Echinacea Products Containing Echinilin® - Relating Pre-clinical, Clinical and Postmarketing Surveillance Data

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ABSTRACT

Access to safe and efficacious dietary supplements is an important part of a personal health and wellness regimen pursued by many US and Canadian consumers. Of the dietary supplements available, Echinacea-containing preparations are among the most popular, being sixth in US sales in 2008. Broadly viewed as an immunostimulant by consumers, Echinacea is taken primarily to decrease the risk of contracting colds, flu and generalized upper respiratory infections, to shorten the duration and severity of such illnesses and to otherwise boost the immune system prophylactically. To ensure that consumers have continued access to safe dietary supplements, manufacturers must periodically identify and assess the occurrence and severity of adverse events. This article assesses the occurrence and severity of adverse events for products containing the Echinacea extract Echinilin®.

INTRODUCTION

Adverse Events

Adverse event reporting for drugs, medical devices, and dietary supplement products is recognized as an important means of identifying signals that could have direct clinical impact on consumers. The Food and Drug Administration (FDA), Center for Food Safety and Nutrition (CFSAN) defines adverse event and serious adverse event as follows:

- An adverse event is defined as "any health-related event associated with the use of a dietary supplement that is adverse." (Section 761(a)(1) of the FD&C Act (21 U.S.C. 379aa-1(a)(1))
  (http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/DietarySupplements/ucm072966.htm#adverse)

- A serious adverse event is “an adverse event that results in death, a life-threatening experience, inpatient hospitalization, a persistent or significant disability or incapacity, or a congenital anomaly or birth defect; or requires, based on reasonable medical judgment, a medical or surgical intervention to prevent an outcome described above.” (Section 761(a)(2) of the FD&C Act (21 U.S.C. 379aa-1(a)(2)) (http://www.fda.gov/Food/)
Identifying possible adverse events with the use of a dietary supplement product is accomplished by first, conducting safety evaluations in pre-clinical (i.e., animal) testing then, monitoring for adverse events with clinical studies in humans and postmarketing surveillance. In the United States, the goal of a clinical study is to determine efficacy, with a secondary goal of identifying adverse events. Because clinical trial data are obtained under strictly controlled conditions, this signal detection mechanism is very sensitive. The other means of identifying and following evolving adverse events for supplement products is through postmarketing surveillance, which has two significant advantages over clinical trials: (1) it provides on-going surveillance of all users (as opposed to the small sample size in a clinical trial) and; (2) as a process, it is relatively inexpensive (Fletcher, 1991).

**Echinacea Products**

The genus *Echinacea* (Family Asteraceae) comprises about a dozen species of herbaceous perennials indigenous throughout the eastern and central US and southern Canada. The three species used most commonly in supplemental preparations are *Echinacea angustifolia*, *E. purpurea* and *E. pallida*. Fresh and dried roots and aerial parts and fresh-pressed juice from flowering tops are prepared into tinctures, teas, juices, powders, tablets or capsules that may also contain additional ingredients, including other botanical ingredients. In the US and Canada, *Echinacea*-containing products are marketed as dietary supplements for oral administration only; intravenous (I.V.) products for use in medical settings are common in other countries, including Germany (Block and Mead, 2003). Regardless of final form, *Echinacea*-containing preparations are used by consumers primarily because they are perceived as having immunostimulant properties. Of all the dietary supplements currently available, *Echinacea*-containing preparations are among the most popular, being sixth in USA sales in 2008 (Kennedy and Seely, 2010).

Few safety studies for *Echinacea* preparations are available in the scientific literature, possibly because the flowering herb has an exceptionally long history of safe

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1 By definition, dietary supplements may only be taken orally.

**PRE-CLINICAL STUDY**

In one published safety evaluation (Mengs *et al.*, 1991), the toxicological effects of orally and intravenously administered fresh-pressed *E. purpurea* juice\(^2\) (also known as Echinacin\(^{\circledR}\) or Echinaguard\(^{\circledR}\)) from the aerial parts of the plant were examined in rats and mice for periods up to four weeks. Four mutagenicity assays and one cell-transformation assay were also performed with freeze-dried residues (lyophilizates) of the juice. Each study was conducted in accordance with the internationally accepted guidelines of the Organisation for Economic Co-operation and Development (OECD) for “Good Laboratory Practice” and with the OECD or EC (European Commission) recommendations for technical methods.

In the acute studies, a single dose of 15,000\(^3\) mg/kg bw *E. purpurea* juice was administered by gastric tube to eight-week old Wistar rats (eight males and eight females; ~200 g each) with eight-week old NMRI mice (eight males and eight females; ~20 g each) each receiving 30,000 mg/kg bw in the same manner. Following administration, the animals were observed for 14 days before termination and necropsy. No deaths occurred during the observation period, nor were abnormalities in appearance or behavior reported. No changes attributable to *E. purpurea* juice were observed in any organ at necropsy. The oral LD\(_{50}\) for *E. purpurea* juice in the rat was > 15,000 mg/kg bw and in the mouse, > 30,000 mg/kg bw. In a parallel study by the same authors, single doses of *E. purpurea* juice were administered *via* I.V. to rats (5,000 mg/kg bw) and mice (10,000 mg/kg bw).

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\(^2\) One milliliter of this raw unpurified *E. purpurea* juice preparation is equivalent to 1.5 – 2.5 g of crude *Echinacea* herb.

\(^3\) Rats receiving 15,000 mg/kg bw/day *E. purpurea* juice consumed the equivalent of 5.1 – 7.5 g crude *Echinacea* per day (25.5 – 37.5 g/kg bw/day).
Although minor reactions (sedation and dyspnea) to the I.V. administration procedure occurred, no other effects were observed.

In the subacute study, *E. purpurea* juice was administered *via* gastric tube at levels of 0, 800, 2400 or 8000\(^4\) mg/kg bw/day for 28 days to four groups of rats (18 males and 18 females *per* group). During the study, body weight, food consumption, ophthalmology, clinical chemistry, hematology and histopathology were evaluated for toxicological effects. No mortalities occurred. At the end of the study, a statistically significant decrease in plasma alkaline phosphatase (AP) in male rats of the 2400 and 8000 mg/kg bw/day dose groups (*P* < 0.01 and *P* < 0.05, respectively) and a statistically significant increase in prothrombin time (PTT) in female rats of the same groups (also *P* < 0.01 and *P* < 0.05, respectively) were reported. Although statistically significant, neither the change in AP nor the change in PTT was considered to be toxicologically significant because both changes were within accepted physiological variation for the strain and because neither was proportional to dose. No significant differences in body weight or food consumption occurred among the groups at any time point; in addition, there were no reported changes from control in ophthalmology, necropsy findings or histopathology. The reported no-observed-adverse-effect level (NOAEL) for fresh-pressed *E. purpurea* juice was 8000 mg/kg bw/day (equivalent to 13.6 – 20 g/kg bw/day of the raw herb), the highest dose administered and a dose that approximates thirty times the maximum daily dose in humans.

In the first mutagenicity assay, the bacterial mutation (Ames) assay, the mutagenic potential of *E. purpurea* juice lyophilizate was evaluated at concentrations up to 5000 \(\mu\)g/plate in five test strains of *Salmonella typhimurium* (TA 98, TA 100, TA 1535, TA 1537 and TA 1538); no evidence of toxicity or mutagenicity was observed with or without metabolic activation. Metabolic activation was induced using an S-9 mixture containing the liver homogenate from male Wistar rats that had been injected intraperitoneally with 500 mg/kg bw Aroclor 1254 and sacrificed five days afterward. Similarly, in the *in vitro* mouse lymphoma cell gene mutation assay, no statistically significant increase in mutation frequency was found in mouse lymphoma cells treated

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\(^4\) Rats receiving 8000 mg/kg bw/day *E. purpurea* juice consumed the equivalent of 2.72 – 4 g crude *Echinacea* per day (13.6 - 20 g/kg bw/day).
with *E. purpurea* juice lyophilizate at concentrations up to 5000 µg/mL, with or without metabolic activation. The third assay, *in vitro* human lymphocyte analysis also showed no mutagenic effect of the juice lyophilizate at concentrations up to 5000 µg/mL with or without metabolic activation; aberration frequency in the human lymphocyte cells was consistent among treatment and controls. In the micronucleus assay, femoral bone marrow smears from mice orally treated one time with *E. purpurea* juice (25,000 mg/kg bw) and sacrificed 24, 48 or 72 hours afterward, showed no increase in micronucleated polychromatric erythrocytes (PCE) compared to bone marrow smears from control animals. To evaluate the unscheduled DNA synthesis (UDS) potential of *E. purpurea* juice lyophilizate, a cell transformation assay with lyophilizate concentrations up to 55 µg/mL was performed; no morphological transformations were induced in Syrian hamster embryo cells exposed to the lyophilizate. In each of these five supportive assays, cells exposed to *E. purpurea* juice lyophilizate and cells from animals dosed with *E. purpurea* juice responded similarly to assay negative controls and unlike the corresponding positive controls.\(^5\)

The results of these studies indicate that fresh-pressed *E. purpurea* juice was well tolerated in the rat, with an oral NOAEL of 8000 mg/kg bw/day (equivalent to 13.6 – 20 g/kg bw/day of the raw herb), the highest dose level tested. No adverse effects were observed at dose levels approximately thirty times the maximum normal daily dose a human would ingest. Further, *E. purpurea* juice and its lyophilized residues were demonstrated to lack mutagenic potential and to not cause chromosomal aberration or cell transformation.

**CLINICAL TRIAL**

An herb believed by the general population to have unique immunostimulatory properties, *Echinacea* is included in many dietary supplement products. Because most *Echinacea*-containing preparations are not standardized, clinical trials studying the effectiveness of these products have often produced inconclusive results, most likely due to insufficient quantities or deficiencies in the preparation quality of *Echinacea* materials.

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\(^5\) Statistical significance was not generally determined for the positive control compared to the negative control.
For this reason, the need to evaluate a high quality standardized preparation of Echinacea such as Echinilin® (sold in the US as Echinamide®) for effectiveness and for incidence of adverse reaction led to a clinical trial evaluating the effect of Echinilin® on the severity and duration of the common cold in otherwise healthy subjects.

Similar to the E. purpurea juice Echinacin® used in the preclinical studies, Echinilin® is prepared from freshly harvested E. purpurea. While Echinacin® is the pressed juice, however, Echinilin® is an extract purified to primarily contain three active components, alkamides, cichoric acid and polysaccharides (at concentrations of 0.25, 2.5 and 25.5 mg/mL, respectively). Compared to Echinacin®, Echinilin® lacks many of the impurities present in the raw juice of the E. purpurea plant. Echinacin® is also somewhat more concentrated than Echinilin® as one milliliter of Echinacin® is equivalent to 1.5 – 2.5 g of the crude Echinacea herb whereas one milliliter of Echinilin® is equivalent to approximately one gram of the plant. The clinical trial, a randomized, double-blind, placebo-controlled study conducted at the University of Alberta, Edmonton, Canada showed that Echinilin®, a standardized formulation prepared from freshly harvested E. purpurea, administered orally for a total of seven days to volunteers developing the initial symptoms of a cold, was well tolerated with only mild to moderate adverse effects, similar to those seen with placebo (Goel et al., 2004). The primary objective of the study was to evaluate the effect of orally administered Echinilin® on the duration and severity of the common cold, while the secondary objective was to evaluate adverse reaction to Echinilin® in comparison to placebo.

Two hundred and eighty-two male and female volunteers aged 18 – 65 years with a history of two or more colds in the past year but otherwise in good health, were enrolled in the clinical trial and were randomized to either the Echinilin® or placebo group. Exclusionary criteria included recent vaccination against influenza and allergy to ragweed, among other criteria. At the onset of the first symptoms of a naturally acquired cold, subjects were to begin the seven-day treatment program consisting of 10 doses per day on the first day and four doses per day on the six subsequent days. Each dose

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6 Multiple sclerosis, tuberculosis, diabetes, cancer, lupus, asthma, fibromyalgia, HIV/AIDS, cardiovascular disease, the taking of immunosuppressive drugs (e.g., corticosteroids, cyclosporine), pregnancy and/or lactation.
consisted of 4 mL of Echinilin® or placebo mixed into half a glass of water before drinking. Of the enrolled subjects, a total of 128 developed a cold (59 Echinilin®, 69 placebo) and complied with at least the first two days of the protocol by taking 14 doses of the study formulation within 48 hours of symptom onset; these subjects were included in the ITT (intention to treat) population. Because 17 individuals from the ITT population failed to comply fully with the trial criteria, they were excluded from the more restrictive (i.e., most compliant) PP (per Protocol) population. A total of 111 subjects, 54 in the Echinilin® (28 women, 26 men) and 57 in the placebo (41 women, 16 men) groups developed colds and fully complied with trial criteria; these subjects were included in both the ITT and PP populations.

Dosing compliance was recorded daily into a log, as was a self-assessed severity of 13 cold symptoms. Each symptom was scored on a ten-point scale as “no symptom” (0 points), mild (1 – 3 points), moderate (4 – 6 points) or severe (7 – 9 points) in nature. Each day a Total Daily Symptom Score (TDSS) was generated by adding all symptom scores for that day. Each subject having a cold was also examined by a nurse on Days 3 (after 14 doses) and 8 (after the course of treatment). The nurse assessed the severity of cold symptoms, screened the subjects for secondary complications such as sinusitis, bronchitis, pneumonia and otitis media, and collected fasting blood samples for white blood cell differential counts. Subjects were contacted periodically during the seven-day treatment to assess compliance, to ask whether they thought they were taking Echinilin® or placebo and to request that any adverse reaction be recorded in the log.

The parameters assessed during the clinical trial included the change in the seven-day means of the TDSS results, the change in individual symptom scores, the duration of

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7 One milliliter of Echinilin® (Echinamide®) is equivalent to approximately one gram of crude Echinacea herb. Subjects consumed the equivalent of 40 g crude Echinacea on Day 1 of dosing (~0.67 g/kg bw) and 16 g on each of the subsequent six days (~0.27 g/kg bw/day).

8 Echinacea and placebo extracts were prepared to look, taste and smell the same. Each extract was mixed with ethanol (40% final concentration) before being packaged into individual amber bottles for each subject. Each subject was directed to measure 4 mL of the formulation from his/her bottle using a syringe supplied for the purpose and mix the liquid with half a glass of water prior to swallowing. Both test and placebo formulations were supplied in identical bottles making it impossible for subjects and investigators to distinguish one from the other which ensured the double blinding for the study.

9 Sore throat, runny nose, stuffy nose, watery eyes, chills, malaise, fever, headache, sore muscles, hoarseness, shortness of breath, sneezing and cough.
symptoms indicated by the number of days a symptom was scored above three points, the
treatment response rate (i.e., the number of subjects reporting a decrease of at least 50% in
their maximum TDSS), and the incidence of adverse effects.

**Efficacy and Adverse events**

Prior to statistical analysis, the data were logarithmically transformed because the
distribution was not normal. To determine the effect of treatment and time on TDSS and
individual symptom scores, Type III repeated-measures analysis of variance (ANOVA)
was performed. To determine the effect of treatment on the duration of the individual
symptoms, a one-way ANOVA was used. To evaluate the closeness of the self-assessed
and nurse-assessed individual and total symptom scores, Pearson correlation coefficients
were determined (Goel *et al.*, 2004).

In the PP population, statistical analysis showed the average TDSS for self-
assessed cold symptom severity was significantly lower in the Echinilin® group (by
23.1%) than in the placebo group ($P < 0.01$). On a symptom basis, the seven-day means
for severity of runny nose, sore throat, stuffy nose, fatigue, headache and chills were,
respectively, 27%, 25%, 22%, 31%, 39% and 44% lower in the Echinilin® group than in
the placebo group ($P < 0.05$ for all). Cough was the only symptom that scored higher in
the Echinilin® group than in the placebo group. Additionally, Pearson correlation
coefficients were significantly high, indicating that self-assessed scores and nurse-
assessed scores were extremely similar for cough, runny nose, stuffy nose, sore throat,
fatigue and for total symptoms ($P < 0.0001$ for all). Blinding was demonstrated to be
adequate at the end of the study as approximately 50% of subjects incorrectly guessed
which formulation they had received.

In the ITT population, results were similar albeit less pronounced than results in
the PP population. The average TDSS for self-assessed cold symptom severity was
significantly lower in the Echinilin® group (by 17.6%) than in the placebo group ($P <
0.05$). On a symptom basis, the seven-day means for severity were significantly
decreased in the Echinilin® group compared to the placebo group only for fatigue and
headache ($P < 0.05$ for both). Cough was again the only symptom that scored higher in
the Echinilin® group than in the placebo group. Due to a lack of compliance by 17 subjects in the ITT population, Pearson correlation coefficients were not determined.

In the PP population, cold duration was reduced by ~1.5 days (27%) in the Echinilin® group compared to the placebo group with symptom severity dropping to 50% of maximum by Day 4 for subjects receiving Echinilin® but not until Day 5.5 for placebo subjects. On Day 7, 95% of the members of the Echinilin® group exhibited symptoms at < 50% of their reported maxima; 33% of the members of the placebo group still exhibited symptoms at > 50% of their reported maxima. In the ITT population, these findings were again similar, although not as pronounced. In both populations, all individual symptoms, except cough, were of shorter duration when treated with Echinilin® than when treated with placebo. Among the ITT population, a secondary complication in the form of bronchitis developed in seven participants, two individuals from the Echinilin® group and five from the placebo group. No significant differences were observed in the white blood cell differential counts in the Echinilin® and placebo groups.

Several incidents of non-severe adverse effect were reported by both the treatment and placebo groups of the ITT population. Gastrointestinal effects (e.g., nausea, heartburn and constipation) were reported in 8/59 (13%) of the Echinilin® subjects and in 6/69 (9%) of the placebo subjects taking at least 14 doses over a two day period. Unpleasant tongue sensations (e.g., itching, burning and numbness) were reported in 8/59 (13%) of the Echinilin® subjects and in 8/69 (11%) of the placebo subjects. No allergic events were reported for either group during the study. Differences between the treatment and placebo groups were not statistically significant. The results showed that both formulations were well-tolerated; side effects, when they occurred, were sufficiently mild that no subjects withdrew from the study.

**POSTMARKETING SURVEILLANCE**

From January 2004 through August 2010, 156 unsolicited and spontaneously reported adverse event complaints were collected by the Factors Group of Nutritional Companies, Inc. for their Echinilin®-containing products sold (74.2 million single servings) over this period in Canada and the US. Review of this information indicated that the reports were obtained from consumers themselves calling in with a specific
complaint, generally without additional information being collected at the time of the reporting (i.e., age, medical background, length of use of the product or uses of prescription medications, over-the-counter drugs (OTCs) or other supplements). Of the 156 reports collected, 154 were minor and two reported adverse events that fit the definition of a serious adverse event, but without mortality. In the first, received September 2007, a female customer indicated internal bleeding after taking an Echinilin®-containing product. She fainted and either went or was transported to a hospital. Because she later declined to fill out a “Customer Report of Adverse Reaction Form”, no other details of her condition are known and the event was not reported to Health Canada. In the second complaint, received February 2009, a female customer suffered breathing difficulties and a swollen, discolored tongue 15 minutes after having taken three softgels of an Echinilin®-containing product in December 2008. The customer was transported by ambulance to the hospital where Benadryl was administered. Based on the report, she had previously ingested five softgels of the same Echinilin®-containing product on each of two days, then one softgel three times over the course of the third day and had also been taking Biaxin 500 ml for one week prior to the event. The customer completed a “Customer Report of Adverse Reaction Form” and the event was reported as a “Suspected Adverse Drug Reaction” to Health Canada. Health Canada did not follow up with the Factors Group or take further action.

All adverse event reports (AERs) were reviewed, grouped into ten different categories and analyzed to determine if specific trends in the adverse events were present. Because no spontaneous report had more than one complaint, the 156 individual complaints were placed in the appropriate categories and generated 156 total categorized, individual AERs. The categories include:

1. Gastrointestinal (GI) symptoms
2. Allergic reaction
3. Respiratory-oral symptoms
4. Increased blood pressure/tachycardia
5. Internal bleeding
6. Rash/hives/burning
7. Headaches
8. Dizziness
9. Watering eyes
10. Unspecified
The GI and Respiratory-oral symptoms (Categories 1 and 2, respectively) were further subdivided as follows:

1a. Nausea  
1b. Vomiting  
1c. Diarrhea  
1d. Abdominal pain/cramps  
1e. Abdominal bloating  
1f. Flatulence  
1g. Heartburn/upset stomach

3a. Breathing difficulties  
3b. Swollen/tightened throat  
3c. Gagging/coughing  
3d. Burning/sore throat, mouth, tongue  
3e. Swollen/numb mouth, tongue

The number and percentages of the total AERs for Echinilin®-containing products collected since 2004 are found in Table 1.

[[Table 1. here]]

The results obtained following the analysis of the collected AERs reflect that the majority of the complaints were GI (32.7%) in nature or were unspecified and unconfirmed allergic responses (20.5%). When the GI category is further subdivided, two complaints are found to be reported most frequently: heart burn/upset stomach (56.9%) and nausea (21.6%). Because no additional information was known about the allergic AERs, this category could not be subdivided.

More than 74.2 million single servings\textsuperscript{10} of Echinilin®-containing products were sold from 2004 through August 2010. Comparing the 74.2 million single servings to the total number of spontaneously reported AERs (156 total) for Echinilin®-containing products, and the total number of categorized individual AERs (also 156 total), the percent AERs to total individual servings is 0.0002%. Of the spontaneously reported

\textsuperscript{10} This figure was obtained by using the amount of servings per container multiplied by the number of containers sold since 2004.
AERs, two were serious adverse events suspected of being associated with the consumption of Echinilin®-containing products; the percent of suspected serious AERs to total individual servings is 0.0000027%.

Although some reported adverse effects appear to be associated with the consumption of Echinilin®-containing products, causality could not be established and adverse event association could not be inferred from the collected data. Nevertheless, a minimal level of suspicion has been raised which future postmarketing surveillance may or may not support.

DISCUSSION

The safety, tolerance and spontaneously reported adverse events for Echinacea-containing products were evaluated in a series of preclinical studies (Mengs et al., 1991), a clinical trial (Goel et al., 2004) and postmarketing surveillance, respectively.

A 28-day study with fresh pressed E. purpurea juice orally administered to rats via gastric tube at concentrations of 0, 800, 2400 and 8000 mg/kg bw/day showed no toxicological effects from use of the test substance in any of the test groups (Mengs et al., 1991). The results indicated an oral NOAEL for fresh-pressed E. purpurea juice of 8000 mg/kg bw/day (equivalent to 13.6 – 20 g/kg bw/day of the raw herb), a dose approximately 30 times the maximum daily dose in humans.

Because of its perceived antiviral and immunostimulating properties, Echinacea has been used in many dietary supplement products. Compared to the placebo group, reduced symptomology of an early onset cold was observed within 24 hours of the first dose of Echinilin® (Echinamide®) in the clinical trial (Goel et al., 2004). Throughout the course of treatment, the severity and the duration of all cold symptoms, except for cough, were significantly reduced compared to placebo. The dose schedule for Echinilin® (ten doses the first day (~0.67 g Echinacea per kg bw) and four doses (~0.27 g Echinacea per kg bw) each of the next six days) was also well tolerated by the male and female volunteers who were contracting a cold, but otherwise healthy. The side effects that did occur, primarily gastrointestinal effects (e.g., nausea, heartburn and constipation) and unpleasant tongue sensations (e.g., itching, burning and numbness), were mild in severity and similar to placebo; no subjects withdrew from the trial due to side effects.
The postmarketing data collected for *Echinacea*-containing products are generally consistent with the results obtained from the clinical study and reflect that the most frequent AERs were GI complaints (32.7%), with two complaints reported more frequently – heart burn/upset stomach and nausea. Unpleasant oral sensations including burning and numbness were also reported but in fewer than 10% of AERs. In a departure from the clinical trial which excluded participants having known allergy to ragweed, 20.5% of AERs were unspecified and unconfirmed allergic reactions. There was also one AER of breathing difficulties sufficiently serious that the consumer was treated with Benadryl at a hospital. However, no evidence is known to link this to the product and Health Canada did not contact Factors Group further regarding this incident. Although unpleasant tongue sensations (e.g., itching, burning and numbness) were reported, no allergic events were noted for either the *Echinacea* or placebo group during the clinical trial. Review of the published literature indicates that mild GI symptoms, unpleasant taste/oral sensations and rash are side effects anticipated to occur in some individuals (Barnes *et al.*, 2005, Barrett, 2003, Huntely *et al.*, 2005, Parnham, 1996). For instance, during a six year study (1989 – 1995) in Germany involving over 1200 subjects taking the commercial *E. purpurea* juice Echinacin®, four of thirteen reported adverse events were causally linked to Echinacin® and each was an allergic skin reaction (Parnham, 1996). Although allergic response is most likely to occur in individuals known to be allergic to members of the Asteraceae family (e.g. chamomile, chrysanthemum, daisy, marigold, ragweed), the occurrence of any type of severe allergic reaction is rare (Barnes *et al.*, 2005, Barrett, 2003). Importantly, when the total number of spontaneously reported AERs (156), and the total number of categorized individual AERs (156) were compared to the 74.2 million single servings of *Echinacea*-containing products sold since 2004, it was determined that all AERs were below 0.0003% with SAERs (two incidents), being below 0.000003%. The number of total complaints reported with use of *Echinacea*-containing products is low and proportionately very small when considering the 74.2 million single servings sold.

While the advantages for a postmarketing surveillance system are evident, it is also important to consider several limitations including difficulties with adverse event recognition, underreporting, biases, and report quality. Proving causality in the case of...
spontaneous reports is very difficult because, in essence, spontaneous reports represent case reports or case series which cannot be compared against a control group. Adverse events are seen in users of marketed supplement products, placebo (Green, 1964) and even no-treatment groups (Reidenberg et al., 1968), making the arrival at a firm conclusion about the relationship between exposure to a supplement product and the occurrence of an adverse event difficult. In fact, achieving proof of causality through postmarketing surveillance is unusual (Auriche and Loupi, 1993); and may only just indicate a high degree of probability of an association. Therefore, reporting an adverse reaction does not imply a causal link.

FDA acknowledges that “the recognition of adverse events of any supplement or medical product is quite subjective and imprecise. While an attribution between the medical product [supplement] and the observed event is assumed with all spontaneously reported events, every effort is made to rule out other explanations for the event in question” (FDA, 1995).

Therefore, it can be emphasized that there is critical need for careful, thoughtful review of adverse event reports upon their receipt, which can only be accomplished if the quality of the information collected is adequate.

CONCLUSION

The AERs associated with *Echinacea* and identified in the clinical trial and the information obtained from spontaneously reported adverse events cannot be analyzed side-by-side. However, by looking at the two sets of data it can be concluded that there were no serious adverse events reported through the clinical trial, two serious but not causally linked adverse events reported through post-market surveillance and that the majority of AERs were of a mild GI nature and not significantly different than AERs seen with the intake of the placebo formulation during the clinical trial. These mild unwanted effects are not considered to be toxic in nature but may be indicative of tolerance or even of background health status. In conclusion, evaluating the entire data for Echinilin®-containing *Echinacea* products present herein, it can be inferred that extracts, tinctures and juices prepared from the flowering perennial are well tolerated when used to supplement the diet with this specific product.
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REFERENCES


Table 1. AERs for Echinilin®-containing products since 2004

<table>
<thead>
<tr>
<th>Category</th>
<th># of AERs</th>
<th>% of total AERs</th>
<th>% of Main Category</th>
</tr>
</thead>
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<tr>
<td>1. GI symptoms</td>
<td>51</td>
<td>32.7</td>
<td>-</td>
</tr>
<tr>
<td>1a. Nausea</td>
<td>11</td>
<td>-</td>
<td>21.6</td>
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<tr>
<td>1b. Vomiting</td>
<td>4</td>
<td>-</td>
<td>7.8</td>
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<tr>
<td>1c. Diarrhea</td>
<td>2</td>
<td>-</td>
<td>3.9</td>
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<tr>
<td>1d. Abdominal pain/cramps</td>
<td>3</td>
<td>-</td>
<td>5.9</td>
</tr>
<tr>
<td>1e. Abdominal bloating</td>
<td>1</td>
<td>-</td>
<td>2.0</td>
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<tr>
<td>1f. Flatulence</td>
<td>1</td>
<td>-</td>
<td>2.0</td>
</tr>
<tr>
<td>1g. Heartburn/upset stomach</td>
<td>29</td>
<td>-</td>
<td>56.9</td>
</tr>
<tr>
<td>2. Allergic reaction (unspecified)¹</td>
<td>32</td>
<td>20.5</td>
<td>-</td>
</tr>
<tr>
<td>3. Respiratory-Oral</td>
<td>19</td>
<td>12.2</td>
<td>-</td>
</tr>
<tr>
<td>3a. Breathing difficulties²</td>
<td>1</td>
<td>-</td>
<td>5.3</td>
</tr>
<tr>
<td>3b. Swollen/tightened throat</td>
<td>2</td>
<td>-</td>
<td>10.5</td>
</tr>
<tr>
<td>3c. Gagging/coughing</td>
<td>2</td>
<td>-</td>
<td>10.5</td>
</tr>
<tr>
<td>3e. Burning/sore throat, mouth, tongue</td>
<td>11</td>
<td>-</td>
<td>57.9</td>
</tr>
<tr>
<td>3f. Swollen/numb mouth, tongue</td>
<td>3</td>
<td>-</td>
<td>15.8</td>
</tr>
<tr>
<td>4. Increased blood pressure/ tachycardia</td>
<td>3</td>
<td>1.9</td>
<td>-</td>
</tr>
<tr>
<td>5. Internal bleeding</td>
<td>1</td>
<td>0.6</td>
<td>-</td>
</tr>
<tr>
<td>6. Rash/hives/burning</td>
<td>8</td>
<td>5.1</td>
<td>-</td>
</tr>
<tr>
<td>7. Headaches</td>
<td>8</td>
<td>5.1</td>
<td>-</td>
</tr>
<tr>
<td>8. Dizziness</td>
<td>1</td>
<td>0.6</td>
<td>-</td>
</tr>
<tr>
<td>9. Watering eyes</td>
<td>1</td>
<td>0.6</td>
<td>-</td>
</tr>
<tr>
<td>10. Unspecified</td>
<td>32</td>
<td>20.5</td>
<td>-</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>156</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

¹ (i.e., “Allergic reaction”)  
² Serious adverse event (detailed in text)  
³ (i.e., “Felt ill”, “Made sick”, “Bad reaction”)