officinale*), are not prohibited.

A survey by the Canadian Food Inspection Agency (CFIA), in January, 2003 showed that many products on the Canadian market (with or without a Drug Identification Number [DIN]) do not specify the species of comfrey they contain. It is also possible that products labelled to contain common comfrey may actually contain the prohibited species of comfrey due to species misidentification or other factors like cultivation and harvesting. Thus, the consumer, and Health Canada, have no way of knowing if these products are safe, or if they contain prohibited ingredients (echimidine) in violation of the *Regulations*.

The safety of Canadians is of paramount importance in the regulation of all health products. Unsaturated PAs such as echimidine, have been shown to be toxic to tissues other than the liver, and there is evidence that some of these substances are carcinogens in animals. Reports published in the peer-reviewed international scientific literature clearly associate oral exposure of comfrey and PAs with the occurrence of VOD in animals. Moreover, outbreaks of hepatic VOD in humans, associated with the consumption of PAs, have been reported in other countries over the years and the toxicity of these substances in humans is generally accepted. Details of human toxicity associated with the use of comfrey are described in the references attached, below. In one case, a woman suffering from hepatic VOD had consumed comfrey tea in addition to taking a comfrey-pepsin capsule daily for over six months. Another report describes hepatic VOD in a woman who drank comfrey tea for 1 year. Cases reported in children include VOD in a 13 year old boy who was treated with comfrey leaves for Crohn's disease. A case of fatal VOD occurred in a male who consumed 4-5 steamed comfrey leaves per day for 1-2 weeks. These cases, along with the known toxicity of unsaturated PAs, have raised concern not only in Canada, but internationally.

It should be noted that Health Canada's actions concerning comfrey are consistent with those taken by other international regulatory agencies. The US-FDA issued a letter to trade associations advising manufacturers to remove comfrey-containing products from the market (Lewis C. J. FDA Advises Dietary Supplement Manufacturers to remove comfrey products from the market [Letter]. July 6, 2001). In addition, the American Herbal Products Association has communicated with the US dietary supplement industry regarding the hazards associated with comfrey use (*HerbalGram*. 2001; 53:62. *American Botanical Council*). In Australia, comfrey is not permitted in medicines except at appropriate homeopathic dilutions; in the United Kingdom, comfrey is only available as a tea, unless prescribed by a medicinal herbalist; in Germany, comfrey is not permitted for internal use, and external use is limited to a maximum daily dose of 100 µg per day of PAs for a total period of 4 to 6 weeks, per year; in France, comfrey is not permitted for internal use, and external use is permitted only on intact skin.

All health products, including natural health products, regardless of whether or not they have a DIN, are associated with some risk. It is for this reason that Health Canada monitors the safety of marketed natural health products, and communicates information concerning risk associated with these products to health professionals and the public. The Natural Health Product Regulations require that all natural health products authorized for sale, list on the label, among other things, the proper and common names, and source material of each medicinal ingredient contained in the product. This enables consumers to make informed decisions with respect to the health products they choose to take.

It is not appropriate to make a comparison between the regulatory action taken for comfrey and those taken for other products, without considering the benefit/risk ratio for each product, the available alternative therapies, the comparability of the indications for the product, as well as the risk mitigation/risk management measures. When a signal is detected suggesting that a safety problem exists with a therapeutic product, a post-market benefit-risk assessment is conducted to evaluate the new balance between the product's benefits and risks.

In addition, unlike for pharmaceutical products, the manufacturing, harvesting and processing of comfrey-containing products have not been standardized. Standardization of natural health products is one of the objectives of the Natural Health Product Regulations.

In 2002, Health Canada established an internal scientific working group to examine the issue of comfrey. A representative from the Natural Health Products Directorate (NHPD) sat on this working group, as did representatives from all relevant Directorates in the Health Products and Food Branch. Scientific evidence for liver toxicity due to comfrey-containing products was obtained from published studies in peer-reviewed international journals (please see the attached list of references).

Regulatory decisions for marketed health products are made in an objective and evidence-based manner. In the case of comfrey, the scientifically known risk of serious liver toxicity associated with specific PAs (such as the prohibited echimidine) in prickly and Russian comfrey was regarded as outweighing any benefits from the use of these plants. It should be noted that the present actions taken by Health Canada on all therapeutic comfrey products is the result of lack of proper labelling, specifically the lack of species identification. DIN-held products will be reviewed to ensure that they do not contain the two prohibited species or echimidine; the Canadian public will be informed as to the results of this review. Therapeutic comfrey products without DINs are now required to obtain a Natural Product Number from the NHPD. As noted, the Natural Health Product Regulations require labels to provide the scientific name of plant ingredients.

The mandate of the Marketed Health Products Directorate (MHPD) is to ensure the consistent coordination of safety surveillance, assessment and risk communication activities for all health products currently on the Canadian market. Surveillance, assessment and risk communication activities for NHPs are the purview of the Natural Health Products Division within the MHPD. The term "health products" includes both pharmaceutical drugs and NHPs but does not include foods.

The following are the literature reports of human toxicity, specifically associated with comfrey, which you requested. These papers are publically available.

Abbott, P.J. (1988). Comfrey: assessing the low-dose health risk. *Med. J. Australia* 149(11-12): 678-682

Anderson, P.C. and McLean, A.E.M. (1989). Comfrey and liver damage. *Human Toxicol.* 8: 68-69

Bach, N., Thung, S.N. and Schnaffner, F. (1989). Comfrey herb tea-induced hepatic veno-occlusive disease. *Am. J. Med.* 87(1): 97-99

Culvenor, C.C.J. (1983). Estimated intakes of pyrrolizidine alkaloids by humans. A comparison with dose rates causing tumours in rats. *J. Toxicol. Environ. Health* 11: 625-635.

Furmanova, M., Guzewska, J. And Beldoska, B. (1983). Mutagenic effects of aqueous extracts of *Symphytum officinale* L. And of its alkaloidal fractions. *J. Appl. Toxicol.* 3(3): 127-130.

Mattocks, A.R. (1980). Toxic Pyrrolizidine alkaloids in comfrey. *Lancet* 2:1136-137

McDermott, W.V. and Ridker, P.M. (1990). The Budd-Chiari syndrome and hepatic veno-occlusive disease. *Arch. Surg.* 125: 525-527

Ridker, P.M., Okhuma, S., McDermott, W.V., Trey, C. and Huxtable, R.J. (1985). Hepatic veno-occlusive disease associated with consumption of pyrrolizidine-containing dietary supplements. *Gastroenterol.* 88: 1050-1054

Roulet, M., Laurini, R., Rivier, L. And Calame, A. (1988). Hepatic veno-occlusive disease in newborn infant of a woman drinking herbal tea. *J. Pediatr.* 112: 433-436.

Weston, C.F.M., Cooper, B.T., Davies, J.D. and Levine, D.F. (1987). Ven-occlusive disease of the liver secondary to ingestion of comfrey. *Brit. Med. J.* 2: 183

Yeong, M.L., Swinburn, B., Kennedy, M., Nicholson G. (1990). Hepatic veno-occlusive disease associated with comfrey ingestion. *J. Gastroenterol. Hepatol.* 5: 211-214

For further information regarding marketed health products, email questions can be addressed to MHPD_DPSC@hc-sc.gc.ca.

I hope this information is helpful to you.

Marketed Health Products Directorate
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