



Adverse reactions with natural health products in children

A practical guide for recognizing and reporting

Mano Murty, MD, CCFP, FCFP¹
Kevin Bernardo, ND, BHsc (Hon.)¹
Ron Tam, MD, FRCPC^{1,2}
Stephanie Jack, MSc¹
Margaret Zimmerman¹

¹ Marketed Health Products Directorate, Health Canada

² Department of Paediatrics, University of Ottawa

What is the epidemiology of complementary and alternative medicine?

Epidemiological studies show that the use of complementary and alternative medicine (CAM) is increasing in the general population, including among children.¹⁻⁵ Natural health product (NHP) use in children has been estimated to be as high as 33% in some countries.⁶ Over 9% of Canadians are using some form of CAM on a regular basis.⁷ The belief that NHPs are safe and less toxic than pharmaceuticals is widespread. This may account for their popular use in general health maintenance (e.g., vitamin supplements) as well as their use in a variety of ailments, such as respiratory, gastrointestinal and dermatological disorders,⁸ often without consultation with a health care practitioner (HCP). Indirect adverse reactions can also occur when NHPs are used in situations where urgent medical attention is required and treatment is delayed. Disclosure of adverse reactions (ARs) associated with NHP use is reported to be poor.^{9,10} HCPs are often not aware of an AR until it becomes serious enough to warrant clinical intervention.

What is a natural health product?

NHPs are widely available in grocery stores, retail pharmacies, health food stores, ethnic communities and on the Internet. The definition of NHPs varies from country to country. In Canada, the term 'natural health product' encompasses a wide variety of substances (Table 1).



As per the NHP Regulations (Table 2), all NHPs require a product licence before they can be legally sold in Canada. Once an NHP has been assessed and granted market authorization by Health Canada, the product bears an eight-digit product licence number preceded by the letters NPN (natural product number) or DIN-HM (homeopathic medicine number). The NPN or DIN-HM on the product label informs consumers that the product has been reviewed and is authorized by Health Canada for safety and efficacy, provided that the product is being used according to its recommended directions for use included in the product labelling. Certain NHPs have been assigned an EN (exemption number), indicating the product is authorized for legal sale in Canada while the application is under review by Health Canada.

What are potential NHP-related safety issues in children?

Similar to pharmaceutical products licenced in Canada, the majority of NHPs are not tested in the paediatric population; therefore, clinical effects and toxicity are relatively unknown in this group. As the use of NHPs increases, the potential for developing side effects, or ARs, also increases. Many times, exposure and consumption data for NHPs is unknown, thus quantifying safety issues remains a challenge. False or misleading advertising may also pose a safety issue due to misuse by parents or caregivers, especially in children with a serious or chronic illness. Inadequate labelling, which may or may not reflect the actual ingredients and indications for appropriate use, is another potential safety issue. Although Canada has implemented labelling standards for authorized (licenced) NHPs, many NHPs available to consumers through importation or Internet purchase may have inadequate or misleading labels. Furthermore, clinical trials and safety data on NHPs are sparse. Even when safety studies are available on individual ingredients, the effects of multiple ingredients used in combination are usually not well studied. Adulteration of some NHPs with pharmaceutical ingredients and contamination with microbials or heavy metals are major safety issues. Another concern with all health products, including NHPs, is counterfeit products, which may not contain the active ingredient found in authorized products bearing the same name.

These and other emerging safety issues reinforce the importance of careful monitoring and reporting of NHP-related events.

How is adverse reaction reporting done in Canada?

Although most NHPs are considered lower risk products, serious ARs associated with some NHPs continue to be reported. Health Canada has established the Canada Vigilance (CV) Program, which collects ARs to all health products, including NHPs. In Canada, ARs generated from passive and active surveillance systems can be entered in the CV database. The Canadian Paediatric Surveillance Program (CPSP) is an example of an active surveillance system that collects AR reports that are shared with Health Canada and entered into the CV database. Spontaneous reports submitted voluntarily by consumers and HCPs are also entered into the CV database. Industry must report to Health Canada all serious domestic and all serious unexpected foreign ARs associated with all of their marketed health products.

From January 1, 2004 (when Canada's NHP regulations came into effect) to October 31, 2011, the CV Program has received 2,148 case reports of ARs associated with NHPs. One hundred and eighty (180) case reports involved children (up to 18 years old). Of these, 108 are noted to be serious.¹¹ AR reporting is estimated to be



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<10% for pharmaceuticals and <1% for NHPs.¹² This may be due to several factors, such as lack of awareness that NHP-associated ARs can occur, lack of access to toxicity data and published safety studies on NHP ingredients, and lack of awareness that there are voluntary requirements for reporting by HCPs and consumers. Another limitation is that AR reports are received with incomplete or missing information. These limitations pose challenges in assessing causality and estimating the prevalence of the safety issue.

What HCPs should know?

As causality is verified based on the available data in the AR reporting form, it is important for HCPs to inquire about all health products, including NHPs, during routine history taking. Reactions can be categorized into two types:

- Type A (dose-related/predictable toxicity) such as associated toxicity of consumption of camphor/eucalyptus products in children, or
- Type B (idiosyncratic, not dose-related/unpredictable) such as anaphylaxis.

Acute ARs associated with NHPs are easier to recognize than chronic symptoms that may become serious or change over time. Interactions with pharmaceuticals or NHPs are important to prevent, particularly those with a narrow therapeutic range (e.g., warfarin).¹³ Reactions with NHPs can also be misinterpreted and attributed to a pharmaceutical or to a disease process, thereby delaying appropriate management. An NHP can contain a wide range of active ingredients, and with variability in their constituents. Some of these constituents may also have inherent toxicity (e.g., aristolochic acids, thujone). Therefore, an AR cannot be attributed to a single NHP ingredient unless the suspect product contains a single ingredient and no other confounders are present. Table 3 outlines the critical elements needed to conduct a proper causality assessment as well as an overall safety assessment of the product.

Parents and caregivers need to be encouraged to disclose to their HCP all the health products that they are giving to their children. This will assist the HCP in the recognition of the type of AR, whether it is due to inherent toxicity or interactions with other pharmaceuticals, NHPs and foods, or whether it is a product quality issue. HCPs are encouraged to report any ARs related to health products to the CPSP, even when only a suspicion is present.

Where can HCPs find reliable NHP data sources?

To enhance their patient care, HCPs can readily access some reliable NHP data sources as outlined in Table 2.

How does Health Canada use the AR information?

Serious and medically significant (International Conference on Harmonization [ICH] guidelines) cases are reviewed in order to determine the probability or likelihood of the suspect product(s) being causally linked to the AR. The causality assessments are then reviewed along with a scientific review of the published literature (case reports, clinical trial, pre-clinical toxicological data) and any additional information issued by international regulatory agencies. Furthermore, information from other databases



(such as World Health Organization) is also taken into consideration. The clinical and scientific assessment of the totality of evidence enables Health Canada to identify true safety signals. If a product sample is available for testing in a case where adulteration and/or contamination is suspected as having contributed to the AR, Health Canada may carry out laboratory analysis to screen for adulterants and/or contaminants. Health Canada may require the company to provide additional data on safety and/or quality of their product. Such information contributes to such regulatory activities as revising/updating labelling information, issuing a recall/stop sale (if serious public health issue), or issuing a risk communications to inform clinicians (e.g., Dear Health Care Practitioner letter, Canadian Adverse Reaction Newsletter [CARN]), and/or to consumers (e.g., Public Advisory; *It's Your Health* articles; Foreign Product Alerts [FPAs]).

Key points

- Report an AR, even if it is not clear whether the health product is causally related to the AR. Health Canada assesses the report in the broader context, taking into consideration the totality of evidence (databases, foreign regulatory agencies, literature).
- Ask about the use of all health products in each clinical encounter. Consumers of all ages are using NHPs and sometimes mixing them with other health products, increasing the risk of interaction and toxicity.
- Inquire how your patients obtained their NHPs. Determining consumer access to NHPs is challenging, as new and foreign products are coming into the Canadian marketplace with or without authorization.
- Stay alert as novel products come onto the market with new combinations of ingredients. A strong vigilance program for NHPs is critical for the well-being of Canadian consumers.
- Continue to participate in the CPSP and the Health Canada – Canada Vigilance (HC-CV) Program, as there is a need for HCPs and other relevant stakeholders to work together to increase AR reporting.

Safety surveillance of health products is an ongoing process that is a shared responsibility among the federal regulator (Health Canada) who reviews and monitors the health product, the manufacturer who makes the product and is responsible for monitoring it, the CPSP and the HC-CV Program who collect timely national data, the HCP who provides advice to the patient, and the informed consumer who uses it.¹⁴

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Adverse reactions with natural health products in children (continued)

Table 1
Natural health product substances

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| <ol style="list-style-type: none"> 1. Vitamins and minerals 2. Probiotics 3. Amino acids and essential fatty acids 4. Traditional and homeopathic medicines 5. Synthetic duplicates of natural ingredients 6. Plants, algae, bacteria, fungi, nonhuman animal materials 7. Extracts or isolates of those listed in 6 |
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Table 2
Websites on natural health products (NHPs) for clinicians¹⁵

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| <ul style="list-style-type: none"> • Health Canada: <ul style="list-style-type: none"> ➢ To view all AR reports received by Health Canada: www.healthcanada.gc.ca/medeffect ➢ Licenced NHP database: webprod.hc-sc.gc.ca/lnhpd-bdpsnh/start-debuter.do?language-langage=english ➢ NHP Ingredient Database Online Solution – to search for various ingredients and licencing information on products sold in Canada: webprod.hc-sc.gc.ca/nhpid-bdipsn/search-rechercheReq.do ➢ Drug Products Database: webprod.hc-sc.gc.ca/dpd-bdpp/index-eng.jsp ➢ Exempted Products Database – to search for NHPs with an exemption number (EN) granted by the Minister under the provisions of the NHPs Unprocessed Product Licence Applications Regulations: webprod3.hc-sc.gc.ca/product-produit/search-rechercheReq.do?lang=eng ➢ Natural Health Products – to access current regulations, licencing and safety: www.hc-sc.gc.ca/dhp-mps/prodnatur/legislation/docs/regula-regle_over-apercu-eng.php • National Centre for Complementary and Alternative Medicine: nccam.nih.gov • Natural Standard Database: www.naturalstandard.com • Natural Medicines Comprehensive Database: www.naturaldatabase.com • Medline Plus (from the US National Library of Medicine): www.nlm.nih.gov/medlineplus • CAMline: www.camline.ca/naturalhealthprod/naturalhealthprod.php • Mayo Clinic: www.mayoclinic.com |
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Table 3
Essential data elements in a CPSP reporting form
www.cps.ca/English/surveillance/CPSP/Studies/Questionnaire/ADR.pdf

Core information	Adverse reaction, suspect product, patient, reporter
Medical information	Age, gender, weight, past and current health history, current medications with start/stop dates, including the details for the suspect product, product exposure prior to AR, dechallenge/rechallenge information, lab investigation, medical intervention
Product information	Brand name (with any name extensions) and ingredients (including type of extract[s]), dose, duration of use, licence (NPN, DIN-HM, EN), lot number, date of expiry*
Market Authorization Holder information	Contact name and address

* Some NHPs have the same name but contain different formulations/ingredients. Copy of label is preferred.



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Additional reading

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Adverse reactions with natural health products in children (continued)



Quiz

- 1. The definition of natural health products (NHPs) includes which of the following substances?**
 - a) Vitamins and minerals
 - b) Antibiotics and prednisone
 - c) Probiotics
 - d) a and c
 - e) a and b

- 2. Canada has a safety surveillance program of NHPs.**
 - a) True
 - b) False

- 3. Who can report an adverse reaction (AR) to an NHP?**
 - a) The patient or the health care provider
 - b) The manufacturer or the pharmacist
 - c) The researcher or the CPSP participant
 - d) All of the above

- 4. Which statement(s) is/are reflective of AR reporting?**
 - a) The reporting rate is very low
 - b) Reports often contain insufficient clinical details to determine causality
 - c) Prevalence of an AR associated with a particular health product can be established using spontaneous AR reporting systems
 - d) a and b
 - e) b and c

- 5. With respect to ARs associated with NHPs, what additional reporting element is strongly recommended to include in the case report?**
 - a) A copy of the product label
 - b) The patient's telephone number
 - c) Copies of the patient's medical chart
 - d) The patient's health card number

- 6. Which of the following is/are common safety issue(s) associated with some NHPs in the paediatric population?**
 - a) Relatively unknown clinical effects and toxicity
 - b) Inadequate labelling of actual ingredients and indications for appropriate use
 - c) Effects of multiple ingredients used in combination are usually not well studied
 - d) Adulteration with pharmaceutical ingredients and contamination with microbials or heavy metals
 - e) All of the above

RESOURCES

Answers: 1-d, 2-a, 3-d, 4-d, 5-a, 6-e