Heather Throop/HC-SC/GC/CA
2007-12-13 08:06 PM

To Heather Throop/HC-SC/GC/CA@HWC
cc
bcc
Subject Fw: Comment: EMPowerplus - CT trial / related AR

History: This message has been forwarded.

----- Forwarded by Heather Throop/HC-SC/GC/CA on 2007-12-13 08:06 PM -----

Chris Turner
2007-02-16 10:58 AM

To: mano_murty@hc-sc.gc.ca
cc: vicky_hogan@hc-sc.gc.ca, David K Edwards/HC-SC/GC/CA@HWC, Marielle McMorran/HC-SC/GC/CA@HWC, heather_sutcliffe@hc-sc.gc.ca, Robin Marles/HC-SC/GC/CA@HWC, heather_throop@hc-sc.gc.ca, jenna_griffiths@hc-sc.gc.ca, diana_dowthwaite@hc-sc.gc.ca, darrin_denne@hc-sc.gc.ca, jason_berg@hc-sc.gc.ca, cindy_evans@hc-sc.gc.ca, david_clapin@hc-sc.gc.ca, ken_polk@hc-sc.gc.ca, Tamantha Bedard/HC-SC/GC/CA@HWC, Susan Robertson/HC-SC/GC/CA@HWC, Omer Boudreau@hc-sc.gc.ca, supriya_sharma@hc-sc.gc.ca
Subject: Comment: EMPowerplus - CT trial / related AR

s.23

Mano:

- As far as I know the goal is still to issue that Information Update early next week;
- Just to document the point I made yesterday that possibly a "Foreign Product Alert" should have been the risk communications vehicle used as suggested in the Comms fact sheet, i.e., "risks related to foreign products not authorized for sale in Canada and not found on the Canadian marketplace, but which may have entered the country through personal importation or by purchase over the Internet". **Perhaps Comms can comment if they prefer to change this to a FPA since it is not too late to do that change.** An e-mail notice is sent to the Health Canada media list when a new product is added to the Foreign Product Alert table on the Health Canada website.The problem is the degree of precision and the overlap in the fact sheet on HC risk communication vehicles. I suggest that Comms may want to work to refine the descriptions and perhaps develop a table/grid to aid in decisions about which HC risk communications vehicle/product to use (including information on any differences in dissemination attached to the different vehicles) and to attach that suggested decision grid to the proposed "Triggers" guidance document being developed by the Branch Risk Communications WG;
- Just make sure that CADRIS search is up to date and that no more recent reports have been received in MHPD or in NHPD as part of the submission for the NPN.

FYI:
Information Update
This new product is used when there is information to be conveyed about a product that carries a lower level of risk or that affects a very small group of people. The Information Update may also be used to indicate the progress of Health Canada's review of a risk situation or to reinforce safety recommendations previously issued. Information Updates are posted on the Health Canada website and distributed using the Health Canada media e-mail list and through MedEffect when marketed health products are involved. Updates may also be issued through Canada News Wire when warranted.

Foreign Product Alert
This new web-based communication product advises consumers of health risks related to foreign products not authorized for sale in Canada and not found on the Canadian marketplace, but which may have entered the country through personal importation or by purchase over the Internet. An e-mail notice is sent to the Health Canada media list when a new product is added to the Foreign Product Alert table on the Health Canada website.

----- Forwarded by Chris Turner/HC-SC/GC/CA on 2007-02-16 10:44 AM -----

Hoda Eid
2007-02-16 10:31 AM

To: Mano Murty/HC-SC/GC/CA@HWC
cc: Carole Gauthier <Carole_Gauthier@hc-sc.gc.ca>, "Dr. Chris Turner" <chris_turner@hc-sc.gc.ca>, Jenna_griffith@hc-sc.gc.ca, John Patrick Stewart/HC-SC/GC/CA@HWC, Kathleen Lafleur <Kathleen_Lafleur@hc-sc.gc.ca>, Laura De Curtis/HC-SC/GC/CA@HWC, Micheline Ho/HC-SC/GC/CA@HWC, Robin Marles/HC-SC/GC/CA@HWC, Simon Carvalho/HC-SC/GC/CA@HWC, Susan Robertson/HC-SC/GC/CA@HWC, Trudy Hall/HC-SC/GC/CA@HWC, Vicky Gow <vicky.gow@ubu.ca>
Subject: Re: EMPowerplus - CT trial / related AR

Hello Mano,

[redacted]

Thanks,
Hoda

s.23

Mano Murty

Mano Murty
16/02/2007 08:23 AM

To: Hoda Eid/HC-SC/GC/CA@HWC
cc: Carole Gauthier <Carole_Gauthier@hc-sc.gc.ca>, "Dr. Chris Turner" <chris_turner@hc-sc.gc.ca>, Jenna_griffith@hc-sc.gc.ca, John Patrick Stewart/HC-SC/GC/CA@HWC, Kathleen Lafleur <Kathleen_Lafleur@hc-sc.gc.ca>, Micheline Ho/HC-SC/GC/CA@HWC, Susan Robertson/HC-SC/GC/CA@HWC, Trudy Hall/HC-SC/GC/CA@HWC, Vicky Gow <vicky.gow@ubu.ca>, Laura De Curtis/HC-SC/GC/CA@HWC, Robin Marles/HC-SC/GC/CA@HWC, Simon Carvalho/HC-SC/GC/CA@HWC
Subject: Re: EMPowerplus - CT trial / related AR

Hi Hoda
We have redrafted the public communication piece to focus on the ARs and is to go out asap.
This additional piece of information relating to a 2001 CT needs to be captured as well, to strengthen the message of potential health risks associated with the use of this product, specifically in the paediatric population.
When do you estimate the receipt of this info/case report?
Thank you in advance for your assistance.
Mano

Hoda Eid

Hoda Eid
2007-02-15 03:50 PM

To: Mano Murty/HC-SC/GC/CA@HWC
cc: Carole Gauthier <Carole_Gauthier@hc-sc.gc.ca>, "Dr. Chris Turner" <chris_turner@hc-sc.gc.ca>, Jenna_griffith@hc-sc.gc.ca, Kathleen Lafleur <Kathleen_Lafleur@hc-sc.gc.ca>, Micheline Ho/HC-SC/GC/CA@HWC, Trudy Hall/HC-SC/GC/CA@HWC, Vicky Gow <vicky.gow@ubu.ca>, Susan Robertson/HC-SC/GC/CA@HWC, John Patrick Stewart/HC-SC/GC/CA@HWC
Subject: Re: APPROVED -Truehope - MHPD intorductory para for the risk assessment

s.23

Hello Mano,

[redacted] In the meatime, Mr. Serge Durant is looking at whether they have a copy of this file.

I will let you know if I have further information.

Hoda

Mano Murty

Mano Murty
15/02/2007 09:06 AM

To: Vicky Gow <vicky.gow@ubu.ca>
cc: Carole Gauthier <Carole_Gauthier@hc-sc.gc.ca>, "Dr. Chris Turner" <chris_turner@hc-sc.gc.ca>, Jenna_griffith@hc-sc.gc.ca, Kathleen Lafleur <Kathleen_Lafleur@hc-sc.gc.ca>, Trudy Hall/HC-SC/GC/CA@HWC, Micheline Ho/HC-SC/GC/CA@HWC, Hoda Eid/HC-SC/GC/CA@HWC
Subject: Re: APPROVED -Truehope - MHPD intorductory para for the risk assessment

Hi Vicky
Thank you for the note/comments.

- All 9 domestic case reports had serious ARs, most requiring medical intervention.
- Re: CT paediatric case report - I have contacted Dr. Hoda Eid and hopefully will get the info soon (before posting our advisory).
- FYI - Below is the revised document (32 pages) of HRA done by NHPD (incorporating most of our comments below). This was briefly discussed at yesterday's meeting.

EMPowerplus HRA 119864 2007-02-13.doc

Vicky Gow <vicky.gow@ubu.ca>

Vicky Gow
<vicky.gow@ubu.ca>
2007-02-14 09:59 PM

To: Mano Murty <Mano_Murty@hc-sc.gc.ca>
cc: Jenna_griffith@hc-sc.gc.ca, "Dr. Chris Turner" <chris_turner@hc-sc.gc.ca>, Carole Gauthier <Carole_Gauthier@hc-sc.gc.ca>, Kathleen Lafleur <Kathleen_Lafleur@hc-sc.gc.ca>
Subject: APPROVED -Truehope - MHPD intorductory para for the risk assessment

Mano:

This intro para reads fine as a first cut and I am not inclined to spend a lot of time fine-tuning the wording as it will surely receive input from several others before it is finalized.

The only 2 comments I will make at this point are as follows:

1) were all 9 case reports associated with actual negative health outcomes or were some of them documenting the potential for negative health outcomes. If any were of the latter type then we should consider adding the word 'potential' in front of the words health risk (which is used several times in this para).

s.19(1)

2) don't forget that once you add the 10th case report [redacted] to the causality assessment document you will need to go back to this para to update the case no.

Thanks,

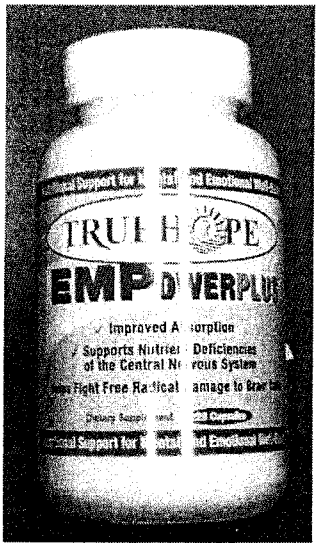
-vicky

Carole Gauthier wrote:
> Carole Gauthier
> Office of Risk Management / Bureau de la gestion des risques
> Director General Office / Bureau du directeur général
> Marketed Health Products Directorate / Direction des produits de santé
> commercialisés
> Tel: 613-952-9433
> Fax: 613-952-7738
> ----- Forwarded by Carole Gauthier/HC-SC/GC/CA on 02/14/2007 03:21 PM -----
>
> Mano Murty
> To: Robin Marles/HC-SC/GC/CA@HWC
> 02/12/2007 05:42 PM cc: Trudy Hall/HC-SC/GC/CA@HWC, Jenna Griffiths/HC-SC/GC/CA@HWC, Scott Jordan/HC-SC/GC/CA@HWC, Vicky Hogan/HC-SC/GC/CA@HWC, Micheline Ho/HC-SC/GC/CA@HWC, Diana Dowthwaite/HC-SC/GC/CA@HWC, Jenny McLaughlin/HC-SC/GC/CA@HWC
> Subject: VFA - Truehope - MHPD intorductory para for the risk assessment
>
>
>
>
> Hi Robin
> As requested this morning, here is the introductory para to use in your
> product risk assessment report.
> Feel free to edit and please forward the final version.
> Thanks
> Mano
>
> Health Canada has been made aware of new information with regard to the
> product, EMPower and the health risk associated with the promotion of this
> product.
> The risk assessment has been made taking into account the totality of

> evidence based on the following components:
> 9 domestic adverse reaction reports (ARR) have been received by Health Canada, all being serious associated with the use of the product EMPowerplus;
> the ARR relate to worsening of psychiatric symptoms in those patients with serious underlying medical problems such as bipolar disorder, depression;
> the worsening of symptoms mostly relate to taking the product and discontinuing prescription medications or taking the product in conjunction with prescribed medications without consulting a healthcare practitioner;
> medical advice is being given by non-medically qualified personnel from a call centre operated by Synergy Group of Canada Inc., that can impact on patient use / adjustment of their prescribed medications, which in turn, can lead to adverse reaction.
> advertising material, including a newsletter and websites make reference to the product being effective for treating serious psychiatric illness, when in fact the efficacy and safety profile has not been established by clinical trials etc.
> one patient support newsletter makes reference to the product's use in subpopulations such as infants, pregnant /lactating women when in fact, safety profile in these subpopulation has not been established through research studies;
> Conclusion: The serious health risk is identified from the way the product
> is being used and promoted.
>
>

Health Risk Assessment

Product Name:	EMPowerplus
Manufacturer / Legal Agent in Canada:	Manufactured for: Truehope Nutritional Support Ltd. Cardston AB T0K 0K0
Site Licence:	Submission #111469 for importation refused 2007-02-01 for failure to provide requested information
Product Licence:	Submission #120449 under assessment (not identical formulation)
Requested by:	HPFB Inspectorate
Date Requested:	2007-01-04
Date Completed:	2007-01-06
File Number:	119864
Approved by:	Robin Marles 2007-01-08, revised 2007-02-13
Product Classification:	Natural Health Product according to labelled dose of the product sample provided by Inspectorate. Drug requiring a prescription according to Truehope web site loading dose recommendation.
Compliance Priority:	Product Category 1, superseded by the Risk-Based Approach



Issue/History:
Health Canada has been made aware of new information with regard to the product, EMPowerplus, and the health risks associated with the promotion of this product. This risk assessment has been made taking into account the totality of evidence based on the following components:

- 9 domestic adverse reaction reports (ARR) have been received by Health Canada, all being serious, associated with the use of the product EMPowerplus;
- the ARR relate to worsening of psychiatric symptoms in those patients with serious underlying medical problems such as bipolar disorder, depression;
- the worsening of symptoms mostly relate to taking the product and discontinuing prescription medications or taking the product in conjunction with prescribed medications without consulting a healthcare practitioner;
- medical advice is being given by non-medically qualified personnel from a call centre operated by Synergy Group of Canada Inc., that can impact on patient use / adjustment of their prescribed medications, which in turn, can lead to adverse reaction;
- advertising material, including a newsletter and websites make reference to the product being effective for treating serious psychiatric illness, when in fact the efficacy and safety profile has not been established by clinical trials etc.;
- one patient support newsletter makes reference to the product's use in subpopulations such as infants, pregnant or breast-feeding women when in fact, the safety profile in these subpopulation has not been established through research studies.

Analysis:

Table 1: Medicinal Ingredients in EMPowerplus

Medicinal Ingredient	Quantity /capsule	Daily Dose (max. 8 capsules)	Daily Dose (max. 15 capsules)	NHP?	Ingredient Category
Vitamin A (as retinyl palmitate)	384 IU	3072 IU	5760 IU	Yes	Vitamin
Vitamin C (as ascorbic acid)	40 mg	320 mg	600 mg	Yes	Vitamin
Vitamin D (as cholecalciferol)	96 IU	768 IU	1440 IU	Yes	Vitamin
Vitamin E (as d-alpha tocopheryl succinate)	24 IU	192 IU	360 IU	Yes	Vitamin
Vitamin B_1 (as thiamine mononitrate)	1.2 mg	9.6 mg	18 mg	Yes	Vitamin
Vitamin B_2 (as riboflavin)	0.9 mg	7.2 mg	13.5 mg	Yes	Vitamin
Vitamin B_3 (as niacinamide)	6 mg	48 mg	90 mg	Yes	Vitamin
Vitamin B_5 (as d-calcium pantothenate)	1.45 mg	11.6 mg	21.75 mg	Yes	Vitamin
Vitamin B_6 (as pyridoxine hydrochloride)	2.4 mg	19.2 mg	36 mg	Yes	Vitamin
Vitamin B_9 (as folic acid)	96 µg	768 µg	1440 µg	Yes	Vitamin

Vitamin B_{12} (as cyanocobalamin)	60 µg	480 µg	900 µg	Yes	Vitamin
Vitamin H (biotin)	72 µg	576 µg	1080 µg	Yes	Vitamin
Calcium	88 mg	704 mg	1320 mg	Yes	Mineral
Phosphorus	56 mg	448 mg	840 mg	Yes	Mineral
Magnesium	40 mg	320 mg	600 mg	Yes	Mineral
Potassium	16 mg	128 mg	240 mg	Yes	Mineral
Iodine (from Pacific kelp)	13.6 µg	108.8 µg	204 µg	Yes	Mineral
Zinc	3.2 mg	25.6 mg	48 mg	Yes	Mineral
Selenium	13.6 µg	108.8 µg	204 µg	Yes	Mineral
Copper	0.475 mg	3.8 mg	7.125 mg	Yes	Mineral
Manganese	0.65 mg	5.2 mg	9.75 mg	Yes	Mineral
Chromium	41.6 µg	332.8 µg	624 µg	Yes	Mineral
Molybdenum	9.6 µg	76.8 µg	144 µg	Yes	Mineral
Iron	0.925 mg	7.4 mg	13.875 mg	Yes	Mineral
Proprietary blend:	*111 mg*	*888 mg*	*1665 mg*		
D,L-phenylalanine	~24 mg*	~192 mg*	~360 mg*	Yes	Amino acid
L-glutamine	~12 mg*	~96 mg*	~180 mg*	Yes	Amino acid
citrus bioflavonoids	~16 mg*	~128 mg*	~240 mg*	Yes	Plant extract
grape seed	~3 mg*	~24 mg*	~45 mg*	Yes	Plant extract
choline bitartrate	~36 mg*	~288 mg*	~540 mg*	Yes	Isolate
inositol	~12 mg*	~96 mg*	~180 mg*	Yes	Isolate
Ginkgo biloba	~2.4 mg*	~19.2 mg*	~36 mg*	Yes	Plant material
L-methionine	~4 mg*	~32 mg*	~60 mg*	Yes	Amino acid
germanium sesquioxide	~1.4 mg*	~11.2 mg*	~21 mg*	Yes	Isolate
boron	~160 µg*	~1.3 mg*	~2.4 mg*	Yes	Mineral
vanadium	~79.6 µg*	~637 µg*	~1.2 mg*	Yes	Mineral
nickel	~1.9 µg*	~15.2 µg*	~28.5 µg*	Yes	Mineral

* The quantity of each component of the proprietary blend is not listed on the label but an estimate is provided here as a guide based on information provided in Appendix 1.

Discussion:

Ingredients

The formulation of EMPowerplus has changed over the last few years (see Appendix 1), showing a trend to increasing quantities of medicinal ingredients per capsule and a reduction in the maximum daily loading dose recommendation. On the Truehope web site (www.truehope.com/_research/Nutrient%20Deficiency.asp, accessed 2007-02-13) a rationale is provided for why, in their opinion, there is a relationship between nutrient deficiencies and mental illness, and why each of the medicinal ingredients in the EMPowerplus product contributes to the treatment of mental illness.

Table 2. Comparison of EMPowerplus Ingredient Daily Doses to IOM (2006) Daily Tolerable Upper Levels of Intake (UL) for Infants, Children, Adults, and Pregnancy

Medicinal	Amount/Daily	Amount/Daily	Selected UL Values

Ingredient	Dose (8 capsules)	Dose (15 capsules)	0-6m/1-3y/4-8y/19+/Pregnancy
Vitamin A (as retinyl palmitate)	3072 IU = 928 µg RAE	5760 IU = 1741 µg RAE	600/600/900/3000/2800 µg RAE
Vitamin C (as ascorbic acid)	320 mg	600 mg	ND/400/650/2000/1800 mg
Vitamin D (as cholecalciferol)	768 IU = 19.2 µg	1440 IU = 36 µg	25/50/50/50/50 µg
Vitamin E (as d-alpha tocopheryl succinate)	192 IU = 129 mg ATE	360 IU = 241 mg ATE	ND/200/300/1000/800 mg ATE
Vitamin B_1 (as thiamine mononitrate)	9.6 mg	18 mg	None established, see below
Vitamin B_2 (as riboflavin)	7.2 mg	13.5 mg	None established, see below
Vitamin B_3 (as niacinamide)	48 mg	90 mg	ND/10/15/35/30 mg
Vitamin B_5 (as d-calcium pantothenate)	11.6 mg	21.75 mg	None established, see below
Vitamin B_6 (as pyridoxine hydrochloride)	19.2 mg	36 mg	ND/30/40/100/80 mg
Vitamin B_9 (as folic acid)	768 µg	1440 µg	ND/300/400/1000/800 µg
Vitamin B_{12} (as cyanocobalamin)	480 µg	900 µg	None established, see below
Vitamin H (biotin)	576 µg	1080 µg	None established, see below
Calcium	704 mg	1320 mg	ND/2500/2500/2500/2500 mg
Phosphorus	448 mg	840 mg	ND/3000/3000/4000/3500 mg
Magnesium	320 mg	600 mg	ND/65/110/350/350 mg
Potassium	128 mg	240 mg	None established, see below
Iodine	108.8 µg	204 µg	ND/200/300/1100/900 µg
Zinc	25.6 mg	48 mg	4/7/12/40/34 mg
Selenium	108.8 µg	204 µg	45/90/150/400/400 µg
Copper	3.8 mg	7.125 mg	ND/1/3/10/8 mg
Manganese	5.2 mg	9.75 mg	ND/2/3/11/9 mg
Chromium	332.8 µg	624 µg	None established, see below
Molybdenum	76.8 µg	144 µg	ND/300/600/2000/1700 µg
Iron	7.4 mg	13.875 mg	40/40/45/45 mg
D,L-phenylalanine	~192 mg*	~360 mg*	None established, see below
L-Glutamine	~96 mg*	~180 mg*	None established, see below
Citrus bioflavonoids	~128 mg*	~240 mg*	None established, see below
Grape seed	~24 mg*	~45 mg*	None established, see below
Choline (as choline	~288 mg*	~540 mg*	ND/1000/1000/3500/3000 mg

bitartrate)			
Inositol	~96 mg*	~180 mg*	None established, see below
Ginkgo biloba	~19.2 mg*	~36 mg*	None established, see below
L-Methionine	~32 mg*	~60 mg*	None established, see below
Germanium sesquioxide	~11.2 mg*	~21 mg*	None established, see below
Boron	~1.3 mg*	~2.4 mg*	ND/3/6/20/17 mg
Vanadium	~637 µg*	~1.2 mg*	ND/ND/ND/1.8/ND mg
Nickel	~15.2 µg*	~28.5 µg*	ND/0.2/0.3/1/1 mg

* The quantity of each component of the proprietary blend is not listed on the label but an estimate is provided here as a guide based on information provided in Appendix 1.
Abbreviations: ND= Not Determinable; RAE = Retinol Activity Equivalents; ATE = Alpha-Tocopherol Equivalents

Dosage

The current packaging/formulation has a revised product label recommendation of a maximum dose of 7 to 8 capsules per day (the maintenance dose according to the web site) while the web site recommends the following:

> Q. What is a loading dose? How does it differ from a maintenance dose?
> A. An initial loading dose of the supplements is required to address not only the body's daily requirements but has also been designed to make up deficiencies that may have been present for years. Our experience puts the recommended loading dose at a level where the majority of people will respond optimally to the supplement (usually 15 caps or 4 scoops of powder per day). Some may actually see some benefit in taking more, and yet others respond to less than the recommended loading dose. The recommended dose, as noted in the Nutrient Protocol, begins small and gradually increases until the participant reaches the recommended dosage or until he or she demonstrates a sensitivity to the supplements' inclusion in the diet. These participants would have to increase their intake very slowly and may peak at a dose below the average optimal dose. However, unless the participant has a sensitive digestive system, it is recommended that the participant attempt to reach the loading dose within a short period of time to optimize the speed of response to the supplements. It is recommended that the loading dose be maintained for a number of months after the symptoms subside before reducing the supplement to a maintenance dose (usually 9 caps or 2 scoops of powder per day). This assures that optimum stability has been achieved. The maintenance dose for any participant is determined solely by the ability to maintain wellness on the program and can range from 9 caps (2 scoops of powder) to the full loading dose of 15 caps (4 scoops of powder) (http://www.truehope.com/_faqs/faqs.asp#4 accessed 2007-02-13).

With respect to dosing for particular subpopulations, the Truehope web site provides the following information:

> Q. Is EMPowerplus good for children? If yes, how much should they take?
> A. Many children have benefited from taking EMPowerplus. Because EMPowerplus is essentially food ingredients, dosage is determined more by nutrient requirement than by body weight. Children often have high nutrient requirements to meet the needs of a growing body and therefore can often benefit from close to adult-like dosages. Of course, very small children (under six years of age) generally see benefit from a lower dosage of EMPowerplus (http://www.truehope.com/_faqs/faqs.asp#4 accessed 2007-02-13).

With respect to taking the product during pregnancy or breast-feeding, the product label provides the following recommendation:

> "Note: Pregnant or lactating women, diabetics, hypoglycemics and people with known medical conditions should consult with a physician."

At 8 capsules per day, none of the medicinal ingredients exceeds the limits permissible without a prescription. However, http://www.truehope.com/_empowerplus/empSafety.asp (accessed 2007-01-09), the Truehope web site, lists daily amounts based on a "full loading dose of 15 capsules per day." Under these conditions of use, EMPowerplus would need to be sold by prescription because at that dose the Schedule F limits would be exceeded for vitamin D (EMPowerplus 1440 IU vs. Schedule F >1000 IU) and folate (EMPowerplus 1440 µg vs. Schedule F >1000 µg).

Risk Assessment

Vitamin A. At 8 and 15 capsules the dose of vitamin A exceeds the UL values for infants and children. Neither dose exceeds the UL for adults and pregnancy. The UL for adults is based on liver abnormalities; for women of childbearing age teratogenicity is the critical adverse effect. These doses would therefore present an unacceptable risk to the health of infants and children.

Vitamin C. At 8 capsules the dose exceeds the UL for infants but not for children. At 15 capsules the dose exceeds the UL for infants and children. Neither dose exceeds the UL for adults and pregnancy. Since vitamin C has very low toxicity (UL is based on osmotic diarrhoea and gastrointestinal disturbance seen only at very high doses e.g. >3 g/day), these doses may present a low level of risk to infants but not to other lifestages.

Vitamin D. At 8 capsules the dose is below all ULs; at a dose of 15 capsules per day, the daily dose of Vitamin D (1440 IU = 36 µg/day) exceeds the UL for infants but not the other lifestages. Nevertheless, according to the current Schedule F listing, the 15 capsule dose would require the product to be sold by prescription. Excessive intakes of Vitamin D can cause hypercalcemia, including the calcification of soft tissues, and reduced renal function (IOM 2006). Thus the 15-capsule dose of EMPowerplus may present a risk to infants.

Vitamin E. At 8 capsules the dose exceeds the UL for infants but not for children. At 15 capsules the dose exceeds the UL for infants and children but not adults. The risk to health of excess intake of vitamin E includes hemorrhagic toxicity and diminished blood coagulation in individuals who are deficient in vitamin K or on anticoagulant therapy (IOM 2006), so the risks to health are limited to those specific subpopulations.

Thiamine. The IOM did not establish a UL for thiamine due to lack of data on the adverse effects of excess consumption (IOM 2006). Supplements that contain up to 50 mg thiamine/day are widely available over-the-counter without reports of serious adverse reactions. The absorption of thiamine from the jejunum is limited at high doses and at elevated plasma concentrations thiamine is actively excreted (IOM 2006). The Expert Committee on Vitamins and Minerals from the United Kingdom Food Standards Agency (EVM, 2003) recommends an upper limit of intake of 50 mg/day. The amount of thiamine in an 8-capsule daily dose of EMPowerplus (9.6 mg) is much lower than that amount and therefore is unlikely to pose a significant risk to health.

A daily dose of 15 capsules contains 18 mg of thiamine which, for the same reasons, is also unlikely to pose a significant risk to health.

Riboflavin. The IOM did not establish a UL for riboflavin due to insufficient data available on the effects of excessive intake (IOM 2006). Riboflavin has low water solubility which limits its gastrointestinal absorption; it is also rapidly excreted in the urine (IOM 2006). The EVM (2003) recommends an upper limit of intake of 40 mg/day. The amounts of riboflavin in an 8-capsule daily dose (7.2 mg) or 15-capsule dose (13.5 mg) of EMPowerplus are much lower than this value and therefore are unlikely to pose a significant risk to health.

Vitamin B_3 (Niacinamide). At doses of 8 capsules or 15 capsules per day, the daily dose of niacinamide (48 mg and 90 mg, respectively) exceeds the UL values for all lifestages. These ULs are based on the adverse effect of flushing symptoms of nicotinic acid (niacin) (IOM 2006). EMPowerplus contains niacinamide, which is not associated with flushing symptoms (Murray 1996). For adults, the quantities of niacinamide present in both the 8- and 15-capsule doses of EMPowerplus do not pose a significant risk to health. For infants and children the ULs are exceeded by up to 9x – theoretically there could be a potential for liver toxicity but this has been observed mainly with high doses of slow- or sustained-release nicotinic acid administered therapeutically, e.g. for the treatment of hyperlipidemia (IOM 2006).

Vitamin B_5 (Pantothenate). The IOM did not establish a UL for pantothenic acid due to insufficient data; no adverse effects have been associated with high intakes (IOM 2006). The EVM (2003) recommends an upper limit of intake of 200 mg/day. The amount of pantothenate in an 8-capsule daily dose (11.6 mg) or 15-capsule daily dose (21.75 mg) of EMPowerplus is much lower than this amount and therefore is unlikely to pose a significant risk to health.

Vitamin B_6 (Pyridoxine). At 8 capsules the dose exceeds the UL for infants but not for children. At 15 capsules the dose slightly exceeds the UL for infants and children but not adults. Very large doses have been associated with the development of sensory neuropathy and skin lesions, but those effects are seen at 20x the UL, so at the 8- and 15-capsule doses, the risks to health from excess intake of pyridoxine appear to be low.

Folate. At 8 capsules the dose exceeds the UL for infants and children, and at a dose of 15 capsules per day, the daily dose of folate (1440 µg) exceeds the UL values for all lifestages (1000 µg) and would require the product to be sold by prescription. The UL established by the IOM (2006) is based on the ability of high-dose folate supplementation to mask Vitamin B_{12} deficiency and result in the progression of the adverse neurological effects associated with such a deficiency. The 15-capsule dose of EMPowerplus also contains 480 µg of Vitamin B_{12}; but since B_{12} deficiency is often a result of a deficiency of intrinsic factor, which is essential for B_{12} absorption, this product's vitamin B_{12} content only partially mitigates this risk. No risk information that would capture this concern is present on the product label. Thus the high level of folate in a 15-capsule dose of this product poses a risk to the health of those people deficient in Vitamin B_{12}.

Vitamin B_{12}. The IOM did not establish a UL for Vitamin B_{12} due to insufficient data; no adverse effects have been associated with intakes as high as 3.7 mg (IOM 2006). When large doses of

B_{12} are taken orally, absorption is limited. Excretion is proportional with the amount present in the body (IOM 2006). The EVM (2003) recommends an upper limit of intake of 2000 µg/day. The amounts of Vitamin B_{12} present in an 8-capsule (480 µg) or 15-capsule (900 µg) daily dose of EMPowerplus are much lower than this level and therefore are unlikely to pose a significant risk to health.

Biotin. The toxicity of biotin has been reported to be very low (Marks *et al.* 1989), even at doses as high as 200 mg orally in adults (IOM 2006). The 8-capsule daily dose of EMPowerplus provides 576 µg, and the 15-capsule dose provides 1080 µg of biotin, levels that are unlikely to pose a significant risk to health.

Calcium. No UL was established for infants due to the lack of data on adverse effects in this age group but an adequate intake is considered to be 210-270 mg/day. Doses of 8 capsules (704 mg Ca) or 15 capsules (1320 mg Ca) per day are only 28% and 53% (respectively) of the UL for children, adults or pregnancy. The effects of excess calcium intake include kidney stones, hypercalcemia with renal insufficiency, and a decreased absorption of certain minerals (IOM 2006). Therefore, at the 8- and 15-capsule doses, there may be the potential for a low risk to infants due to concerns regarding a possible lack of ability to handle excess amounts of calcium, but these doses are not likely to pose a significant risk to the health of other lifestages.

Phosphorus. No UL was established for infants due to the lack of data on adverse effects in this age group but an adequate intake is considered to be 100-275 mg/day. Doses of 8 capsules or 15 capsules per day do not exceed the UL for children, adults or pregnancy. The effects of excess phosphorus intake are hyperphosphatemia which is mainly a problem with individuals with end-stage renal disease or in cases of vitamin D intoxication, and calcification of non-skeletal tissues, particularly the kidneys (IOM 2006). Therefore, at the 8- and 15-capsule doses, there may be the potential for a low risk to infants due to concerns regarding a possible lack of ability to handle excess amounts of phosphorus, but these doses are not likely to pose a significant risk to the health of other lifestages.

Magnesium. Doses of 8 and 15 capsules exceed the ULs for infants and children. At a dose of 15 capsules per day, the daily dose of magnesium (600 mg/day) also exceeds the adult UL (350 mg/day). This UL was based on the adverse effects of diarrhea, nausea and abdominal cramps, which have been shown to occur in a small number of subjects taking 360-380 mg/day of supplemental magnesium (IOM 2006). However, many other clinical trial subjects have not exhibited these symptoms at doses significantly higher than the UL (IOM 2006). Furthermore, magnesium salts such as magnesium oxide, magnesium hydroxide, and magnesium carbonate are permitted for use in Canada in antacid products at quantities of 1.9-3.3 grams per day for up to two weeks (Therapeutic Products Directorate Antacids Labelling Standard, available at: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/label-etiquet-pharm/antacid_antiacid_e.html, accessed January 31, 2007). Therefore, at the 8 and 15 capsule doses, there is a potential for risk to infants and children from the gastrointestinal effects. However, despite exceeding the UL, the doses of magnesium present in 8 or 15 capsules of EMPowerplus are not likely to pose a significant risk to the health of adults or pregnant women.

Potassium. The IOM did not establish a UL for potassium as there is no evidence that excessive intake from foods is likely to cause adverse effects in healthy people. However, high-dose potassium supplementation has potential toxicity acutely and chronically (IOM 2006). The Adequate Intake value for potassium in infants is 0.4 g/day, children 3 g/day, and in adults and pregnancy 4.7 g/day (IOM 2006). The quantities of potassium in an 8-capsule and 15-capsule daily dose of EMPowerplus (128 mg and 240 mg, respectively) are fractions of this and therefore are unlikely to pose a significant risk to health except in cases of individuals with impaired potassium excretion, where hyperkalemia can cause cardiac arrhythmias.

Iodine. Doses of 8 and 15 capsules exceed the ULs for infants, and the 15 capsule dose is at the UL for children, but these doses do not exceed the ULs for adults and pregnancy. The risks of excess intake are mainly related to thyroid dysfunction. Therefore, at the 8- and 15-capsule doses, there is a potential for risk to the health of infants and children.

Zinc. The 8-capsule dose (25.6 mg Zn) exceeds the UL for infants and young children. The 15-capsule dose (48 mg Zn) exceeds the UL for adults (40 mg/day). This UL was based on the adverse effects of excess zinc supplementation on copper status, but other adverse effects associated with excessive intake of supplemental zinc include suppression of the immune system (seen at 300 mg/day for 6 weeks in adults), a decrease in high density lipoprotein (HDL) cholesterol, and gastrointestinal distress (seen at doses ≥50 mg/day) (IOM 2006). The 15-capsule daily dose of EMPpowerplus, if taken for long duration, may have an adverse effect on copper status but this daily capsule dose also contains 7.125 mg of copper, so the likelihood of this adverse effect occurring is low. However, both the 8- and 15-capsule doses present potential risks to the gastrointestinal and immune system health of children and infants.

Selenium. The 8- and 15-capsule doses exceed the UL for infants and children but not for adults and pregnancy. The risks of excess intake of selenium include hair and nail brittleness and loss, gastrointestinal disturbances, fatigue, and nervous system abnormalities (IOM 2006). Therefore, at the 8- and 15-capsule doses, there is a potential for risk to the health of infants and children.

Copper. The 8- and 15-capsule doses exceed the UL for infants and children but not for adults and pregnancy. The risks of excess intake of copper include are mostly related to gastrointestinal disturbance and liver damage (IOM 2006). Therefore, at the 8- and 15-capsule doses, there is a potential for risk to the health of infants and children.

Manganese. The 8- and 15-capsule doses exceed the UL for infants and children but not for adults; however the 15-capsule dose exceeds the UL for pregnancy. The main risk of excess manganese intake is neurotoxicity (IOM 2006). Therefore, at the 8- and 15-capsule doses, there is a potential for risk to the health of infants, children and the unborn child.

Chromium. The IOM did not establish a UL for chromium because of insufficient data; no adverse effects have been associated with excess intakes from food or supplementation, probably due at least in part to its very poor absorption (IOM 2006). The Expert Group on Vitamins and Minerals (EVM) (2003) could not derive a Safe Upper Limit due to lack of data but recommended a chromium intake limit of 150 µg/kg bw/day, based on an animal study by Anderson *et al.* (1997), and allowing uncertainty factors of 10 for inter-species variation and 10

for inter-individual variation. Therefore, the upper limit for a 70 kg individual would be 10.5 mg from diet and supplements. The Scientific Committee on Food of the European Commission did not clearly identify a tolerable upper intake level for chromium, but stated that "In a number of limited human studies, there was no evidence of adverse effects associated with intake of chromium up to a dose of 1 mg chromium/day." The amounts of chromium in an 8-capsule (332.8 μg Cr) or 15-capsule (624 μg Cr) daily dose of EMPowerplus are much lower than either of these recommended limits of intake and therefore are unlikely to pose a significant risk to health. However, caution may be warranted particularly for infants and children due to insufficient information on the effects of chronic intake of chromium, and individuals with pre-existing renal and liver disease who may be particularly susceptible to the adverse effects of excess chromium.

Molybdenum. The IOM did not establish a UL for molybdenum in infants due to the lack of data on adverse effects in this age group and concern regarding the lack of ability to handle excess amounts. The adequate intake was set at 2-3 μg/day, a level greatly exceeded by the 8- and 15-capsule doses, but these doses do not exceed the ULs for children, adults and pregnancy. Therefore, at the 8- and 15-capsule doses, there is a potential for risk to the health of infants.

Proprietary blend. Quantity information for the remaining ingredients was not provided on the product label or the Truehope website (www.truehope.com) as it is a "proprietary blend." However, the quantitative composition of the Proprietary Blend from other formulations of EMPowerplus is provided in Appendix 1 for comparative purposes. A brief summary of the safety information available regarding each of these ingredients follows.

> *D,L-Phenylalanine*. D,L-phenylalanine refers to a racemic mixture of D- and L-phenylalanine at a ratio of 1:1. L-Phenylalanine is an essential amino acid that contributes to protein biosynthesis, whereas D-phenylalanine does not. There is partial metabolism of ingested D-phenylalanine to L-phenylalanine (Lehmann et al. 1983). The recommended dietary allowance (RDA) of L-phenylalanine is calculated as a mixture of L-phenylalanine and the essential amino acid L-tyrosine – for adults 19 years and older it is 33 mg/kg/day of L-phenylalanine + L-tyrosine. Using the adult male reference body weight of 70 kg, the RDA is 2.3 g/day. The RDA for pregnancy is higher: 44 mg/kg/day, which corresponds to an RDA of approximately 3.1 g L-tyrosine + L-phenylalanine/day. The mean daily intake for all life stage and gender groups of L-phenylalanine from food and supplements is 3.4 g/day but may be as high as 7.7 g/day in adult males. According to the NHANES III, the mean intake of L-phenylalanine in infants is 0.84 g/day; for children 1-3 years is 2.25 g/day. Data are not available on the effects of chronic ingestion of supplemental phenylalanine by apparently healthy adults – there is insufficient information to set a UL. Adverse effects were not evident following acute single oral doses of L-phenylalanine as high as 10 g in 13 adult men (IOM 2005). One gram of D-phenylalanine was safely administered to 30 adults daily for 4 weeks (Walsh *et al.* 1986).
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> However, persistently elevated levels of L-phenylalanine in the plasma before and during infancy and childhood can result in irreversible brain damage, growth retardation, and dermatologic abnormalities. Phenylalanine is well established to have teratogenic effects when fetal exposure is excessive. The fetal demand for phenylalanine for protein

synthesis is exceeded by the placental supply of phenylalanine by only a small amount, suggesting that the safety margin of placental transfer may be small. High maternal plasma phenylalanine levels are associated with high incidence of mental retardation, microcephaly, intrauterine growth delay, and congenital heart malformations in the fetus. The most common cause of excess plasma levels is phenylketonuria (PKU), a genetic disorder that impairs phenylalanine hydroxylase acitivity resulting in accumulation of phenylalanine and its catabolic byproducts above normal levels (IOM 2005). The issue of phenylketonuria is specifically addressed by a cautionary statement on the EMPowerplus label: "**Phenylketonurics:** Contains phenylalanine." Nevertheless, supplementation of L-phenylalanine in pregnancy or women of childbearing potential, infants and children should be contraindicated to minimize the potential risks to health.

With respect to the use of EMPowerplus in patients with serious mental disorders, while DL-phenylalanine at 150-200 mg/day for 30 days has been shown in one small double-blind clinical trial to have potential for the treatment of depression (Beckmann *et al.* 1979), high doses (100 mg/kg) of L-phenylalanine exacerbated the development and severity of tardive dyskinesia in patients with schizophrenia (Mosnik *et al.* 1997) and unipolar depression (Gardos *et al.* 1992). Potential interactions of supplementary phenylalanine with levodopa and monoamine oxidase inhibitors are summarized in the Natural Medicines Comprehensive Database (www.naturaldatabase.com accessed 2007-02-10). The FDA has received reports of a number of illnesses, including those similar to the eosinophilia myalgia syndrome associated with L-tryptophan consumption, in individuals using dietary supplements containing phenylalanine (FDA 1993), suggesting possible contamination problems.

In conclusion, while the quantities of D,L-phenylalanine in an 8- and 15-capsule daily dose (~192 mg and 360 mg, respectively) of EMPowerplus are approximately 1/1000 or less of the average daily intake of healthy adult males and are therefore not expected to pose a significant risk to health to that subpopulation, the quality of the product is not known and these doses of EMPowerplus do pose a risk to health in pregnancy, breastfeeding, infants, children, and other susceptible subpopulations.

L-Glutamine. L-glutamine is a dispensable amino acid, i.e. it is not generally considered to be essential although it may be conditionally essential for patients with certain health problems, e.g. when the body is subject to such metabolic stress situations as trauma, cancer, sepsis and burns (PDR 2007, IOM 2006). The daily intake of L-glutamine from food in adults is 5 to 10 grams (PDR 2007). One-time doses of L-glutamine up to 0.57 g/kg/day (up to 40 g/day) in healthy adults did not elicit any sign of adverse effects (Ziegler *et al.* 1990). Thirty grams of L-glutamine daily for seven days elicited no adverse reactions in a small study of patients undergoing gastrointestinal surgery (Quan *et al.* 2004). While short-term administration of 50-60 g/day has been demonstrated to cause no adverse effects in hospital patients, this assessment may not be appropriate for chronic supplementation in healthy subjects of all age groups. Glutamine supplementation's short-term benefits for the immune system may be absent or become detrimental under chronic administration, the effects of glutamine on intermediary metabolism could potentially lead to the development of metabolic diseases such as

diabetes or coronary artery disease, and neurotoxic effects have been demonstrated for glutamate and ammonia, the two products of glutamine degradation (Garlick 2001, IOM 2006). By analogy with arginine, theoretically supplementation with L-glutamine may have either inhibitory or stimulatory effects on specific tumour types, but preliminary evidence reviewed in the Natural Medicines Comprehensive Database (www.naturaldatabase.com, accessed 2007-02-12) suggests this may not present a significant risk since several tumour types were shown to either not increase or actually be reduced. Reported adverse reactions to L-glutamine supplementation are mainly gastrointestinal (constipation, bloating) and not common. There is one older report of two hypomanic patients whose manic symptoms were exacerbated following the use of 2 to 4 g daily of L-glutamine. The symptoms resolved when the L-glutamine was stopped. These patients were not rechallenged, nor are there any other reports of this nature. Pregnant women and nursing mothers should avoid supplemental L-glutamine unless prescribed by a physician. Those with renal or hepatic failure should exercise caution in the use of supplemental L-glutamine (PDR 2007). Glutamine seems safe in amounts that do not exceed 650 mg per kg in children 3 to 18 according to a clinical study in pediatric oncology (Ward *et al.* 2003). The quantities of L-glutamine in an 8- and 15-capsule daily dose (~96 mg and ~180 mg), respectively, of EMPowerplus are much lower than the normal intake or therapeutic dosage values and are therefore not expected to pose a significant risk to health to adults, but may not be appropriate for pregnant women or infants.

Citrus bioflavonoids. A diet high in fruits and vegetables provides 132 mg/day of the bioflavonoid hesperetin and 29 mg/day of naringenin (Erlund *et al.* 2002). One gram/day of citrus flavonoids were safely administered to Type II diabetic women for 3 weeks (Blostein-Fujii *et al.* 1999) and the specific citrus flavonoids diosmin and hesperidin have been given at doses of 900 mg and 100 mg daily, respectively for 90 days (Misra *et al.* 2000). The quantities of citrus bioflavonoids in an 8- and 15-capsule daily dose of EMPowerplus (~ 128 mg and ~240 mg, respectively) therefore are not expected to pose a significant risk to health to adults, pregnant women, or children.

Grape seed. In humans, oral doses of 300 mg of grape seed extract (> 90% procyanidins) for three days and 300 mg for 4 days were used safely with mild side effects (Vogels *et al.* 2004; Nuttall *et al.* 1998). A dose of 200 mg per day for two months was also well tolerated (Preuss *et al.* 2000). The quantities of grape seed in an 8- and 15-capsule daily dose of EMPowerplus (~24 mg, and ~45 mg, respectively) are lower than these values and therefore are not expected to pose a significant risk to health to adults or pregnant women. The evidence for the safety of grape seed in infants and children is lacking, but it is not expected to pose a significant risk to their health as only minor gastrointestinal adverse effects of its intake in adults have been identified.

Choline bitartrate. The 8- and 15-capsule doses exceed the UL for infants but not for children, adults and pregnancy. The risks of excess intake of choline are hypotension and fishy body odour (the basis for the UL). Therefore, at the 8- and 15-capsule doses, there is a potential for risk to the health of infants, but not for adults or pregnancy.

Inositol. The average American diet supplies 1 g of inositol per day (Wardlaw, 1999). The quantities of inositol in an 8- and 15-capsule dose of EMPowerplus (~96 mg and ~180 mg respectively) are just a small fraction of this daily intake and therefore are unlikely to pose a significant risk to health to infants, children, pregnant women and other adults.

L-Methionine. The IOM did not establish a UL for methionine as the data regarding the adverse effects in adults was insufficient. Based on a review of the literature, Garlick (2006) concluded that L-methionine at doses of 100 mg/kg/day (7 g in a 70 kg adult) provides about 7 times the daily requirement for sulphur amino acids and repeated consumption for one week resulted in increased plasma homocysteine, which plays a role in the progression of cardiovascular disease. Reducing the dose to 250 mg/day (~4 mg/kg) provides a chronic dose that is safe (Garlick 2006). Infants metabolize L-methionine faster than adults (IOM 2002) and according to NHANES III consume 0.37-0.69 g of dietary L-methionine per day. Children 1-3 years old consume approximately 1.1 g of dietary L-methionine.

Excessive L-methionine intake may cause nausea, vomiting, drowsiness, and irritability, and may aggravate existing conditions of acidosis and liver damage (Reynolds 1993). L-Methionine supplementation should be contraindicated in patients with cancer (Epner 2001, Epner *et al.* 2002). The 8- and 15- capsule daily doses provide ~32 mg and ~60 mg, respectively, of L-methionine, so these doses of EMPower are unlikely to pose a significant risk to healthy adults, although as indicated above, subpopulations with acidosis, liver disease or cancer may be at risk. Using the recommendation of Garlick (2006) of 4 mg/kg and the IOM (2006) reference body weights, estimates can be calculated for safe intake levels for the different life stage groups: 0-6 mo: 24 mg/day; 7-12 mo: 36 mg/day; 1-3 y: 48 mg/day; 4-8 y: 80 mg/day. Based on these estimates, the 8-capsule dose may pose a risk to the health of infants and the 15-capsule dose may pose a risk to the health of infants and children.

Ginkgo biloba. In clinical trials in adults, 120-240 mg daily of G*ingko biloba* leaf extract was used for up to a year (Oken *et al.* 1998; Le Bars *et al.* 1997). The 8- and 15-capsule daily doses of contain ~19.2 mg and ~36 mg, respectively, of *G. biloba* and therefore are unlikely to pose a significant risk to healthy adults. The data regarding the use of *G. biloba* in infants and children are lacking but considering the low daily doses it is not expected to pose a significant risk to the health of these subpopulations.

Germanium sesquioxide. The average estimated dietary intake of germanium in humans is 1.5 mg/day (range 0.4 to 3.4 mg/day) (Schauss 1991a). A low level (60 μg or less) of germanium intake from sodium germanate altered the mineral composition of bone and liver and decreased tibial DNA in the rat (Seaborn and Nielsen 1994). While limited animal studies suggest a possible role for germanium as an "ultratrace mineral" nutrient (Seaborn and Nielsen 1994, Shils *et al.* 1999), no biological requirement has been established – it does not appear to be essential (PDR 2007, Tao and Bolger 1997). For that reason no UL has been set by the IOM (2006). The organic derivative spirogermanium has been the subject of Phase I and Phase II clinical trials as a potential

antitumor drug, where it showed some moderate benefits in three types of malignancies but 40% of patients experienced marked, yet transient neurotoxicity (Schauss 1991b). With respect to the safety of organic forms versus inorganic forms of germanium, Kaplan *et al.* (2004a) has published a detailed review. Approximately 30% of an ingested dose of germanium sesquioxide is absorbed from the small intestine (PDR 2007) and it has been shown to be completely excreted from the body mainly via the kidneys within 72 hours (Miyao *et al.*, 1980). Wistar rats were given 120 mg/kg daily of germanium sesquioxide for 6 months. Renal function and histology were evaluated and there was no difference between the germanium sesquioxide-fed rats and the control group (Samai *et al.*, 1991). A large dose of germanium sesquioxide in rats for six months (1 g/kg/day) was associated with no toxicity (Anger *et al.* 1992). Germanium sesquioxide administered intravenously, orally and intraperitoneally at doses of 25, 50, and 75 mg/kg in humans has been shown to be without adverse effect (Miyao *et al.* 1980). Although the available evidence thus suggests that germanium sesquioxide is not likely to have significant toxicity, a conclusive study of differential nephrotoxicity of organic germanium compounds has not been published yet. However, there have been more than 30 case reports in humans where prolonged intake of germanium products (at a total dose of ingested germanium of 15 to 300 g; exposure duration of 2 to 36 months) and observed germanium accumulation has led to acute renal failure or dysfunction including kidney tubular degeneration. Other adverse effects included anemia, muscle weakness, and peripheral neuropathy. Germanium dioxide is known to cause renal toxicity and its presence as a contaminant of organic germanium compounds is suspected to be the cause of these adverse reactions (Schauss 1991a&b, Tao and Bolger 1997, Kaplan *et al.* 2004b, PDR 2007). For that reason quality control (e.g. by analytical techniques such as Inductively-Coupled Plasma – Mass Spectrometry, Kyrstek and Ritsema 2004), as would be assured through the product and site licensing processes, is essential. The quantities of germanium sesquioxide in the 8- and 15-capsule daily doses of EMPowerplus are ~11.2 mg and ~21 mg, respectively. These levels are 7 to 14x the average daily intake but much lower than the doses given to humans in the Phase I clinical trial of Miyao *et al.* 1980. In the absence of inorganic germanium contamination these doses of germanium sesquioxide are not expected to pose a significant risk to health. However, the quality of EMPowerplus is not known and the data for germanium sesquioxide consumption by infants and children is scant; given this lack of information its long-term use may pose a risk to health.

Boron. A clear biological function for boron in humans has yet to be established, but observations of deficiency effects on growth and development suggest a beneficial role for boron in human health, e.g. in the metabolism of vitamin D and estrogen (IOM 2006). Several human experiments have shown that dietary boron manipulation may affect blood composition, copper, estrogen, thyroid and testosterone metabolism, and most notably calcium metabolism. Neilson (1998) has proposed that boron exerts its effects on calcium and hormone metabolism by affecting cell membrane functions or stability, or that boron may act as a metabolic regulator through forming esters or complexes with a variety of substrate or reactant compounds.

The amount of boron in EMPowerplus is in line with the levels of boron authorized by the Australian Therapeutic Goods Administration in 14 licensed self-care health products

containing boron at doses up to 3 mg/day (mostly less, e.g. 0.4 to 1.5 mg). The boron, as boric acid or borax, is provided mainly in combination with calcium as supplements to treat and prevent osteoporosis, help repair connective tissue, relieve muscular aches, pains, cramps, and spasms, and support bone mineralization (Michael Wiseman, TGA, e-mail to Robin Marles, NHPD, 2007-02-05 7:05 pm; Australian Register of Therapeutic Goods (ARTG) System, https://www.tgasime.health.gov.au accessed 2007-02-05).

No evidence of carcinogenicity was observed from oral exposure to boron compounds in rats and mice (Dieter 1994). No evidence of genotoxicity was found in mammalian cell mutation in vitro assay (Weir and Fisher 1972; Benson *et al.* 1984, National Toxicology Program 1987). The U.S. EPA (2004) concluded that the available data are inadequate for a proper evaluation of the human carcinogenic potential of boron.

The reproductive tract appears to be a consistent target for boric acid/borax exposure in dogs, rats, mice and rabbits. Reproductive effects include testicular atrophy, inhibition of sperm formation, loss of germ cells, and changes in epididymal sperm morphology. Developmental effects include decreased fetal body weight, increased fetal cardiovascular malformations, skeletal malformations, and malformations of the central nervous system. The Lowest Observed Adverse Effect Levels (LOAELs) and No Observed Adverse Effect Levels (NOAELs) for reproductive and developmental toxicity in rats, mice and rabbits range from 13-79 mg/kg b.w./day and 9.6-58.5 mg/kg b.w./day, respectively (see Appendix 1 for the specific outcomes/adverse effects and corresponding LOAEL/NOAEL) (Price *et al.* 1996a&b, Ku *et al.* 1993, Heindel *et al.* 1992, Lee *et al.* 1978, Weir and Fisher 1972). In mice, 263-776 mg/kg b.w./day intake increased their mortality (Heindel *et al.* 1992). Doses of 25.3 mg B/kg b.w./day or greater have resulted in renal effects including reduced or increased kidney size and tubular dilatation in rats, mice and dogs (Pahl *et al.* 2005).

In a study using Sprague Dawley rats, Price *et al.* (1996a) concluded that the NOAEL was 9.6 mg boron/kg b.w./day for fetal effects. Developmental toxicity was noted to be occurring at lower doses than maternal effects, which were limited to increased relative kidney weight with 0.2% boric acid (25.3 mg B/kg b.w./day) (Price *et al.* 1996a). This is a well-reported study and used by many international authorities (UK, WHO, DRI) as basis for their safe upper level calculations. In Phase II of the above study (Price *et al.* 1996a), dams were allowed to deliver and rear their litters until postnatal day 21. There were no offspring body weight effects observed through postnatal day 0-21, no treatment-related skeletal variations observed on postnatal day 21 and minor skeletal malformations of the ribs remained elevated only at the highest dose (25.3 mg/kg b.w./day). The NOAEL and LOAEL for phase II of this study was 12.9 mg/kg b.w./day and 25.3 mg B/kg b.w./day, respectively; however, it should be noted that testicular development, a primary endpoint of concern, was not assessed.

A study by Weir and Fisher (1972) identified a NOAEL of 8.8mg B/kg b.w./day and LOAEL of 29 mg B/kg b.w./day for testicular effects in dogs. However, this study has many limitations, and it is not considered to be a critical study for reference dose derivation by most authorities because:

- the NOAEL and LOAEL were taken from two different studies of two different durations and the LOAEL is more than two times higher than the NOAEL;
- the sample size was too small. There were only 4 test animals per group, and only two control animals;
-testicular damage in one of four control animals was observed, and the histopathological findings were considered to be "non compound-induced."
An analysis of the unpublished original boric acid and borax dog studies reviewed by Weir and Fisher revealed that testicular effects were observed in dogs within the high-dose groups (8.8 mg B/kg and 9.4 mg B/kg boron) mid-dose groups (3.0 mg B/kg and 3.6 mg B/kg) and low-dose groups (1.4 mg B/kg and 1.6 mg B/kg). Moreover, the 90-day boric acid and borax dog studies, which were also included in the Weir and Fisher 1972 paper, reported occurrence of decreased absolute and testicular weights at 4.2 mg/kg and 0.4 mg/kg, respectively. While there is some doubt as to the significance of these results given the small sample size and doubt as to whether or not they are treatment related, these effects cannot be dismissed. Another concern is the lack of pathological evaluation of boron effects on female reproductive organs in these studies.

Human data on the safety of boron are limited. Chronic exposure from drinking water in Turkey with boron levels of up to 29 mg B/L was not associated with significant toxicity or lower fertility rates (Cöl and Cöl 2003, Sayli *et al.* 1998). The lethal dose of boric acid is not known. Previously it was proposed to be 15-20 g (equal to 2620-3500 mg B) for human adults, 3-6 g (524-1050 mg B) for infants, and 1-3 g (175-524 mg B) for newborns (Dixon *et al.* 1976, Siegel and Wason 1986). Death was thought to result in approximately five days as a result of circulatory failure. However, in an examination of 748 cases of boric acid ingestion, Litovitz *et al.* (1988) found minimal to no acute toxicity at these intake levels or higher. Symptoms including dermatitis, alopecia, anorexia and indigestion occurred in patients receiving high doses of 5 mg B/kg (e.g. >300 mg)/day for the treatment of epilepsy. Withdrawal of treatment resulted in recovery from these effects without sequelae (Culver and Hubbard 1996).

The ULs for boron established by the IOM (2006) are based on the reproductive and developmental effects in animals. The 8- and 15-capsules daily doses of EMPowerplus contain ~1.3 mg and ~2.4 mg, respectively. Taking into account the 95th percentile of dietary intake of 2.5 mg/day from food and 0.86 mg/day from water, even with these doses of EMPowerplus the total daily intake of boron is lower than the ULs established by the IOM for children, adults and pregnancy. The amount of boron provided by the 8- and 15-capsule doses is unlikely to pose a significant risk to the health of non-pregnant adults. However, taking into consideration the potential for reproductive and developmental toxicity, the amount of boron present in these doses of EMPowerplus may present a risk to the health of infants and children directly or through consumption by pregnant or breastfeeding women.

Vanadium. A functional role for vanadium in humans has not been identified and further studies are needed, but observations of deficiency effects on growth and development suggest a beneficial role for vanadium in human health, e.g. it may increase the action of insulin and it stimulates cell proliferation and differentiation (IOM 2006). Vanadium at

doses higher than the UL established by the IOM of 1.8 mg daily can lead to gastrointestinal upset; the UL is based on renal toxicity in animals as the critical adverse effect. Due to insufficient data, caution should be exercised regarding consumption of vanadium supplements by pregnant and breastfeeding women, children and infants. Supplemental high dose (60 mg/day) vanadium use is widespread in athletes and borderline diabetics. However, less than 5% of ingested vanadium is absorbed and very little absorbed vanadium remains in the body. The highest mean intake of vanadium for the U.S. population was 18 µg/day (IOM 2006). The quantities of vanadium in the 8- and 15-capsule daily doses of EMPowerplus are ~637 µg and ~1.2 mg; even taking dietary intake into account, these values are lower than the UL and therefore are unlikely to pose a significant risk to health to adults even with chronic intake. The IOM did not establish a UL for vanadium for infants, children and pregnant women due to a lack of data and a concern regarding the lack of ability of these subpopulations to handle excess amounts. The amount of vanadium provided by EMPowerplus therefore may pose a risk to these lifestages.

Nickel. The UL for nickel established by the IOM (2006) for adults and pregnancy is based on general systemic toxicity and is 1 mg/day and for children 1-3 years is 0.2 mg/day, values much higher than the quantities of nickel in an 8- and 15-capsule daily dose. Taking into account the 99th percentile intake of nickel from the diet of 0.5 mg/day, at these doses of EMPowerplus the total daily intake values are well below the established UL. Therefore, the nickel content of EMPowerplus is unlikely to pose a significant risk to health to adults and pregnant women. The IOM did not establish a UL for infants due to the lack of data on adverse effects and concern regarding the ability of this subpopulation to handle excess amounts. Therefore, the nickel in this product poses an unacceptable risk to infants.

Claims

The claims on the EMPowerplus product label, "Supports nutrient deficiencies of the central nervous system," "Helps fight free radical damage to brain cells," and "Nutritional support for mental and emotional well-being," have not been assessed yet by Health Canada in the context of the natural health product licence application submission #120449. However, the health claim, "Nutritional support for mental and physical well-being," was authorized for Truehope EMP (NPN 80000383) so evidence may have been provided in submission #120449 to support such claims for authorization of this most recent formulation of EMPowerplus as a natural health product.

Included as a package insert with EMPowerplus when delivered to the consumer is a "Participant Support Newsletter" called "Common Ground, Volume 1, Issue No. 2, Fall 06," that contains a testimonial in which a woman suffering from depression describes how she was experiencing troubling side effects while on prescribed medicines for her condition but after three months on EMPowerplus while weaning herself gradually off her prescribed medications she no longer has symptoms of depression and has fewer side effects from the prescription medication. There is also a book review describing how the daughter of the co-founder of Truehope completely recovered from bipolar disorder using EMPowerplus. The newsletter also describes a case of two

parents who both suffered from bipolar disorder and how the mother during pregnancy took each day between 18 and 24 EMPowerplus capsules, 10 Truehope BMD tablets (which also eased morning sickness) and fish oils. She is taking full doses while nursing and intends to add the supplement to the baby's soft foods. The article states that "when keeping to the full dose on a regular basis, there are no signs of postpartum depression."
On the Truehope web site there are four "Case series" describing how individuals with serious psychological disorders responded to treatment with EMPowerplus:

- an adult male suffering from symptoms of depression and bipolar affective disorder was treated unsuccessfully with prescription psychiatric drugs, but within eight weeks of active treatment on the "Truehope Program" he was virtually symptom free and off his medication;
- a young woman who had been suffering from major psychiatric symptoms since the age of seven and was diagnosed with bipolar disorder was treated unsuccessfully in hospitals and was incarcerated for behavioural problems but in the three months following the start of her participation in the nutrient program she fully recovered from any of the psychiatric symptoms she previously exhibited, and her son who is now seven years old was diagnosed with severe ADHD but also recovered using the Truehope nutrient program;
- a woman who had been suffering from symptoms of bipolar disorder since the age of 24 entered the Nutrient Program at age 45 and found significant relief in the first four weeks and continues to remain stable without any exacerbation of symptoms;
- a male child who had behavioural problems from age 12 months was diagnosed with bipolar disorder and was entered into the nutrient program at age 5, after which he sleeps well, his mood and emotional control are excellent, and there are no explosive mood swings (www.truehope.com/_research/researchCase.asp accessed 2007-02-13).

The Truehope Program is described as "a combination of the nutritional product, EMPowerplus, along with data collection systems, a Nutrient Protocol, and a unique approach to support that were designed to create an alternative intervention for those who may have a central nervous system imbalance. The product, systems, and protocol are the by-product of university and field research. Each has been designed using our experience and the knowledge of qualified research advisors" (www.truehope.com/_faqs/faqs.asp accessed 2007-02-13).

The Truehope web site describes the product as follows: "EMPowerplus is a unique nutritional product developed by Truehope over a five-year period following extensive research with individuals suffering with bipolar disorder (manic depression) and other mental health disorders. Thousands have now been able to take control of their mental health using only EMPowerplus" (www.truehope.com/_faqs/faqs.asp accessed 2007-02-13).

The Truehope web site describes the company as follows: "Truehope Nutritional Support Ltd. is a non-profit company dedicated to sharing its knowledge world-wide to offer hope to all who suffer from bipolar disorder (manic depression), anxiety disorder (panic attacks), ADD/ADHD and other mental illnesses. Since 1996, Truehope has been steadily involved in research and individual case series to validate our support process and the effectiveness of our alternative mental health treatment, EMPowerplus. Our goal is to help the thousands who suffer with mental illness to find the hope and health they are seeking." The Synergy Group of Canada Inc. is described as "a non medical research group dedicated to researching and overcoming the

disorders of the central nervous system." (http://www.truehope.com/_about/aboutus.asp accessed 2007-02-13).

This information is followed by a description of the tragedies in the life of the co-founder (Anthony Stephan) whose wife committed suicide while suffering bipolar disorder and whose son and daughter were both diagnosed with bipolar disorder:

> "Joseph Stephan exhibited signs of attention deficit disorder as a child. By the time he entered puberty, the symptoms were escalating into panic attacks, delusions and violent fits of rage. Ultimately, he was diagnosed with BAD shortly after Debbie's death.
>
> Joseph was first treated with lithium, an element used to make batteries, which caused severe side effects. When he refused to take it, he lapsed into severe mania and panic within a couple of days.
>
> Then, on January 20, 1996, Joseph started using the nutritional supplementation program created by his father and David Hardy. The results were dramatic and immediate. Within four days he was off the lithium; within two weeks, his mood and emotional control improved immensely. In the years since, he has maintained his well being and has had no recurring symptoms of BAD.
>
> Autumn Stringam's recovery is, if anything, more dramatic than her brother's. At 12, she showed signs of suffering from Bipolar Disorder, a condition which deteriorated throughout her teens. She married Dana, had a child at 20, and was subsequently diagnosed with Bipolar Affective Disorder I with rapid cycles; a daily seesaw of mania and depression. Those eventually gave way to regular visual and aural hallucinations and the belief her husband and other family members were conspiring to kill her. These visions often led her to act out violently.
>
> Following a particularly terrifying episode, Autumn was admitted to a psychiatric ward. After many adjustments to her medications, she was released a few weeks later. Drugged and with her cognition impaired, she "broke through" her medications frequently and was extremely unstable.
>
> After threatening suicide, she was again hospitalized. Upon release, she was taking a pharmaceutical cocktail of Haldol, Rivotril, Ativan, Epival and Cogentin, a combination that failed to control her psychosis. She continued to rapid cycle.
>
> Told Autumn would require round-the-clock adult supervision, Dana took her to her father to begin the alternative treatment, which had helped Joseph. Within four days she was forced to eliminate Haldol and Rivotril because of the drastically increasing side effects. Ativan was no longer required when hallucinations ceased. After one week on the program, she returned home to her husband. Less than a month later, she reduced, then eliminated, the mood stabilizer Epival. Her only "medication" now was the nutrient supplement which would become Empowerplus.

> Autumn's recovery exceeded the expectations of her psychiatrist, doctor and family. The woman who was expected to remain a prisoner of BAD, confined by a medley of psychotropic drugs and pursued by thoughts of suicide for the rest of her life, continues to be healthy and stable to this day." (http://www.truehope.com/_about/aboutus.asp accessed 2007-02-13).

Under the heading of "Success stories of Truehope Participants," the Truehope web site provides additional testimonials with respect to successful treatment with EMPowerplus of bipolar affective disorder and other diseases including Asperger's Syndrome, fibromyalgia, unipolar depression, and anxiety disorders (www.truehope.com/_success_stories/success.asp accessed 2007-02-13.) The Truehope web site also presents information regarding potential benefits of mineral-vitamin supplementation in the treatment of children with ADHD, bipolar, ODD, Aspergers, Generalized Anxiety Disorder, depression, Prader Willi Syndrome, and rage (www.truehope.com/_research_presentation/EMPPresentationV11_files/slide0036.htm, accessed 2007-02-12).

The inclusion as a package insert with the EMPowerplus product of the "Participant Support Newsletter" and statements made on the web site (http://www.truehope.com/) with respect to treatment of bipolar disorder, anxiety disorder, ADD/ADHD and other mental health disorders are considered to be extensions of the label claims and therefore are subject to assessment for compliance with the *Natural Health Products Regulations* and the *Food and Drugs Act*.

EMPowerplus has not been fully assessed or approved by the NHPD for its safety, efficacy and quality and the dose used by pregnant and breastfeeding women or given to infants could pose a risk to the health of these subpopulations. The product label cautions pregnant and lactating women, diabetics, hypoglycemics and people with known medical conditions to consult with a physician. It warns consumers about the risk of accidental overdose of iron-containing products leading to fatal poisoning of children under 6 and recommends that the product be kept out of the reach of children. Thus, there are inconsistencies between the product insert and the product label.

Truehope is advocating the use of EMPowerplus for the treatment of serious psychiatric conditions. A product identical to EMPowerplus in the list of ingredients (but not in the quantity of each ingredient due to periodic reformulation) has been studied in several small open-label clinical trials. Nineteen adults with bipolar disorder took this similar product (32 capsules daily) for an average of 13 months with relative safety; the side effects were mostly gastrointestinal and were ameliorated by taking the product with food (Simmons 2003). Eleven adults took 32 capsules daily for 6 months with similar outcome (Kaplan *et al.* 2001). Nine children took 18 capsules daily for up to 17 weeks with similar side effects (Kaplan *et al.* 2004). Expert testimony presented on March 20th and 24th, 2006, in the trial, "The Provincial Court of Alberta: Her Majesty the Queen -v- The Synergy Group of Canada and Truehope Nutritional Support – Accused, No. 040608200P1," provided additional information on case studies demonstrating the efficacy of formulations of EMPowerplus against serious mental diseases in certain patients. The experts, Dr. Bonnie Kaplan and Dr. Charles Popper, clearly expressed their opinions that further clinical trials of EMPowerplus are warranted.

Thus, there are case studies and several limited clinical studies that provide some promising evidence for the efficacy of the combination of ingredients in EMPowerplus to treat some cases of mental diseases such as bipolar affective disorder, but appropriate treatment of these conditions requires health care practitioner supervision and monitoring.

Consumers are being asked to stop taking other psychiatric medicines while using EMPowerplus due to observed adverse changes in the effects of those medicines when patients are taking EMPowerplus. However, the withdrawal of conventional medicines and establishment of the proper dosage level for EMPowerplus require careful management by a trained healthcare practitioner.

It is clear from a review of the evidence that the use of EMPowerplus under these conditions is not without risks. The Marketed Health Products Directorate has prepared two documents: causality assessment of adverse reaction reports to EMPowerplus and a summary of "near miss" reports which are attached to this HRA as Appendices 2 and 3. Please note that these reports may relate to different formulations of the product similar to those described in Appendix 1.

Briefly, appendices describe nine domestic adverse reaction reports (ARR) that have been received by Health Canada, all being serious, associated with the use of the product EMPowerplus. The ARR relate to worsening of psychiatric symptoms in those patients with serious underlying medical problems such as bipolar disorder, depression. The worsening of the symptoms mostly relate to taking the product and discontinuing prescription medications or taking the product in conjunction with prescribed medications without consulting a healthcare practitioner.

With regard to risk mitigation activities by Truehope Nutritional Support Ltd., the following statements appear on their web site:

> Q. Are there any side effects with EMPowerplus?
> A. Although EMPowerplus in general is extremely well tolerated, the one consistent side effect reported is that of mild stomach upset or nausea. Be sure to take the supplement with food to minimize the chances of stomach upset.
>
> Occasionally, participants may also experience headache, loose stool or diarrhea, flatulence and/or constipation. A small number of participants have reported mild excitability or inability to sleep when the supplement is taken too late in the evening.
>
> Q. What if EMPowerplus doesn't seem to be helping me?
> A. Although research shows that EMPowerplus provides a powerful answer to many intrusive issues, it is not the complete answer to everyone's problems. Investigations into factors that may interfere with the effectiveness of the supplement almost always prove beneficial. Interfering factors such as parasites, microbial imbalances (i.e. yeast infections), interactions with other supplements and medications, and poor bowel function, may all make it difficult to fully benefit from the nutrients. Begin the Nutrient Program by following the recommended dosage. By working closely with your Truehope Assistant and providing the feedback on how you are feeling, a system of support can be designed that will optimize your response to the nutrients.

Q. Does EMPowerplus interfere with drugs?
A. As near as can be determined, there are no specific interactions with the ingredients of EMPowerplus and psychotropic medications. However, as EMPowerplus is being proven to have the effect of restoring normal body chemistry, the continued use of psychotropic medications may have a negative effect on the body. Such would be the case if a healthy person took medications that he or she did not require. In such an event, the medication would create symptoms of illness - not wellness
(http://www.truehope.com/_faqs/faqs.asp, accessed 2007-02-13).

With regard to offering advice that can be interpreted as medical in nature, the Truehope web site provides the following statements:

Truehope has helped thousands suffering from Bipolar disorder, anxiety/panic attacks, ADD/ADHD and other mental illnesses – let us help you!
(http://www.truehope.com/_contact/contact.asp, accessed 2007-02-13).

Q. Do I need to have a Doctor supervise me on the Truehope Nutrient Program or can I just depend on a Truehope Assistant for my support?
A. If you are currently under a doctor's supervision we encourage you to discuss the Truehope Program with your doctor. Since few doctors are trained in nutrition, and most will have had no prior experience with our program, you can expect them to have questions and concerns regarding this program. If your doctor is willing, we will contact him / her and make every effort to appropriately address any issues. If you are not currently under a doctor's supervision, our Truehope Assistants will assist in educating you about the Truehope Program and provide the support you need. Our Truehope Assistants are not doctors and will not prescribe or diagnose, but instead, are available to offer educational resources and support to you. At times, our Truehope Assistants may encourage you to seek a doctor to provide further help.
(http://www.truehope.com/_faqs/faqs.asp, accessed 2007-02-13).

<u>More on Truehope and EMPowerplus for health professionals</u>

We have many inquiries from health professionals about the Truehope Program and our research projects. We welcome the involvement of all medical practitioners who desire to help their patients achieve and maintain mental and emotional health.

Truehope has published a comprehensive document for health care professionals that is designed to answer any questions you may have regarding EMPowerplus and the nutrient protocol for its usage. Please contact us online or phone 1-888-878-TRUEHOPE (1-888-878-3467) to obtain a copy.

Please take a moment to review the exciting research in the treatment of bipolar disorder and other mental illnesses using EMPowerplus, including a recently published summary from the Journal of Clinical Psychiatry. This independent research empirically validates the successes we've had in reducing/eliminating the symptoms of bipolar disorder and other mental illnesses in thousands of individuals.

http://www.truehope.com/_health_professionals/doctors.asp, accessed 2007-02-13).

An EMPowerplus product, not identical to the formulation presented in this HRA, is the subject of a product licence application, #120449, submitted to the Natural Health Products Directorate on January 22, 2007, by The Synergy Group of Canada Inc. The applicant originally requested an amendment to their previous licence for the related product Truehope EMP (NPN 80000383). However, as the quantities of some of the medicinal ingredients per capsule have changed and boron is included as a medicinal ingredient in contrast to Truehope EMP, they were informed by NHPD that a new submission was required. The applicant has complied and has requested cross-referencing to the previous licence for the majority of the evidence requirements. They have also provided additional evidence as requested and the application is currently undergoing safety, efficacy, and quality assessment. The Product Licence Application could potentially lead to the issuance of market authorization for the self-care conditions of use proposed for that formulation of the EMPowerplus product.

Truehope Nutritional Support Ltd. applied to the Natural Health Products Directorate for a Site Licence, submission #111469 for the purpose of importation of natural health products. This application was refused on 2007-02-01 for failure to provide requested information. No request for reinstatement has been made, nor has a new application been received as of 2007-02-13.

Please note that the HRA for this product was based on the information available in the HRA request, product label, package insert that was supplied with the product and the Truehope web site. Since information on the quantity per unit dose of some of the ingredients is not available and these quantity values will affect the risk assessment, the conclusions of this HRA are based on certain assumptions identified above.

Conclusions:
According to the available information, the use of the formulation of EMPowerplus that is the subject of this HRA as a multi-ingredient natural health supplement following the instructions and cautions on the current product label would not be likely to pose a significant risk to healthy adults who are not pregnant.

However, EMPowerplus does pose potential risks to the health of consumers for the following reasons:

1. The product being sold contains ingredients that at the dosage recommended on the product label and on the Truehope web site present potential risks in pregnancy, infants and children, both directly and through breast-feeding.
2. Truehope Nutritional Support Ltd. recommends on their web site a daily loading dose of EMPowerplus that provides prescription levels of vitamin D and folate, in the absence of a DIN as a prescription drug.
3. Truehope Nutritional Support Ltd. advocates through package insert promotional material and advertising on the web site to consumers the use of the EMPowerplus to treat serious mental and physical health conditions not suitable for self-care since they require healthcare practitioner intervention.
4. Truehope Nutritional Support Ltd. advocates through package insert promotional material and advertising on the web site to consumers using EMPowerplus discontinuance of

prescribed medicines without proper supervision by a healthcare practitioner (i.e. prescription status for these conditions of use would be more appropriate).

5. Truehope Nutritional Support Ltd. recommends conditions of use for EMPowerplus that may be related to the nine adverse reaction and "near miss" reports summarized in Appendices 2 and 3.

A Health Hazard category has not been assigned to the level of risk to health in this case because those categories are based on the Health Products and Food Branch Inspectorate Recall Policy (POL-0016), but the recommendations made here do not require a product recall.

In view of the serious health risks that have been identified with how EMPowerplus is being marketed, Synergy Group of Canada Inc. and Truehope Nutritional Support Ltd. Need to take the following steps:

1. Remove all of the abovementioned representations that violate the Food and Drugs Act from the website, www.truehope.com; from the Participant Support Newsletter; and from any other information used by Synergy Group of Canada Inc. or by Truehope Nutritional Support Ltd. to market this product;
2. Ensure the employees officers or agents of either Synergy Group of Canada Inc. or of Truehope Nutritional Support Ltd. do not make any of the abovementioned representations; and
3. Otherwise ensure medical advice is not provided by non-medically qualified personnel in patient support activities provided by Truehope Nutritional Support Ltd or by Synergy Group of Canada Inc.

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Appendix 1. Some EMPowerplus* Formulation Changes

Medicinal Ingredient	**EMPower + 2002-06 Quantity/ capsule** (32 capsules/ day max)[1]	**EMPowerplus 2003-11 Quantity/ capsule** (18 capsules/ day max)[2] **& Truehope EMP PLA #100391**	**EMPowerplus 2003-05 Quantity/ capsule** (18 capsules/ day max)[2]	**EMPowerplus 2007-01 Quantity/ capsule** (15 capsules/ day max)[3]	**Truehope EMP NPN80000383 Quantity/ capsule** (9 capsules/ day max)	**EMPowerplus 2007-01-22 PLA #120449 Quantity/ capsule** (8 capsules/ day max)
Vitamin A (as retinyl palmitate)	300 IU (416 IU on web)	320 IU	355 IU	384 IU	96 µg (175 IU)	115.2 µg (253 IU)
Vitamin C (as ascorbic acid)	31.25 mg	33.3 mg	33.3 mg	40 mg	33.3 mg	39.96 mg
Vitamin D (as cholecalciferol)	50 IU	80 IU	89 IU	96 IU	2 µg (80 IU)	2.4 µg (96 IU)
Vitamin E (as d-alpha tocopheryl succinate)	12.5 IU	20 IU	22.3 IU	24 IU	13.4 mg (16.2 IU)	16.08 mg (19.5 IU)
Vitamin B_1 (as thiamine mononitrate)	0.625 mg	1.0 mg	1.11 mg	1.2 mg	1.0 mg	1.2 mg
Vitamin B_2 (as riboflavin)	0.688 mg	0.75 mg	0.83 mg	0.9 mg	0.8 mg	0.96 mg
Vitamin B_3 (as niacinamide)	3.125 mg	5.0 mg	5.57 mg	6.0 mg	5.0 mg	6 mg
Vitamin B_5 (as d-calcium pantothenate)	0.75 mg	1.2 mg	1.3 mg	1.45 mg	1.2 mg	1.44 mg
Vitamin B_6 (as pyridoxine hydrochloride)	0.875 mg	2.0 mg	2.2 mg	2.4 mg	2.0 mg	2.4 mg
Vitamin B_9 (as folic acid)	50 µg	80 µg	89 µg	96 µg	80 µg	96 µg
Vitamin B_{12} (as cyanocobalamin)	31.25 µg	50 µg	55.7 µg	60 µg	50 µg	60 µg
Vitamin H (biotin)	3.125 µg	60 µg	6.7 µg	72 µg	60 µg	72 µg
Calcium	68.75 mg	73 mg	81.3 mg	88 mg	73.3 mg	87.96 mg
Phosphorus	43.75 mg	47 mg	51.7 mg	56 mg	46.7 mg	56.0 mg
Magnesium	31.25 mg	33.3 mg	37 mg	40 mg	33.3 mg	56.04 mg
Potassium	12.5 mg	13.3 mg	14.7 mg	16 mg	13.3 mg	16.0 mg
Iodine (from Pacific kelp)	9.375 µg	11.3 µg	11 µg	13.6 µg	11.3 µg	13.6 µg
Zinc	2.5 mg	2.7 mg	3.0 mg	3.2 mg	2.7 mg	3.24 mg
Selenium	12.5 µg	11.3 µg	14.7 µg	13.6 µg	11.3 µg	13.56 µg
Copper	0.375 mg	0.4 mg	0.44 mg	0.475 mg	0.4 mg	0.48 mg
Manganese	0.5 mg	0.53 mg	0.59 mg	0.65 mg	0.5 mg	0.636 mg
Chromium	31.25 µg	34.7 µg	36.7 µg	41.6 µg	34.7 µg	41.64 µg
Molybdenum	8.3 µg	8.0 µg	9.7 µg	9.6 µg	8.0 µg	9.6 µg
Iron	0.75 mg	0.76 mg	0.89 mg	0.925 mg	0.8 mg	0.9 mg

Proprietary blend:	*94.6 mg*	*92.3 mg*	*138 mg*	*111 mg*	*92.4 mg*	*111 mg*
D,L-phenylalanine	37.5 mg	20 mg			20 mg	24 mg
L-glutamine	18.75 mg	10 mg			10 mg	12 mg
citrus bio-flavanoids	12.5 mg	13.3 mg			13.3 mg	15.96 mg
grape seed	3.125 mg	2.5 mg			2.5 mg	3 mg
choline bitartrate	12.5 mg	30 mg			30 mg	36 mg
inositol	4.16 mg	10 mg			10 mg	12 mg
Ginkgo biloba	2.5 mg	2.0 mg			2.0 mg	2.4 mg
L-methionine	2.08 mg	3.3 mg			3.3 mg	3.96 mg
germanium sesquioxide	1.25 mg	1.15 mg			1.2 mg	1.44 mg
boron	125 µg	133.3 µg			none	159.96 µg
vanadium	62.5 µg	66.3 µg			66.3 µg	79.56 µg
nickel	8.4 µg	1.6 µg			1.6 µg	1.92 µg

[1]Therapeutic Products Directorate Memorandum #02-110730-366, Health Hazard Assessment – EM Power, July 18, 2002

[2]Truehope web site information and product label photographs provided in an e-mail from Sandra Jarvis of the Health Products and Food Branch Inspectorate Western Operational Centre to Melissa Johnson of NHPD, 2004-02-25 5:42 pm.

[3]Product label and Truehope web site accessed 2007-01-09

* EMPowerplus , E.M.Power Plus (or E.M. Power +) is an acronym for Essential Mineral Power Plus. The plus includes vitamins, antioxidants and amino acids. With our new formulation, we have changed the name to simply read "EMPowerplus." The name can also be interpreted EMPOWER, defined as; to enable or to promote self-actualization (http://www.truehope.com/_faqs/faqs.asp, accessed 2007-02-13).

Appendix 2. Truehope Adverse Reaction Causality Assessments Prepared by MHPD

Attached file: Jan25.07 Truehope AR Causality assessments.wpd

Appendix 3. Truehope Near Miss Summary Prepared by MHPD

Attached file: Jan25.07 Truehope Near Miss summary.wpd