



Hogan Lovells US LLP
 555 Thirteenth Street, NW
 Washington, DC 20004
 T +1 202 637 5600
 F +1 202 637 5910
 www.hoganlovells.com

#781

By Federal Express

May 7, 2018

Office of Food Additive Safety (HFS-200)
 Center for Food Safety and Applied Nutrition
 Food and Drug Administration
 5001 Campus Drive
 College Park, MD 20740-3835

**Re: GRAS Notice for Alpha-Tocopherol (Vitamin E)**

Dear Sir or Madam:

We hereby submit the enclosed GRAS notice for the alpha-tocopherol (vitamin E), an underconsumed nutrient in the U.S., to be used as a substitute for other commercially available forms of alpha-tocopherol that are added to foods. While typical use levels will vary depending on the manufacturer and the product, the maximum use levels in foods for children four and over and adults is 15 mg/serving (i.e., 100% of the Reference Daily Intake (RDI or DV) of vitamin E). The maximum use levels in foods for infants six month and older is 2.5 mg/serving (i.e., 50% of the RDI or DV) for children one through three years old is 3 mg/serving (i.e., 50% of the RDI or DV). The statutory basis of the GRAS conclusion is scientific procedures.

The NutriFusion product can be included in baby foods (excluding use as a supplement to breast milk or infant formula) for infants from six to 12 months and children from one to four years old. Examples of these products include baby and toddler pureed fruits and vegetables, dinners, dairy-based foods intended for children six months up to four years, and toddler meals. The NutriFusion product is intended to be used only as a substitute for the existing commercially available forms of alpha-tocopherol on the market. In other words, the NutriFusion vitamin E extract is intended to be used in food categories that currently are formulated with other forms of alpha-tocopherol.

The GRAS notice does not contain any designated confidential business information. In accordance with the Agency's guidelines, we have enclosed one original copy of the GRAS notice, and one complete electronic copy of the GRAS notice on a compact disk (CD).

The notified substance was also the subject of GRAS Notice No. 690, which we requested the agency to cease its review on June 20, 2017. NutriFusion submitted the GRN No. 690 to FDA through the voluntary GRAS notice program following a pre-submission meeting on April 26, 2016. During the meeting, the agency encouraged NutriFusion to submit a single GRAS notice for the vitamin blends extracted from fruits and vegetables. We understand that when FDA received the GRAS notice, it ran into difficulty completing its review given the variability in the composition of the vitamin blends. We also understand FDA has since determined that GRAS notifications should be limited to single ingredients rather than blends. We agreed to withdraw the GRAS notice and to submit separate GRAS notices.

Hogan Lovells US LLP is a limited liability partnership registered in the District of Columbia. "Hogan Lovells" is an international legal practice that includes Hogan Lovells US LLP and Hogan Lovells International LLP, with offices in: Alicante Amsterdam Baltimore Beijing Berlin Brussels Caracas Colorado Springs Denver Dubai Dusseldorf Frankfurt Hamburg Hanoi Ho Chi Minh City Hong Kong Houston London Los Angeles Luxembourg Madrid Miami Milan Moscow Munich New York Northern Virginia Paris Philadelphia Prague Rio de Janeiro Rome San Francisco Shanghai Silicon Valley Singapore Tokyo Ulaanbaatar Warsaw Washington DC Associated offices: Budapest Jakarta Jeddah Riyadh Zagreb. For more information see www.hoganlovells.com

May 7, 2018

We are confident that the current GRAS notice, which only covers a single vitamin extract, addresses the questions FDA had regarding the identity and composition of the notified substance. We have already submitted a GRAS notice (designated by FDA as GRN 000769) for ascorbic acid (vitamin C) in March, 2018. We plan to submit GRAS notices for other single vitamin extracts in the future.

We are committed to cooperating with the Agency and believe an open dialog is one of the most effective ways to accomplish that objective. If any questions arise in the course of your review, please contact us, preferably by telephone or e-mail, so that we can provide a prompt response.

Sincerely,

(b) (6)



Martin J. Hahn

Partner

Hogan Lovells US LLP

martin.hahn@hoganlovells.com

202 637 5926

HOGAN LOVELLS US LLP

GRAS Notice for Alpha-Tocopherol (Vitamin E) Extracted from Fruit and Vegetable Sources

May 07, 2018

Table of Contents

	Page
1.0 GRAS Statement and Certification	2
1.1 Claim of Exemption.....	2
1.2 Name and Address of the Notifier	2
1.3 Name of the Notified Substance.....	2
1.4 Intended Conditions of Use.....	2
1.5 Statutory Basis of GRAS Conclusion	2
1.6 GRAS Statement	3
1.7 Availability of Information	3
1.8 Trade Secret and Confidential Information.....	3
1.9 GRAS Certification.....	3
1.10 Signature	3
2.0 Identity, Method of Manufacture, Specifications, and Physical or Technical Effect	4
2.1 Identity.....	4
2.2 Characteristic Properties.....	4
2.3 Quantitative Composition	4
2.4 Manufacturing Process	4
2.5 Specifications.....	6
2.6 Stability Data.....	7
2.7 Detailed Information on Intended Use.....	8
4.0 Self-limiting Levels of Use	10
5.0 Experience Based on Common Use in Food before 1958	11
6.0 GRAS Narrative.....	12
6.1 Overview.....	12
6.2 Safety Assessment	13
6.3 Safety Conclusion	14
7.0 List of Supporting Data and Information.....	16

1.0 GRAS Statement and Certification

1.1 Claim of Exemption

On behalf of NutriFusion LLC (NutriFusion), Hogan Lovells US LLP (Hogan) is submitting this generally recognized as safe (GRAS) notice summarizing the data and information supporting NutriFusion's conclusion that its intended use of alpha-tocopherol (vitamin E) extracted from edible portions of commonly consumed fruits and vegetables using conventional extraction procedures are GRAS for use in foods intended for infants from six to 12 months of age, toddlers and young children from one to four, and the general population four and over, when used as a substitute for other commercially available sources of vitamin E.

1.2 Name and Address of the Notifier

NutriFusion LLC
10641 Airport Pulling Rd N., Suite 31
Naples, FL, 34109-7330

1.3 Name of the Notified Substance

Alpha-tocopherol (vitamin E) from edible fruits and vegetables.

1.4 Intended Conditions of Use

The NutriFusion alpha-tocopherol (vitamin E) will be used as a substitute for other commercially available forms of vitamin E that are added to foods. The NutriFusion product can be included in baby foods (excluding use as a supplement to breast milk or infant formula) for infants from six to 12 months and children from one to four years old. Examples of these products include baby and toddler pureed fruits and vegetables, dinners, dairy-based foods intended for children six months up to four years, and toddler meals. The NutriFusion product is intended to be used only as a substitute for the existing commercially available forms of vitamin E on the market. In other words, the NutriFusion vitamin E extract is intended to be used in food categories that currently are formulated with other forms of vitamin E.

While typical use levels will vary depending on the manufacturer and the product, the maximum use levels in foods for children four and over and adults is 15 mg/serving (i.e., 100% of the Reference Daily Intake (RDI or DV) of vitamin E)). The maximum use levels in foods for infants six month and older is 2.5 mg/serving (i.e., 50% of the RDI or DV) for children one through three years old is 3 mg/serving (i.e., 50% of the RDI or DV).

1.5 Statutory Basis of GRAS Conclusion

Through scientific procedures in accordance with 21 CFR § 170.30(a) and (b).

1.6 GRAS Statement

The notified substance is not subject to the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act based on NutriFusion's conclusion that the notified substance is GRAS under the conditions of the intended use.

1.7 Availability of Information

A complete copy of the data and information that was used as a basis for this GRAS conclusion can be provided to the FDA upon request, and is also available for FDA's copying and reviewing during customary business hours at:

Martin J. Hahn
Hogan Lovells US LLP
555 Thirteenth Street, NW
Washington, DC 20004

1.8 Trade Secret and Confidential Information

This GRAS notice does not contain data or information that is exempt from disclosure under the Freedom of Information Act, 5 U.S.C. 552.

1.9 GRAS Certification

To the best of our knowledge, the GRAS notice is a complete, representative, and balanced submission that includes unfavorable information, as well as favorable information, known to us and pertinent to the evaluation of the safety and GRAS status of the use of the substance.

1.10 Signature

(b) (6)

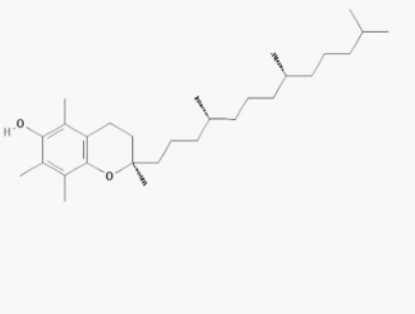


Martin J. Hahn
Hogan Lovells US LLP
martin.hahn@hoganlovells.com
202 637 5926

2.0 Identity, Method of Manufacture, Specifications, and Physical or Technical Effect

2.1 Identity

Chemical identity information for vitamin E can be summarized in **Table 1**, below.

Name	CAS Number	Molecular Formula	Molecular Weight	Synonyms
Vitamin E	59-02-9		431	Alpha-Tocopherol

The vitamin E extract also contains food starch and silicon dioxide that encapsulate the vitamin E.

2.2 Characteristic Properties

Appearance: Free-flowing Powder

2.3 Quantitative Composition

Constituent	Lot#- 100701A2	Lot#- 100701A3	Lot#- 100701A4	Lot#- 100701A5
Vitamin E	53.7%	52.8%	53.1%	53.5%
Total Starch	40.2%	41.8%	40.7%	41.0%
Moisture	5.5%	4.6%	5.1%	5.2%
Silica (as SiO ₂)	0.044%	0.06%	0.052%	0.052%

The results demonstrate the company is able to offer a standardized extract. *See also Attachment 1.*

2.4 Manufacturing Process

The nutrient blend is manufactured from edible portions of fruits and vegetables following good manufacturing practices for food (21 CFR Part 110 and 21 CFR Part 117, Subpart B, when it

becomes effective). All the starting materials have a long history of safe consumption. **Table 3** provides examples of the fruit or vegetable that can be used as a source for the vitamin E.

Table 3. Fruits and Vegetables Sources of Vitamin E	
Fruit/Vegetable Used as the Source (Edible Portions Only)	Specie Names
Mustard greens	<i>Brassica juncea</i>
Swiss chard	<i>Beta vulgaris</i>
Spinach	<i>Spinacia oleracea</i>
Kale	<i>Brassica oleracea var. sabellica</i>

NutriFusion uses various conventional extraction methods to extract the vitamins and will select the method that is most effective depending on the fruit or vegetable matrix and the nutrient(s) that are extracted. The solvents most commonly used are water, ethanol or critical CO₂. Solid phase extraction is also used. The solvent extraction process can be described as follows:

1. Food grade fruits and vegetables are harvested, sorted, garbled (i.e., the desired part of the plant (the edible portion) is separated from other parts of the plant), and dried.
2. The dried plants are prepared for extraction by grinding into a fine powder to maximize the surface area available for extraction.
3. An Individual dried plant, or a blend of dried fruits and vegetables with naturally occurring vitamin E, will then be immersed in solvents commonly used in food processing (e.g., water, alcohol, or critical CO₂).
4. The extraction process can take several days.
5. Once the extraction process is complete the solvent and plant solids are separated by centrifugation.
6. The liquid portion is decanted and stored in a container for later processing.
7. The extraction can be repeated with the solid materials separated by centrifugation as needed (for example, the plant material could first be exposed to an aqueous extraction and after centrifugation, the remaining solids could then be subjected to an ethanol extraction to isolate those remaining vitamins that are soluble in ethanol but not in water).
8. The vitamin E rich liquid is then freeze dried and encapsulated with food grade GRAS ingredients such as a starch to protect the vitamin from oxidation.

The solid phase extraction can be described as follows:

1. Food grade fruits and vegetables are harvested, sorted, garbled, and dried.
2. The dried plants are prepared for extraction by grinding into a fine powder to maximize the surface area available for extraction.
3. An individual dried plant, or a blend of dried fruits and vegetables with naturally occurring vitamin E will be blended together, will then be immersed in solvents commonly used in food processing (e.g., water, alcohol, or critical CO₂).
4. The solution will then pass through a single-use cartridge containing a chromatographic sorbent (e.g., silica particles that have been functionalized on their surface) using appropriate food grade food contact substances that are authorized by FDA for this type of use;
5. Another common food-grade solvent will be used as elute to remove the nutrients retained on the stationary phase.
6. The collected liquid will be stored in a container.
7. The extracted vitamin E is removed from the container, freeze dried, and then encapsulated with food grade GRAS ingredients such as starch to protect the vitamin E from oxidation.

2.5 Specifications

We are attaching the analytical reports on four non-consecutive production lots that demonstrate the products meet the heavy metal and microbiological specifications. We also include vitamin E levels from four non-consecutive production lots.

Table 5. Specifications						
Item	Limit	Method	Lot#- 100701A2	Lot#- 100701A3	Lot#- 100701A4	Lot#- 100701A5
Vitamin E	51.5% - 55%	AOAC-2012.09M	53.7%	52.8%	53.1%	53.5%
Total starch	> 39%	AOAC-925.38	40.2%	41.8%	40.7%	41.0%
Silica (as SiO ₂)	> 0.01%	ICP/OES	0.044%	0.06%	0.052%	0.052%
Arsenic	< 1.0 ppm	USEPA-6010C	< 0.1 ppm	< 0.1 ppm	< 0.1 ppm	< 0.1 ppm
Cadmium	< 0.5 ppm	USEPA-6010C	< 0.1 ppm	< 0.1 ppm	< 0.1 ppm	< 0.1 ppm
Lead	< 1.5 ppm	USEPA-6010C	< 0.1 ppm	< 0.1 ppm	< 0.1 ppm	< 0.1 ppm
Mercury	< 0.2 ppm	USEPA-7471B	< 0.01 ppm	< 0.01 ppm	< 0.01 ppm	< 0.01 ppm
Bismuth	< 0.2 ppm	USEPA-	< 0.1 ppm	< 0.1 ppm	< 0.1 ppm	< 0.1 ppm

Table 5. Specifications						
Item	Limit	Method	Lot#- 100701A2	Lot#- 100701A3	Lot#- 100701A4	Lot#- 100701A5
		6010C				
Antimony	< 0.2 ppm	USEPA- 6010C	< 0.1 ppm	< 0.1 ppm	< 0.1 ppm	< 0.1 ppm
Total Aerobic Plate Count	< 3,000 CFU/g	AOAC- 966.23	< 1 CFU/g	< 1 CFU/g	< 1 CFU/g	< 1 CFU/g
Total Yeast/Mold Count	< 300 CFU/g	FDA BAM 7th Ed.	< 1 CFU/g	< 1 CFU/g	< 1 CFU/g	< 1 CFU/g
<i>E. coli</i> Count	< 3 MPN/g	AOAC- 966.24	< 3 MPN/g	< 3 MPN/g	< 3 MPN/g	< 3 MPN/g
<i>Salmonella</i> Count	Negative	AOAC- 2004.03	Negative	Negative	Negative	Negative
Total Coliforms	< 10 MPN/g	AOAC- 966.24	< 1 MPN/g	< 1 MPN/g	< 1 MPN/g	< 1 MPN/g
<i>Staphylococcus Aureus</i>	< 1 CFU/g	AOAC- 975.55	< 1 CFU/g	< 1 CFU/g	< 1 CFU/g	< 1 CFU/g

See also **Attachment 2**.

2.6 Stability Data

NutriFusion created this innovative source of vitamin E extracted from fruits and vegetables and is merely a supplier of this extract to companies that will then formulate the vitamin E extract into various foods. As such, the customer ultimately is responsible for deciding the level of the vitamin E extract that will be added as well as the data supporting any claims that are made on their finished product throughout the shelf life of the product. The customer, therefore, has the responsibility to determine the level of overages, if any, which should be added to the product at time of formulation to meet the level of vitamin E declared on the label throughout the shelf life of the product.

NutriFusion, nonetheless, is aware of customers that have formulated its vitamin E into foods and dietary supplements and has collected products from commerce to evaluate the level of its vitamin E that can be detected in these commercially available foods. For the stability data, NutriFusion analyzed a dietary supplement containing the NutriFusion vitamin E extract. NutriFusion supplied this dietary supplement company with a nutrient blend that contains vitamin E extracted in 2013. NutriFusion collected two commercially available samples of the dietary supplement from commerce in 2015 and analyzed the product for the levels of vitamins in the product. The analytical report can be found in **Attachment 3**. The data demonstrate the vitamin E extract used to formulate the dietary supplement remained stable throughout this two year period of time. We note the manufacturer of this dietary supplement has established an expiration date of May 2017, demonstrating the manufacturer expects the vitamins to remain stable for at least four years.

NutriFusion also wanted to assess the stability of its nutrient blend including vitamin E extract in a food matrix. NutriFusion supplies a pasta company with one its nutrient blends. The pasta goes through various stages and exposures to heat from the time of manufacture until it is consumed. The pasta company will formulate the flour, vitamin blend, and other ingredients into dough, extrude the pasta in the proper shape, and then subject the extruded pasta to a drying oven to dry the pasta to the desired moisture level. The pasta will be transported and held at retail and by consumers at ambient conditions. When preparing the pasta, the labeled directions for use instruct the consumers to cook the pasta in boiling water for 11-13 minutes.

NutriFusion collected from commerce a 10-month old pasta made by the pasta company that uses the NutriFusion vitamin extract. NutriFusion instructed the laboratory to prepare the pasta according to the labeled directions for use and to analyze the cooked pasta to assess the level of vitamins in the product compared to those declared on the label. The laboratory results and copy of the declared nutrient values are found in **Attachment 4** and summarized in the table below. As the data indicate, the level of vitamin E in the cooked 10-month old pasta is in line with the declared nutritional claims.

Table 6: Stability of Vitamin E in Cooked Pasta				
Vitamin	Label Declared Value (%DV)	Analytical Value #1 (% DV)	Analytical Value #2 (% DV)	Analytical Value #3 (% DV)
Vitamin E	25	27	29	26

2.7 Detailed Information on Intended Use

The NutriFusion vitamin E extract product is intended for use by infants from six to 12 months of age, toddlers and young children from one to four, and the general population four and over, when used as a substitute for commercially available vitamin E sources. For infants from six to 12 months and children from one to four, the NutriFusion product will be used in baby foods purees (e.g., fruits, veggies, dinners, dairy), toddler meals, and other foods specifically formulated and positioned for children under four. The uses of the NutriFusion vitamin E extract will be substitutional with the currently authorized commercially available vitamin E. Under 21 CFR §182.8890 (“Tocopherols”), there are currently no limits other than cGMPs for vitamin E.

The typical use levels will vary depending on the manufacturer and the product. The maximum recommended use levels in foods for children four and over and adults are 15 mg/serving. The maximum recommended use levels in foods for infants six month and older is 2.5 mg/serving for children one through three years old is 3 mg/serving.

3.0 Dietary Exposure

The intended use of the NutriFusion product will be a substitutional use with the vitamin E extracted from fruits and vegetables replacing other currently authorized commercially available sources of vitamin E and would not increase dietary exposures. According to the Scientific Report of the 2015 Dietary Guideline Advisory Committee and reviews conducted by the

Institute of Medicine (IOM), the current 90th percentile intake of vitamin E from foods and beverages among children 1 through 3 years old and all individuals four and over can be summarized with the table below.

Table 7. Common Vitamins 90th Percentile Intake		
Nutrient	90th Percentile Intake (≥ 4)¹	90th Percentile Intake (1 - 3)
Vitamin E	13.7 mg/day	6.2 mg/d

¹ We adopt the highest 90th percentile intake data reported for different age groups. Also, when there are different 90th percentile intake values reported for male and female, we adopt the higher number for the purpose of conservatism.

4.0 Self-limiting Levels of Use

The use of NutriFusion product is not self-limiting and will be controlled closely through the product formulation.

5.0 Experience Based on Common Use in Food before 1958

The NutriFusion blend was not marketed prior to 1958. The fruit and vegetables used to extract the vitamin E extract, however, have an extensive history of use prior to 1958. Infants, toddlers, young children, and humans four and over have been consuming the fruit and vegetables used as the sources of the vitamins in most instances, for over a millennia. Moreover, in general, the quantity of whole fruit and vegetable used to extract the vitamin E is comparable to typical consumption levels of that fruit or vegetable. See **Table 8**. While the history of use of these fruits and vegetables prior to 1958 is supportive of the GRAS status, this notification is based on scientific procedures and not common use in foods.

6.0 GRAS Narrative

6.1 Overview

The fruit and vegetables used for the extraction have a long safe consumption history and their GRAS status is well-established. NutriFusion uses process methods that are commonly used such as solvent extraction and solid phase extraction in food processing to extract and isolate the vitamins commonly found in various fruits and vegetables. **Table 8** identifies the fruit or vegetable that could be used as a source for vitamin E, the maximum use level (which is set at 100 percent of the RDI for children over four and adults), and the quantity of the whole fruit or vegetable that, if consumed, would provide 100 percent of the RDI.

Source	Maximum Use Level	Vitamin E Source of Fruits/Vegetables	Comparable Quantity of Fruit/Vegetable
Mustard greens	15 mg/serving	2.01 mg/ 100g ²	746.3 g of mustard greens
Swiss chard	15 mg/serving	1.89 mg/100 g ³	793.7 g of Swiss chard
Spinach	15 mg/serving	2.08 mg/ 100g ⁴	721.2 g of spinach
Kale	15 mg/serving	1.54 mg/100g ⁵	974 g of kale

According to 21 CFR §170.30(d), “[a] food of natural biological origin that has been widely consumed for its nutrient properties . . . without known detrimental effects, which is subject only to conventional processing as practiced prior to January 1, 1958, and for which no known safety hazard exists, will ordinarily be regarded as GRAS.” As the above table indicates, the intended use of the NutriFusion vitamin E extract is roughly equivalent in all instances with the consumption of five or more servings of fruits and vegetables per day – the existing dietary recommendation. For example, USDA reports 1 cup of cooked spinach weighs 180 grams,⁶ which would result in 15 mg of vitamin E in about 4 cups (720 grams) or four one-cup servings of spinach. We, therefore, would not expect the NutriFusion vitamin E extract product to contain levels of any unintended soluble constituents from the plant that would present a health or safety concern. We recognize the manufacturing process will result in the extraction of the vitamins as well as any other soluble constituents that may be present in the plant material.

² See USDA National Nutrient Database for Standard Reference Release 28: Report 11270 “Mustard greens, raw.”

³ See USDA National Nutrient Database for Standard Reference Release 28: Report 11147 “Chard, swiss, raw.”

⁴ See USDA National Nutrient Database for Standard Reference Release 28: Report 11458 “Spinach, cooked, boiled, drained, without salt” (1 cup of cooked spinach is reported as weighing 180 grams).

⁵ See USDA National Nutrient Database for Standard Reference Release 28: Report 11233 “Kale, raw.”

⁶ See USDA National Nutrient Database for Standard Reference Release 28: Report 11458 “Spinach, cooked, boiled, drained, without salt” (1 cup of cooked spinach is reported as weighing 180 grams).

Even if there are incidental constituents concentrated in the finished NutriFusion products along with the vitamins, the level of potential dietary intake of these constituents would be comparable or less than what a consumer would otherwise be exposed to when consuming a comparable level of the plant material used to extract the vitamin.

We also recognize it is possible the manufacturing process could extract the constituent in the fruit or vegetable that may be linked to an allergy or sensitivity. Allergic reactions are triggered by proteins while sensitivities can be triggered by other constituents in a food. In addition, individuals with oral allergy syndrome are usually sensitized to one or more pollens and could react to proteins in specific fresh fruits and vegetables that cross-react with the pollen allergens.⁷ We also recognize some consumers experience reactions that can be triggered by constituents in certain fruits and vegetables other than proteins.

As reported in **Table 2**, the GRAS substance is not expected to contain protein. We recognize it is possible one of the allergenic proteins found in the source plant could be present in the extracted vitamin E. To the extent a consumer has an allergy or sensitivity to one of the fruits or vegetables used as the source materials, the vitamin E product could contain that particular substance. Any concerns with allergies and sensitivities are handled through labeling. The labels of the foods bearing the NutriFusion vitamin E extract will identify each fruit or vegetable used in the extraction process. Individuals with a food allergy or sensitivity to one of the fruits or vegetables used in the extraction process, therefore, will be able to identify the possible presence of the plant material and can avoid the product.

We, therefore, view the long history of consumption of fruits and vegetables and the use of conventional food processing extractions methods as supporting the GRAS status of the NutriFusion vitamin E extract. The GRAS status is further demonstrated by a review of the scientific literature. For example, several authoritative bodies including the IOM and the European Food Safety Authority (EFSA) have conducted comprehensive reviews of the safety data related to the vitamins including vitamin E. When comparing the current 90th percentile intake of vitamin E to the safety levels identified by various expert groups, the intended use of the NutriFusion vitamin E extract product can be reasonably expected to be safe.

6.2 Safety Assessment

Vitamin E functions primarily as an antioxidant that prevents the propagation of lipid peroxidation. The Scientific Report of the 2015 Dietary Guidelines Advisory Committee concluded vitamin E is underconsumed among the U.S. population ages 2 years and older. There is no evidence of adverse effects from the consumption of vitamin E in foods. Animal studies show that vitamin E is not mutagenic, carcinogenic, or teratogenic.

Vitamin E is listed as GRAS under 21 CFR §182.8890 (“Tocopherols,”) there are no limitations on use levels other than cGMPs.

⁷ Taylor, Steve L., and Susan L. Hefle. *Food allergies and other food sensitivities* Food Technology 55.9 (2001): 68-84.

- **IOM (2000)** ⁸

The IOM reviewed all data relevant to vitamin E safety and selected hemorrhagic effects as the critical endpoint on which to base the UL for vitamin E for adults. However, the IOM noted the human data fail to demonstrate consistently a causal association between excess vitamin E intake in normal, apparently healthy individuals and any adverse health outcome. The risk of adverse effects resulting from excess intake of α -tocopherols from food and supplements appears to be very low at the highest intakes. The IOM established a UL for adult at 1,000 mg/day and a UL for children 1-3 years at 200 mg/day.

- **European Commission, Scientific Committee on Food (EC SCF 2003)** ⁹

The EC SCF reviewed all the evidence and found no adverse effects for oral vitamin E in humans. The expert panel decided that the critical effect is on blood clotting and that the study by Meydani et al. (1998) provided the best basis for an evaluation of the tolerable upper intake level. ¹⁰ The NOAEL established in this study was 540 mg/day. The UL for vitamin E was established as 270 mg/day for adults after applying an uncertainty factor of 2. The UL for children age from 1 to 3 was established as 100 mg/day.

Vitamin E from conventional sources is currently considered GRAS with no limitations other than GMPs. The vitamin E extracted from fruits and vegetables is a substitutional use and would not increase vitamin E dietary exposure. Based on the safety reviews conducted by IOM and EFSA, even assuming the intended use of vitamin E in the NutriFusion product will replace all the existing uses, the 90th percentile dietary intake of 13.7 mg can reasonably be considered as safe.

6.3 Safety Conclusion

Several expert panels organized by reputable scientific and regulatory agencies including the IOM and EFSA have reviewed the available safety data on the various vitamins and established safety levels when appropriate. The intended use of the NutriFusion vitamin E extract is a substitutional use given that the synthetic vitamin E is currently authorized for use with no limits other than GMPs. The current cumulative intake of vitamin E in children one to three years old, children above four, and adults are all well below the ULs set by the IOM.

⁸ Bendich, Adrienne. "Dietary reference intakes for vitamin C, vitamin E, selenium, and carotenoids institute of medicine washington, DC: National Academy Press, 2000 ISBN: 0-309-06935-1." *Nutrition* 17.4 (2001): 364.

⁹ Scientific Committee on Food of European Commission. "Opinion of the Scientific Committee on Food on the tolerable upper intake level of vitamin E." *Bruxelles: European Commission* (2003).

¹⁰ Meydani, Simin Nikbin, et al. "Assessment of the safety of supplementation with different amounts of vitamin E in healthy older adults." *The American journal of clinical nutrition* 68.2 (1998): 311-318.

Age Groups	90th Percentile Intake (Male) ¹¹	90th Percentile Intake (Female)	UL ¹²
1-3	6.2 mg/day	5.5 mg/d	200 mg/d
4-8	7.5 mg/day	7.7 mg/d	300 mg/d
9-13	9.4 mg/day	8.5 mg/d	600 mg/d
14-18	9.9 mg/day	8.6 mg/d	800 mg/d
19-30	12.8 mg/day	9.5 mg/d	1,000 mg/d
31-50	13.7 mg/day	11 mg/d	1,000 mg/d
50 and over	12.5 mg/day	11.1 mg/d	1,000 mg/d

Vitamin E is also considered an underconsumed nutrient in the U.S. by the 2015 Dietary Guidelines Advisory Committee. The long history of consumption of fruits and vegetables as a source of vitamin E also supports its safety. In addition, the underlying safety reviews establish the safety of including the plant-based vitamin E in the diet.

Overall, the existing dietary intake from the proposed use can be considered safe. We, therefore, are of the view that there is a consensus among experts qualified by scientific training and experience to evaluate the safety that there is reasonable certainty the intended use of the NutriFusion vitamin E extract product is not harmful.

In summary, due to the demonstrated safe consumption history of the fruits and vegetables that are used to make the NutriFusion vitamin E extract product, as well as the expert panels opinions, we concluded that the intended use of NutriFusion vitamin E extract product in foods that are otherwise authorized for the addition of vitamins can be considered GRAS through scientific procedures.

¹¹ Millen, B. E., A. H. Lichtenstein, and S. Abrams. "Scientific Report of the 2015 Dietary Guidelines Advisory Committee." *Washington (DC): Department of Health and Human Services* (2015).

¹² See *supra* note 8.

7.0 List of Supporting Data and Information

All of the following data and information are publicly available.

- USDA National Nutrient Database for Standard Reference Release 28.
- Taylor, Steve L., and Susan L. Hefle. Food allergies and other food sensitivities *Food Technology* 55.9 (2001): 68-84.
- Bendich, Adrienne. "Dietary reference intakes for vitamin C, vitamin E, selenium, and carotenoids institute of medicine washington, DC: National Academy Press, 2000 ISBN: 0-309-06935-1." *Nutrition* 17.4 (2001): 364.
- Scientific Committee on Food of European Commission. "Opinion of the Scientific Committee on Food on the tolerable upper intake level of vitamin E." Bruxelles: European Commission (2003).
- Meydani, Simin Nikbin, et al. "Assessment of the safety of supplementation with different amounts of vitamin E in healthy older adults." *The American journal of clinical nutrition* 68.2 (1998): 311-318.
- Millen, B. E., A. H. Lichtenstein, and S. Abrams. "Scientific Report of the 2015 Dietary Guidelines Advisory Committee." Washington (DC): Department of Health and Human Services (2015).

Attachment 1



1775 Moriah Woods Blvd., Ste. 12 ▪ Memphis, TN 38117 ▪ (901) 398-4001

Cornerstone Report#: 300-17-006
 Attn: William Grand, NutriFusion, LLC.
 Address; 10641 Airport Pulling Road North, Ste 31, Naples, FL 34109.
 Cornerstone Reference #(s): 140693-140695.

Date Sampled: None Given
 Date Received: 10/27/17
 Date of Report: 11/14/17

Quality Conformance Results

Vitamin E Powder Sprayed on Food Starch & Silicon Dioxide Lot#-100701A2

Analysis	Results	Units	Method	Specification Range
Fat Soluble Vitamins				
d-Alpha Tocopherol Acetate	53.7	%, w/w	AOAC-2012.09M	51.5-55.0
Physical				
Total Starch	40.2	%, w/w	AOAC-925.38	>39.0
Moisture	5.5	% w/w	Vac Oven	-
Silica (as SiO ₂)	0.044	%, w/w	ICP/OES	>0.010
Total	99.44%			

Vitamin E Powder Sprayed on Food Starch & Silicon Dioxide Lot#-100701A3

Analysis	Results	Units	Method	Specification Range
Fat Soluble Vitamins				
d-Alpha Tocopherol Acetate	52.8	%, w/w	AOAC-2012.09M	51.5-55.0
Physical				
Total Starch	41.8	%, w/w	AOAC-925.38	>39.0
Moisture	4.6	% w/w	Vac Oven	-
Silica (as SiO ₂)	0.060	%, w/w	ICP/OES	>0.010
Total	99.16%			

Vitamin E Powder Sprayed on Food Starch & Silicon Dioxide Lot#-100701A4

Analysis	Results	Units	Method	Specification Range
Fat Soluble Vitamins				
d-Alpha Tocopherol Acetate	53.1	%, w/w	AOAC-2012.09M	51.5-55.0
Physical				
Total Starch	40.7	%, w/w	AOAC-925.38	>39.0
Moisture	5.1	% w/w	Vac Oven	-
Silica (as SiO ₂)	0.052	%, w/w	ICP/OES	>0.010
Total	98.95%			



1775 Moriah Woods Blvd., Ste. 12 ▪ Memphis, TN 38117 ▪ (901) 398-4001

Cornerstone Report#: 300-17-006
 Attn: William Grand, NutriFusion, LLC.
 Address; 10641 Airport Pulling Road North, Ste 31, Naples, FL 34109.
 Cornerstone Reference #(s): 140696.

Date Sampled: None Given
 Date Received: 10/27/17
 Date of Report: 11/14/17

Quality Conformance Results

Vitamin E Powder Sprayed on Food Starch & Silicon Dioxide Lot#-100701A5

Analysis	Results	Units	Method	Specification Range
Fat Soluble Vitamins				
d-Alpha Tocopherol Acetate	53.5	%, w/w	AOAC-2012.09M	51.5-55.0
Physical				
Total Starch	41.0	%, w/w	AOAC-925.38	>39.0
Moisture	5.2	% w/w	Vac Oven	-
Silica (as SiO ₂)	0.052	%, w/w	ICP/OES	>0.010
Total	99.75%			

Comments

*1mg of d-alpha tocopherol acetate is equivalent to 1.36 IU's.
 All analytical control parameters were within laboratory quality limits. All values are reported on an "as received" basis.*

(b) (6)

Samuel J. LaBonia
 President and Technical Director

Attachment 2



1775 Moriah Woods Blvd., Ste. 12 ▪ Memphis, TN 38117 ▪ (901) 398-4001

Cornerstone Report#: 334-17-003
 Attn: William Grand, NutriFusion, LLC.
 Address: 10641 Airport Pulling Road North, Ste 31, Naples, FL 34109.
 Cornerstone Reference #(s): 141289.

Date Sampled: None Given
 Date Received: 11/30/17
 Date of Report: 12/11/17

Quality Conformance Results

Vitamin E Powder Sprayed on Food Starch & Silicon Dioxide Lot#-100701A2

Analysis	Results	Units	Method	Threshold Limit
Heavy Metals				
Arsenic	<0.1	ppm, w/w	USEPA-6010C	1.0
Cadmium	<0.1	ppm, w/w	USEPA-6010C	0.5
Lead	<0.1	ppm, w/w	USEPA-6010C	1.5
Mercury	<0.01	ppm, w/w	USEPA-7471B	0.2
Bismuth	<0.1	ppm, w/w	USEPA-6010C	0.2
Antimony	<0.1	ppm, w/w	USEPA-6010C	0.2
Microbiology				
E. coli Count (3 Tube MPN)	<3	MPN/G	AOAC-966.24	<3
Total Aerobic Bacteria Count	<1	CFU/G	AOAC-966.23	<3,000
Total Yeast/Mold Count	<1	CFU/G	FDA BAM 7 th Ed.	<300
Total Coliforms Count (3 Tube MPN)	<1	MPN/G	AOAC-966.24	<10
Salmonella Count	Negative	-	AOAC-2004.03	Negative
Staphylococcus Count	<1	CFU/G	AOAC-975.55	<1

(b) (6)

Samuel J. LaBonia
 President and Technical Director



1775 Moriah Woods Blvd., Ste. 12 ▪ Memphis, TN 38117 ▪ (901) 398-4001

Cornerstone Report#: 334-17-003
 Attn: William Grand, NutriFusion, LLC.
 Address: 10641 Airport Pulling Road North, Ste 31, Naples, FL 34109.
 Cornerstone Reference #(s): 141290.

Date Sampled: None Given
 Date Received: 11/30/17
 Date of Report: 12/11/17

Quality Conformance Results

Vitamin E Powder Sprayed on Food Starch & Silicon Dioxide Lot#-100701A3

Analysis	Results	Units	Method	Threshold Limit
Heavy Metals				
Arsenic	<0.1	ppm, w/w	USEPA-6010C	1.0
Cadmium	<0.1	ppm, w/w	USEPA-6010C	0.5
Lead	<0.1	ppm, w/w	USEPA-6010C	1.5
Mercury	<0.01	ppm, w/w	USEPA-7471B	0.2
Bismuth	<0.1	ppm, w/w	USEPA-6010C	0.2
Antimony	<0.1	ppm, w/w	USEPA-6010C	0.2
Microbiology				
E. coli Count (3 Tube MPN)	<3	MPN/G	AOAC-966.24	<3
Total Aerobic Bacteria Count	<1	CFU/G	AOAC-966.23	<3,000
Total Yeast/Mold Count	<1	CFU/G	FDA BAM 7 th Ed.	<300
Total Coliforms Count (3 Tube MPN)	<1	MPN/G	AOAC-966.24	<10
Salmonella Count	Negative	-	AOAC-2004.03	Negative
Staphylococcus Count	<1	CFU/G	AOAC-975.55	<1

(b) (6)

Samuel J. LaBonia
 President and Technical Director



1775 Moriah Woods Blvd., Ste. 12 ▪ Memphis, TN 38117 ▪ (901) 398-4001

Cornerstone Report#: 334-17-003
 Attn: William Grand, NutriFusion, LLC.
 Address: 10641 Airport Pulling Road North, Ste 31, Naples, FL 34109.
 Cornerstone Reference #(s): 141291.

Date Sampled: None Given
 Date Received: 11/30/17
 Date of Report: 12/11/17

Quality Conformance Results

Vitamin E Powder Sprayed on Food Starch & Silicon Dioxide Lot#-100701A4

Analysis	Results	Units	Method	Threshold Limit
Heavy Metals				
Arsenic	<0.1	ppm, w/w	USEPA-6010C	1.0
Cadmium	<0.1	ppm, w/w	USEPA-6010C	0.5
Lead	<0.1	ppm, w/w	USEPA-6010C	1.5
Mercury	<0.01	ppm, w/w	USEPA-7471B	0.2
Bismuth	<0.1	ppm, w/w	USEPA-6010C	0.2
Antimony	<0.1	ppm, w/w	USEPA-6010C	0.2
Microbiology				
E. coli Count (3 Tube MPN)	<3	MPN/G	AOAC-966.24	<3
Total Aerobic Bacteria Count	<1	CFU/G	AOAC-966.23	<3,000
Total Yeast/Mold Count	<1	CFU/G	FDA BAM 7 th Ed.	<300
Total Coliforms Count (3 Tube MPN)	<1	MPN/G	AOAC-966.24	<10
Salmonella Count	Negative	-	AOAC-2004.03	Negative
Staphylococcus Count	<1	CFU/G	AOAC-975.55	<1

(b) (6)

Samuel J. LaBonia
 President and Technical Director



1775 Moriah Woods Blvd., Ste. 12 ▪ Memphis, TN 38117 ▪ (901) 398-4001

Cornerstone Report#: 334-17-003
 Attn: William Grand, NutriFusion, LLC.
 Address: 10641 Airport Pulling Road North, Ste 31, Naples, FL 34109.
 Cornerstone Reference #(s): 141292.

Date Sampled: None Given
 Date Received: 11/30/17
 Date of Report: 12/11/17

Quality Conformance Results

Vitamin E Powder Sprayed on Food Starch & Silicon Dioxide Lot#-100701A5

Analysis	Results	Units	Method	Threshold Limit
Heavy Metals				
Arsenic	<0.1	ppm, w/w	USEPA-6010C	1.0
Cadmium	<0.1	ppm, w/w	USEPA-6010C	0.5
Lead	<0.1	ppm, w/w	USEPA-6010C	1.5
Mercury	<0.01	ppm, w/w	USEPA-7471B	0.2
Bismuth	<0.1	ppm, w/w	USEPA-6010C	0.2
Antimony	<0.1	ppm, w/w	USEPA-6010C	0.2
Microbiology				
E. coli Count (3 Tube MPN)	<3	MPN/G	AOAC-966.24	<3
Total Aerobic Bacteria Count	<1	CFU/G	AOAC-966.23	<3,000
Total Yeast/Mold Count	<1	CFU/G	FDA BAM 7 th Ed.	<300
Total Coliforms Count (3 Tube MPN)	<1	MPN/G	AOAC-966.24	<10
Salmonella Count	Negative	-	AOAC-2004.03	Negative
Staphylococcus Count	<1	CFU/G	AOAC-975.55	<1

(b) (6)

Samuel J. LaBonia
 President and Technical Director

Attachment 3



1775 Moriah Woods Blvd., Ste. 12 • Memphis, TN 38117 • (901) 398-4001 Fax: (901) 398-4223

Cornerstone Report#: 033-15-004
 Attn: Brad Young, AddisonField, Inc.
 Address: 2 Townsend Street, 2-808, San Francisco, CA 94107.
 Cornerstone Reference #(s): 117210-117211.

Date Sampled: 01/15/15
 Date Received: 02/02/15
 Date of Report: 02/13/15

Quality Conformance Results

RDA-12 Dietary Supplement Powder Lot#1304048 MFG:05/2013

Analysis	Results	Units	Method	Specification Range
Physical				
Moisture	1.6	% w/w	Vac Oven	5.0

Fat Soluble Vitamins

Vitamin A	2,680	IU/225mg	AOAC-974.29M	2,514
Vitamin E	18.3	IU/225mg	AOAC-974.29M	15
Vitamin D	279	IU/225mg	AOAC-982.29M	257
Phylloquinone K ₁	52	mcg/225mg	JOECA#42M	42

Water Soluble Vitamins

Vitamin C	39	mcg/225mg	JOECA#94M	31
Thiamin B ₁	745	mcg/225mg	JOCA-A1007M	756
Riboflavin B ₂	910	mcg/225mg	JOCA-A1007M	869
Niacin B ₃	10,115	mcg/225mg	JOCA-A1007M	9,946
Pantothenic Acid	5,020	mcg/225mg	JOCA-A1007M	5,172
Pyridoxine-B ₆	811	mcg/225mg	JOCA-A1007M	970
Biotin B ₇	174	mcg/225mg	JOCA-A1007M	157
Folic Acid B ₉	206	mcg/225mg	JOCA-A1007M	186

Comments

Sample was received in its original packaging.



**CORNERSTONE
LABORATORIES
LLC**

1775 Moriah Woods Blvd., Ste. 12 • Memphis, TN 38117 • (901) 398-4001 Fax: (901) 398-4223

Cornerstone Report#: 033-15-004
 Attn: Brad Young, AddisonField, Inc.
 Address: 2 Townsend Street, 2-808, San Francisco, CA 94107.
 Cornerstone Reference #(s): 117210-117211.

Date Sampled: 01/15/15
 Date Received: 02/02/15
 Date of Report: 02/13/15

Quality Conformance Results

RDA-12 Dietary Supplement Capsules Lot#1304047 MFG:05/2013 Capsule Weight (avg) 410mg

Analysis	Results	Units	Method	Specification Range
Physical				
Moisture	5.1	% w/w	Vac Oven	5.0

Fat Soluble Vitamins

Vitamin A	2,440	IU/capsule	AOAC-974.29M	2,514
Vitamin E	14.8	IU/capsule	AOAC-974.29M	15
Vitamin D	261	IU/capsule	AOAC-982.29M	257
Phylloquinone K ₁	40	mcg/capsule	JOCA#42M	42

Water Soluble Vitamins

Vitamin C	30	mcg/capsule	JOCA#94M	31
Thiamin B ₁	759	mcg/capsule	JOCA-A1007M	756
Riboflavin B ₂	881	mcg/capsule	JOCA-A1007M	869
Niacin B ₃	9,960	mcg/capsule	JOCA-A1007M	9,946
Pantothenic Acid	5,203	mcg/capsule	JOCA-A1007M	5,172
Pyridoxine-B ₆	995	mcg/capsule	JOCA-A1007M	970
Biotin B ₇	162	mcg/capsule	JOCA-A1007M	157
Folic Acid B ₉	180	mcg/capsule	JOCA-A1007M	186

Comments

Sample was received in its original packaging.

(b) (6)

Samuel J. LaBonia
 President and Technical Director

Attachment 4

NUTRI FUSION™

Pasta Study

Background:

1. **NutriFusion™** is a blend of fruits and/or vegetables that can significantly increase the nutritional profile, and therefore the marketability, of food, beverage and supplement products. It does not affect taste or functionality of the products it goes into and is 100% natural.
2. NutriFusion supplies the complex nutrients and phytonutrients from fresh fruits and vegetables.
3. **Three major claims can be made:**
 - % of RDI: Such as 25 % of the recommended daily value for Vitamins A, C, D, E, B1, B2 etc.
 - Source claim: Such as rich in antioxidants, excellent source of Vitamins A, C, D, E, B1, B2 etc.
 - Serving Claims: Such as provides the nutrients from 1 serving of vegetables in each serving of pasta.
4. In certain products, such as baked goods, it can extend shelf life due to the high levels of anti-oxidants (both from vitamins and polyphenols in the fruits & vegetables).

Purpose:

1. The purpose of the study was to see if the pasta prepared at home by the consumer would retain the nutritional value from NutriFusion™ as stated on the nutritional label per the pasta box.
2. The pasta goes through 3 stages of heat in production and consumption:
 - a. Initial production: the flour etc is mixed, cooked and turned into wet pasta.
 - b. The pasta then goes through a 4-6 hour drying oven at 185-195 degrees F. to dry for cutting and packaging.
 - c. Finally, the consumer, at home, cooks the pasta in boiling water for 11-13 minutes.

Methodology:

10 month old pasta was randomly selected for testing.

Background:

- A third-party lab was sent 3 boxes of pasta made with GrandFusion™;
- Finished pasta boxes were randomly selected for testing. Per the box code, the pasta was produced 10 months prior to testing.
- The lab was instructed to cook the pasta per the directions on the box as a normal consumer would at home. [The directions are to boil water, add the pasta, wait for re-boil, and cook for 11 to 13 minutes.]

Results:

1. Attached you will find the nutritional analysis supplied by Cornerstone Labs, Memphis TN.
2. The nutritional results are 100% in line with the original nutritional claims on the box.
3. There was no decline in the nutrients per the nutritional analysis panel on the pasta box.
4. The pasta shows an excellent shelf life; indicating the consumer is benefiting from the bioactive nutrients found in NutriFusion™/GrandFusion™.

Study Completed: July 15, 2013

Why this is important!

Pending Health Crisis:

1. The CDC, the World Health Organization and many other international bodies feel the world is heading to a global health crisis. Heart disease, cancer, and diabetes are assuming epidemic proportions. The number one reason is the lack of protective nutrients in our diets. Why is this happening?
 - Poor diets. We are not getting enough of the protective nutrients in our diets. There's no shortage of calories but the key nutrients that promote health and protect us are missing.
 - Lack of physical activity.
2. Only 6% of individuals achieve their recommended target for vegetables and
3. 8% achieve their recommended target for fruit in an average day per the USDA guidelines.

Source: **The National Fruit & Vegetable Alliance's** National Action Plan report card. Steering Committee Members include:

- CDC, Centers for Disease Control & Prevention,
- American Cancer Society,
- American Diabetes Association,
- American Dietetic Association,
- American Heart Association,
- National Cancer Institute,
- USDA: (Food, Nutrition and Consumer Services, Research, Education and Economics, Marketing and Regulatory Programs).
- California Department of Public Health,
- National Alliance for Nutrition & Physical Activity,
- Produce for Better Health Foundation,
- American Frozen Food Institute,
- Canned Food Alliance,
- Produce Marketing Association,
- United Fresh Produce Association,
- National Council of Fruit & Vegetable Nutrition Coordinators,

<http://www.nfva.org/pdfs/nfva/FINALNAP2010.pdf> **The National Fruit & Vegetable Alliance's** National Action Plan report card



1775 Moriah Woods Blvd., Ste. 12 • Memphis, TN 38117 • (901) 398-4001 Fax: (901) 398-4223

NUTRIFUSION, LLC.
ATTN: WILLIAM J.H. GRAND
3 CLAIRE DRIVE
HILTON HEAD, SC 29928

July 15, 2013

ACCOUNT #: 10-0623

REPORT NUMBER: 179-13-013

Reference: [REDACTED]

LABORATORY REPORT CASE NARRATIVE

On June 28, 2013 three samples were submitted to the laboratory for analyses detailed on the chain of custody accompanying the samples. The samples were received sealed and in good condition. Prior to analysis the samples were prepared as per the box label. There were no analytical problems encountered and the results of the analysis are on the following pages.

If you have any questions about this report please do not hesitate to contact me.

Thank you for using Cornerstone Laboratories.

Sincerely,

(b) (6)

Samuel J. LaBonia
President and Technical Director

NUTRIFUSION, LLC.

July 15, 2013

ACCOUNT #: 10-0623

REPORT NUMBER: 179-13-013

Reference: XXXXXXXXXX

Report Analysis

Laboratory Number: 104220

**Sample ID: Pasta Plus Veggie
Rotini
Serving Size: 56g
Samples Taken: 07/09/13**

<u>Nutrient</u>	<u>Result/Serving</u>	<u>Units</u>	<u>%DV</u>	<u>100% DV</u>	<u>Analysis Date</u>	<u>Analyst</u>
Vitamin A	1,140	IU	23%	5,000	07/10/13	S. LaBonia
Vitamin E	8.2	IU	27%	30	07/10/13	S. LaBonia
Vitamin D	105	IU	26%	400	07/13/13	S. LaBonia
Vitamin C	15.8	mg	26%	60	07/12/13	K. Shinn
Vitamin B1	0.664	mg	44%	1.50	07/12/13	K. Shinn
Vitamin B6	0.593	mg	30%	2.00	07/12/13	K. Shinn
Vitamin K	0.010	mg	13%	0.080	07/14/13	S. LaBonia

Laboratory Number: 104221

**Sample ID: Pasta Plus Veggie
Penne Rigate
Serving Size: 56g
Samples Taken: 07/09/13**

<u>Nutrient</u>	<u>Result/Serving</u>	<u>Units</u>	<u>%DV</u>	<u>100% DV</u>	<u>Analysis Date</u>	<u>Analyst</u>
Vitamin A	1,290	IU	26%	5,000	07/10/13	S. LaBonia
Vitamin E	8.8	IU	29%	30	07/10/13	S. LaBonia
Vitamin D	113	IU	28%	400	07/13/13	S. LaBonia
Vitamin C	14.2	mg	24%	60	07/12/13	K. Shinn
Vitamin B1	0.627	mg	42%	1.50	07/12/13	K. Shinn
Vitamin B6	0.616	mg	31%	2.00	07/12/13	K. Shinn
Vitamin K	0.011	mg	14%	0.080	07/14/13	S. LaBonia

NUTRIFUSION, LLC.

July 15, 2013

ACCOUNT #: 10-0623

REPORT NUMBER: 179-13-013

Reference: XXXXXXXXXX

Report Analysis

Laboratory Number: 104222

Sample ID: Pasta Plus Veggie

Elbows

Serving Size: 56g

Samples Taken: 07/09/13

<u>Nutrient</u>	<u>Result/Serving</u>	<u>Units</u>	<u>%DV</u>	<u>100% DV</u>	<u>Analysis Date</u>	<u>Analyst</u>
Vitamin A	1,206	IU	24%	5,000	07/10/13	S. LaBonia
Vitamin E	7.8	IU	26%	30	07/10/13	S. LaBonia
Vitamin D	96	IU	24%	400	07/13/13	S. LaBonia
Vitamin C	15.0	mg	25%	60	07/12/13	K. Shinn
Vitamin B1	0.651	mg	43%	1.50	07/12/13	K. Shinn
Vitamin B6	0.577	mg	29%	2.00	07/12/13	K. Shinn
Vitamin K	0.015	mg	19%	0.080	07/14/13	S. LaBonia

Nutrition Facts

Serving Size 2 oz dry (56 g)

Amount Per Serving

Calories 200 **Calories From Fat** 10

% Daily Value*

Total Fat	1 g		2 %
Saturated Fat	0 g		0 %
Trans Fat	0g		
Polyunsaturated Fat	0.5 g		
Monounsaturated Fat	0 g		
Cholesterol	0 mg		0 %
Sodium	0 mg		0 %
Total Carbohydrate	41 g		14 %
Dietary Fiber	2 g		24 %
Sugars	2 g		
Protein	7 g		

Vitamin A	20%	Vitamin C	25%
Calcium	0%	Iron	10%
Vitamin D	20%	Vitamin E	25%
Thiamin	40%	Riboflavin	15%
Niacin	20%	Vitamin B6	25%
Folate	30%	Magnesium	15%

* Percent daily values are based on a 2,000 calorie diet. Your daily values may be higher or lower depending on your calorie needs:

	Calories	2,000	2,500
Total Fat	Less Than	65g	80g
Saturated Fat	Less Than	20g	25g
Cholesterol	Less Than	300mg	300mg
Sodium	Less Than	2,400mg	2,400mg
Total Carbohydrate		300g	375g
Dietary Fiber		25g	30g

Calories per gram:

Fat 9 • Carbohydrate 4 • Protein 4

INGREDIENTS

Durum Wheat Semolina, [enriched with iron (ferrous sulfate) and B vitamins (niacin, thiamin mononitrate, riboflavin, folic acid)], nutrients from whole food concentrates (spinach, broccoli, carrot, tomato, beet, shiitake mushrooms), Color (paprika oleoresin, fruit juice concentrate (watermelon, huito), turmeric oleoresin), maltodextrin, gum arabic, ascorbic acid.

HOGAN LOVELLS US LLP

GRAS Notice for Alpha-Tocopherol Acetate (Vitamin E) Extracted from Fruit and Vegetable Sources

May 07, 2018 (Rev. Aug 19, 2018)

Table of Contents

	Page
1.0 GRAS Statement and Certification	2
1.1 Claim of Exemption.....	2
1.2 Name and Address of the Notifier	2
1.3 Name of the Notified Substance.....	2
1.4 Intended Conditions of Use.....	2
1.5 Statutory Basis of GRAS Conclusion	3
1.6 GRAS Statement	3
1.7 Availability of Information	3
1.8 Trade Secret and Confidential Information.....	3
1.9 GRAS Certification.....	3
1.10 Signature	3
2.0 Identity, Method of Manufacture, Specifications, and Physical or Technical Effect	4
2.1 Identity.....	4
2.2 Characteristic Properties.....	4
2.3 Quantitative Composition	4
2.4 Manufacturing Process	4
2.5 Specifications.....	6
2.6 Stability Data.....	7
2.7 Detailed Information on Intended Use.....	8
4.0 Self-limiting Levels of Use	10
5.0 Experience Based on Common Use in Food before 1958	11
6.0 GRAS Narrative.....	12
6.1 Overview.....	12
6.2 Safety Assessment	13
6.3 Safety Conclusion	19
7.0 List of Supporting Data and Information.....	21

1.0 GRAS Statement and Certification

1.1 Claim of Exemption

On behalf of NutriFusion LLC (NutriFusion), Hogan Lovells US LLP (Hogan) is submitting this generally recognized as safe (GRAS) notice summarizing the data and information supporting NutriFusion's conclusion that its intended use of alpha-tocopherol acetate (vitamin E) made from edible portions of commonly consumed fruits and vegetables using conventional extraction procedures are GRAS for use in foods intended for infants from six to 12 months of age, toddlers and young children from one to four, and the general population four and over, when used as a substitute for other commercially available sources of α -tocopherol acetate.

1.2 Name and Address of the Notifier

NutriFusion LLC
10641 Airport Pulling Rd N., Suite 31
Naples, FL, 34109-7330

1.3 Name of the Notified Substance

Alpha-tocopherol acetate (vitamin E) from edible fruits and vegetables.

1.4 Intended Conditions of Use

The NutriFusion alpha-tocopherol acetate (vitamin E) will be used as a substitute for other commercially available forms of alpha-tocopherol acetate that are added to foods. Alpha-tocopherol acetate is listed as a GRAS ingredient with no limits other than GMPs as a nutrient source. See 21 CFR §182.8892 ("[alpha]-Tocopherol acetate"). Alpha-tocopherol acetate is commonly used as a nutrient source and an antioxidant. The proposed use of the α -tocopherol acetate from edible fruits and vegetable would be substitutional and would be used either as a nutrient, an antioxidant, or both. The NutriFusion product can be included in baby foods (excluding use as a supplement to breast milk or infant formula) for infants from six to 12 months and children from one to four years old. Examples of these products include baby and toddler pureed fruits and vegetables, dinners, dairy-based foods intended for children six months up to four years, and toddler meals. The NutriFusion product is intended to be used only as a substitute for the existing commercially available forms of vitamin E on the market. In other words, the NutriFusion α -tocopherol acetate is intended to be used in food categories that currently are formulated with other forms of vitamin E.

While typical use levels will vary depending on the manufacturer and the product, the maximum use levels in foods for children four and over and adults is 15 mg/serving (i.e., 100% of the Reference Daily Intake (RDI or DV) of vitamin E)). The maximum use levels in foods for infants six month and older is 2.5 mg/serving (i.e., 50% of the RDI or DV) for children one through three years old is 3 mg/serving (i.e., 50% of the RDI or DV).

1.5 Statutory Basis of GRAS Conclusion

Through scientific procedures in accordance with 21 CFR § 170.30(a) and (b).

1.6 GRAS Statement

The notified substance is not subject to the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act based on NutriFusion's conclusion that the notified substance is GRAS under the conditions of the intended use.

1.7 Availability of Information

A complete copy of the data and information that was used as a basis for this GRAS conclusion can be provided to the FDA upon request, and is also available for FDA's copying and reviewing during customary business hours at:

Martin J. Hahn
Hogan Lovells US LLP
555 Thirteenth Street, NW
Washington, DC 20004

1.8 Trade Secret and Confidential Information

This GRAS notice does not contain data or information that is exempt from disclosure under the Freedom of Information Act, 5 U.S.C. 552.

1.9 GRAS Certification

To the best of our knowledge, the GRAS notice is a complete, representative, and balanced submission that includes unfavorable information, as well as favorable information, known to us and pertinent to the evaluation of the safety and GRAS status of the use of the substance.

1.10 Signature

(b) (4)

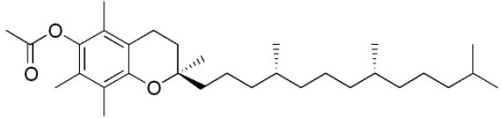


Martin J. Hahn
Hogan Lovells US LLP
martin.hahn@hoganlovells.com
202 637 5926

2.0 Identity, Method of Manufacture, Specifications, and Physical or Technical Effect

2.1 Identity

Chemical identity information for α -tocopherol acetate can be summarized in **Table 1**, below. For purposes of this GRAS notification, we use the terms “Vitamin E Extract” and “ α -tocopherol acetate” interchangeably.

Name	CAS Number	Molecular Formula	Molecular Weight	Synonyms
Vitamin E	58-95-7		472	Alpha-Tocopherol Acetate, Vitamin E Acetate

The α -tocopherol acetate also contains food starch and silicon dioxide that encapsulate the vitamin E.

2.2 Characteristic Properties

Appearance: Free-flowing Powder

Color: White to off-white

2.3 Quantitative Composition

Constituent	Lot#- 100701A2	Lot#- 100701A3	Lot#- 100701A4	Lot#- 100701A5
Vitamin E	53.7%	52.8%	53.1%	53.5%
Total Starch	40.2%	41.8%	40.7%	41.0%
Moisture	5.5%	4.6%	5.1%	5.2%
Silica (as SiO ₂)	0.044%	0.06%	0.052%	0.052%

The results demonstrate the company is able to offer a standardized extract. See also **Attachment 1**.

2.4 Manufacturing Process

The α -tocopherol acetate is manufactured from edible portions of fruits and vegetables following good manufacturing practices for food (21 CFR Part 110 and 21 CFR Part 117, Subpart B, when it becomes effective). All the starting materials have a long history of safe consumption. **Table 3** provides examples of the fruit or vegetable that can be used as a source for the vitamin E.

Fruit/Vegetable Used as the Source (Edible Portions Only)	Specie Names
Mustard greens	<i>Brassica juncea</i>
Swiss chard	<i>Beta vulgaris</i>
Spinach	<i>Spinacia oleracea</i>
Kale	<i>Brassica oleracea var. sabellica</i>

NutriFusion uses various conventional extraction methods to extract the vitamins and will select the method that is most effective depending on the fruit or vegetable matrix and the nutrient(s) that are extracted. The solvents most commonly used are water, ethanol or critical CO₂. Solid phase extraction is also used. The solvent extraction process can be described as follows:

1. Food grade fruits and vegetables are harvested, sorted, garbled (i.e., the desired part of the plant (the edible portion) is separated from other parts of the plant), and dried.
2. The dried plants are prepared for extraction by grinding into a fine powder to maximize the surface area available for extraction.
3. An Individual dried plant, or a blend of dried fruits and vegetables with naturally occurring vitamin E, will then be immersed in solvents commonly used in food processing (e.g., water, alcohol, or critical CO₂).
4. The extraction process can take several days.
5. Once the extraction process is complete the solvent and plant solids are separated by centrifugation.
6. The liquid portion is decanted and stored in a container for later processing.
7. The extraction can be repeated with the solid materials separated by centrifugation as needed (for example, the plant material could first be exposed to an aqueous extraction and after centrifugation, the remaining solids could then be subjected to an ethanol extraction to isolate those remaining vitamins that are soluble in ethanol but not in water).
8. The vitamin E rich liquid is then freeze dried and encapsulated with food grade GRAS ingredients such as a starch to protect the vitamin from oxidation.

The solid phase extraction can be described as follows:

1. Food grade fruits and vegetables are harvested, sorted, garbled, and dried.

2. The dried plants are prepared for extraction by grinding into a fine powder to maximize the surface area available for extraction.
3. An individual dried plant, or a blend of dried fruits and vegetables with naturally occurring vitamin E will be blended together, will then be immersed in solvents commonly used in food processing (e.g., water, alcohol, or critical CO₂).
4. The solution will then pass through a single-use cartridge containing a chromatographic sorbent (e.g., silica particles that have been functionalized on their surface) using appropriate food grade food contact substances that are authorized by FDA for this type of use;
5. Another common food-grade solvent (e.g., acetic acid) can be used as elute to remove the nutrients retained on the stationary phase.
6. The collected liquid will be stored in a container.
7. The extracted vitamin E is removed from the container, freeze-dried, and then encapsulated with food grade GRAS ingredients such as starch to protect the vitamin E from oxidation.

For the vitamin E extract, the GRAS notification is limited to the use of water, acetic acid, ethanol, and critical CO₂ as the solvents. All processing agents and chemicals used in the manufacturing process are food grade.

2.5 Specifications

We are attaching the analytical reports on four non-consecutive production lots that demonstrate the products meet the heavy metal and microbiological specifications. We also include vitamin E levels from four non-consecutive production lots.

Table 5. Specifications						
Item	Limit	Method	Lot#- 100701A2	Lot#- 100701A3	Lot#- 100701A4	Lot#- 100701A5
Vitamin E as α-tocopherol acetate	51.5% - 55%	AOAC-2012.09M	53.7%	52.8%	53.1%	53.5%
Total starch	> 39%	AOAC-925.38	40.2%	41.8%	40.7%	41.0%
Silica (as SiO ₂)	> 0.01%	ICP/OES	0.044%	0.06%	0.052%	0.052%
Arsenic	< 1.0 ppm	USEPA-6010C	< 0.1 ppm	< 0.1 ppm	< 0.1 ppm	< 0.1 ppm
Cadmium	< 0.5 ppm	USEPA-6010C	< 0.1 ppm	< 0.1 ppm	< 0.1 ppm	< 0.1 ppm
Lead	< 1.5 ppm	USEPA-	< 0.1 ppm	< 0.1 ppm	< 0.1 ppm	< 0.1 ppm

Table 5. Specifications						
Item	Limit	Method	Lot#- 100701A2	Lot#- 100701A3	Lot#- 100701A4	Lot#- 100701A5
		6010C				
Mercury	< 0.2 ppm	USEPA- 7471B	< 0.01 ppm	< 0.01 ppm	< 0.01 ppm	< 0.01 ppm
Bismuth	< 0.2 ppm	USEPA- 6010C	< 0.1 ppm	< 0.1 ppm	< 0.1 ppm	< 0.1 ppm
Antimony	< 0.2 ppm	USEPA- 6010C	< 0.1 ppm	< 0.1 ppm	< 0.1 ppm	< 0.1 ppm
Total Aerobic Plate Count	< 3,000 CFU/g	AOAC- 966.23	< 1 CFU/g	< 1 CFU/g	< 1 CFU/g	< 1 CFU/g
Total Yeast/Mold Count	< 300 CFU/g	FDA BAM 7th Ed.	< 1 CFU/g	< 1 CFU/g	< 1 CFU/g	< 1 CFU/g
<i>E. coli</i> Count	< 3 MPN/g	AOAC- 966.24	< 3 MPN/g	< 3 MPN/g	< 3 MPN/g	< 3 MPN/g
<i>Salmonella</i> Count	Negative	AOAC- 2004.03	Negative	Negative	Negative	Negative
Total Coliforms	< 10 MPN/g	AOAC- 966.24	< 1 MPN/g	< 1 MPN/g	< 1 MPN/g	< 1 MPN/g
<i>Staphylococcus Aureus</i>	< 1 CFU/g	AOAC- 975.55	< 1 CFU/g	< 1 CFU/g	< 1 CFU/g	< 1 CFU/g

See also **Attachment 2**.

2.6 Stability Data

NutriFusion created this innovative source of vitamin E extracted from fruits and vegetables and is merely a supplier of this extract to companies that will then formulate the vitamin E extract into various foods. As such, the customer ultimately is responsible for deciding the level of the α -tocopherol acetate that will be added as well as the data supporting any claims that are made on their finished product throughout the shelf life of the product. The customer, therefore, has the responsibility to determine the level of overages, if any, which should be added to the product at time of formulation to meet the level of vitamin E declared on the label throughout the shelf life of the product.

NutriFusion, nonetheless, is aware of customers that have formulated its vitamin E into foods and dietary supplements and has collected products from commerce to evaluate the level of its vitamin E that can be detected in these commercially available foods. For the stability data, NutriFusion analyzed a dietary supplement containing the NutriFusion vitamin E extract. NutriFusion supplied this dietary supplement company with a nutrient blend that contains vitamin E extracted in 2013. NutriFusion collected two commercially available samples of the dietary supplement from commerce in 2015 and analyzed the product for the levels of vitamins in the product. The analytical report can be found in **Attachment 3**. The data demonstrate the vitamin E extract used to formulate the dietary supplement remained stable throughout this two

year period of time. We note the manufacturer of this dietary supplement has established an expiration date of May 2017, demonstrating the manufacturer expects the vitamins to remain stable for at least four years.

NutriFusion also wanted to assess the stability of its nutrient blend including vitamin E extract in a food matrix. NutriFusion supplies a pasta company with one its nutrient blends. The pasta goes through various stages and exposures to heat from the time of manufacture until it is consumed. The pasta company will formulate the flour, vitamin blend, and other ingredients into dough, extrude the pasta in the proper shape, and then subject the extruded pasta to a drying oven to dry the pasta to the desired moisture level. The pasta will be transported and held at retail and by consumers at ambient conditions. When preparing the pasta, the labeled directions for use instruct the consumers to cook the pasta in boiling water for 11-13 minutes.

NutriFusion collected from commerce a 10-month old pasta made by the pasta company that uses the NutriFusion vitamin extract. NutriFusion instructed the laboratory to prepare the pasta according to the labeled directions for use and to analyze the cooked pasta to assess the level of vitamins in the product compared to those declared on the label. The laboratory results and copy of the declared nutrient values are found in **Attachment 4** and summarized in the table below. As the data indicate, the level of vitamin E in the cooked 10-month old pasta is in line with the declared nutritional claims.

Vitamin	Label Declared Value (%DV)	Analytical Value #1 (% DV)	Analytical Value #2 (% DV)	Analytical Value #3 (% DV)
Vitamin E	25	27	29	26

2.7 Detailed Information on Intended Use

The NutriFusion α -tocopherol acetate product is intended for use by infants from six to 12 months of age, toddlers and young children from one to four, and the general population four and over, when used as a substitute for commercially available sources of α -tocopherol acetate. For infants from six to 12 months and children from one to four, the NutriFusion product will be used in baby foods purees (e.g., fruits, veggies, dinners, dairy), toddler meals, and other foods specifically formulated and positioned for children under four. The uses of the NutriFusion α -tocopherol acetate will be substitutional with the currently authorized commercially available vitamin E. Under 21 CFR §182.8892 (“ α -Tocopherol acetate”), there are currently no limits other than cGMPs.

The typical use levels will vary depending on the manufacturer and the product. The maximum recommended use levels in foods for children four and over and adults are 15 mg/serving. The maximum recommended use levels in foods for infants six month and older is 2.5 mg/serving for children one through three years old is 3 mg/serving.

3.0 Dietary Exposure

The intended use of the NutriFusion product will be a substitutional use with the vitamin E extracted from fruits and vegetables replacing other currently authorized commercially available sources of α -tocopherol acetate vitamin E and would not increase dietary exposures. According to the Scientific Report of the 2015 Dietary Guideline Advisory Committee and reviews conducted by the Institute of Medicine (IOM), the current 90th percentile intake of vitamin E from foods and beverages among children 1 through 3 years old and all individuals four and over can be summarized with the table below.

Nutrient	90th Percentile Intake (\geq4) <u>1</u>	90th Percentile Intake (1 - 3)
Vitamin E	13.7 mg/day	6.2 mg/day

While the 2015 Dietary Guideline did not discuss the exposure to vitamin E among infants aged 6-12 months, we can estimate the 90th percentile intake using the following assumption:

- An infant consumes up to 900 grams of infant formula;
- The infant formula contains 9.6 IU/L vitamin (based on product information of a leading brand of infant formula); 2
- The density of infant formula is 1g/ml;
- 90th percentile intake is roughly two times of the average intake.

As such, the 90th percentile intake of vitamin E can be calculated as:

900 grams x 9.6 IU/L x 1L/1000 ml x 1 g/ml x 0.74 mg /IU x 2= 12.79 mg/day.

1 We adopt the highest 90th percentile intake data reported for different age groups. Also, when there are different 90th percentile intake values reported for male and female, we adopt the higher number for the purpose of conservatism.

2 See Product Information: Similac® Advance®, available at: <https://static.abbottnutrition.com/cms-prod/abbottnutrition-2016.com/img/Similac-Advance.pdf>

4.0 Self-limiting Levels of Use

The use of NutriFusion product is not self-limiting and will be controlled closely through the product formulation.

5.0 Experience Based on Common Use in Food before 1958

The NutriFusion α -tocopherol acetate was not marketed prior to 1958. The fruit and vegetables used to extract the vitamin E extract, however, have an extensive history of use prior to 1958. Infants, toddlers, young children, and humans four and over have been consuming the fruit and vegetables used as the sources of the vitamins in most instances, for over a millennia. Moreover, in general, the quantity of whole fruit and vegetable used to extract the vitamin E is comparable to typical consumption levels of that fruit or vegetable. See **Table 8**. While the history of use of these fruits and vegetables prior to 1958 is supportive of the GRAS status, this notification is based on scientific procedures and not common use in foods.

6.0 GRAS Narrative

6.1 Overview

The fruit and vegetables used for the extraction have a long safe consumption history and their GRAS status is well-established. NutriFusion uses process methods that are commonly used such as solvent extraction and solid phase extraction in food processing to extract and isolate the vitamins commonly found in various fruits and vegetables. **Table 8** identifies the fruit or vegetable that could be used as a source for vitamin E, the maximum use level (which is set at 100 percent of the RDI for children over four and adults), and the quantity of the whole fruit or vegetable that, if consumed, would provide 100 percent of the RDI.

Source	Maximum Use Level	Vitamin E Source of Fruits/Vegetables	Comparable Quantity of Fruit/Vegetable
Mustard greens	15 mg/serving	2.01 mg/ 100g <u>3</u>	746.3 g of mustard greens
Swiss chard	15 mg/serving	1.89 mg/100 g <u>4</u>	793.7 g of Swiss chard
Spinach	15 mg/serving	2.08 mg/ 100g <u>5</u>	721.2 g of spinach
Kale	15 mg/serving	1.54 mg/100g <u>6</u>	974 g of kale

According to 21 CFR §170.30(d), “[a] food of natural biological origin that has been widely consumed for its nutrient properties . . . without known detrimental effects, which is subject only to conventional processing as practiced prior to January 1, 1958, and for which no known safety hazard exists, will ordinarily be regarded as GRAS.” As the above table indicates, the intended use of the NutriFusion α -tocopherol acetate is roughly equivalent in all instances with the consumption of five or more servings of fruits and vegetables per day – the existing dietary recommendation. For example, USDA reports 1 cup of cooked spinach weighs 180 grams,7 which would result in 15 mg of vitamin E in about 4 cups (720 grams) or four one-cup servings of spinach. We, therefore, would not expect the NutriFusion α -tocopherol acetate product to contain levels of any unintended soluble constituents from the plant that would present a health or safety concern. We recognize the manufacturing process will result in the extraction of the vitamins as well as any other soluble constituents that may be present in the plant material.

3 See USDA National Nutrient Database for Standard Reference Release 28: Report 11270 “Mustard greens, raw.”

4 See USDA National Nutrient Database for Standard Reference Release 28: Report 11147 “Chard, swiss, raw.”

5 See USDA National Nutrient Database for Standard Reference Release 28: Report 11458 “Spinach, cooked, boiled, drained, without salt” (1 cup of cooked spinach is reported as weighing 180 grams).

6 See USDA National Nutrient Database for Standard Reference Release 28: Report 11233 “Kale, raw.”

7 See USDA National Nutrient Database for Standard Reference Release 28: Report 11458 “Spinach, cooked, boiled, drained, without salt” (1 cup of cooked spinach is reported as weighing 180 grams).

Even if there are incidental constituents concentrated in the finished NutriFusion products along with the vitamins, the level of potential dietary intake of these constituents would be comparable or less than what a consumer would otherwise be exposed to when consuming a comparable level of the plant material used to extract the vitamin.

We also recognize it is possible the manufacturing process could extract the constituent in the fruit or vegetable that may be linked to an allergy or sensitivity. Allergic reactions are triggered by proteins while sensitivities can be triggered by other constituents in a food. In addition, individuals with oral allergy syndrome are usually sensitized to one or more pollens and could react to proteins in specific fresh fruits and vegetables that cross-react with the pollen allergens.⁸ We also recognize some consumers experience reactions that can be triggered by constituents in certain fruits and vegetables other than proteins.

We recognize it is possible one of the allergenic proteins found in the source plant could be present in the extracted vitamin E. To the extent a consumer has an allergy or sensitivity to one of the fruits or vegetables used as the source materials, the vitamin E product could contain that particular substance. Any concerns with allergies and sensitivities are handled through labeling. The labels of the foods bearing the NutriFusion α -tocopherol acetate will identify each fruit or vegetable used in the extraction process. Individuals with a food allergy or sensitivity to one of the fruits or vegetables used in the extraction process, therefore, will be able to identify the possible presence of the plant material and can avoid the product.

We, therefore, view the long history of consumption of fruits and vegetables and the use of conventional food processing extractions methods as supporting the GRAS status of the NutriFusion α -tocopherol acetate. The GRAS status is further demonstrated by a review of the scientific literature. For example, several authoritative bodies including the IOM and the European Food Safety Authority (EFSA) have conducted comprehensive reviews of the safety data related to the vitamins including vitamin E. When comparing the current 90th percentile intake of vitamin E to the safety levels identified by various expert groups, the intended use of the NutriFusion α -tocopherol acetate product can be reasonably expected to be safe.

6.2 Safety Assessment

Vitamin E functions primarily as an antioxidant that prevents the propagation of lipid peroxidation. The Scientific Report of the 2015 Dietary Guidelines Advisory Committee concluded vitamin E is underconsumed among the U.S. population ages 2 years and older. There is no evidence of adverse effects from the consumption of vitamin E in foods. Animal studies show that vitamin E is not mutagenic, carcinogenic, or teratogenic.

Vitamin E is listed as GRAS under 21 CFR §182.8892 (“Tocopherols,”) there are no limitations on use levels other than cGMPs.

⁸ Taylor, Steve L., and Susan L. Hefle. *Food allergies and other food sensitivities* Food Technology 55.9 (2001): 68-84.

- **Absorption, distribution, metabolism, and excretion (ADME) of vitamin E**

The route of vitamin E after oral intake follows in general the pathway of other lipids. Pancreatic and intestinal enzymatic digestion followed by the circulation and distribution to the liver and non-hepatic tissues is the same for all vitamin E forms. ^{9/} Vitamin E absorption from the intestinal lumen is dependent upon biliary and pancreatic secretions, micelle formation, uptake into enterocytes, and chylomicron secretion. ^{10/} In the gastro-intestinal system the absorption rate of vitamin E varies inter-individually between 20%-80%. ^{11/} The transport of vitamin E in blood circulation follows largely that of cholesterol within lipoprotein metabolism. ^{12/} Under normal physiological conditions, vitamin E is mostly transported *via* chylomicrons, very low density lipoproteins (VLDL) and high density lipoproteins (HDL), whereas under fasting conditions low density lipoproteins (LDL) take on this task. ^{13/}

The metabolism of vitamin E starts with one cycle of ω -hydroxylation followed by five cycles of β -oxidation. The principal catabolic pathway is independent of the saturation of the side-chain or the substitution of the chromanol ring system. ^{14/} The major route of excretion of ingested vitamin E is fecal elimination. Excess α -tocopherol, as well as forms of vitamin E not preferentially used, are probably excreted unchanged in bile. ^{15/}

- **Summary of Studies for vitamin E**

Acute toxicity: Mature rats (Charles River COBS, CD) of both sexes were fasted for 16 h prior to administration by gavage of 7000 mg/kg body weight of either alpha-tocopherol poly(ethylene glycol) 1000 succinate (TPGS), polyethylene glycol, or d-alpha-tocopherol acid succinate NF. This was the highest dose practicable. ^{16/} Six of 60 mature rats involved in the test died, 5 within 24 h and 1 within 48 h after treatment. All deaths, however, were attributed to mechanical injury at the time of intubation. The LD50 for the TPGS is >7000 mg/kg body weight for young adult rats of both sexes.

Subchronic toxicity: A 13-week study was conducted by administering d-alpha-tocopherol acetate (vitamin E) in corn oil by gavage to groups of ten male and ten female Fischer 344 rats

⁹ Schmölz, Lisa, et al. "Complexity of vitamin E metabolism." *World journal of biological chemistry* 7.1 (2016): 14.

¹⁰ Gallo- Torres, Hugo E. "Obligatory role of bile for the intestinal absorption of vitamin E." *Lipids* 5.4 (1970): 379-384.

¹¹ Bjørneboe, Anders, Gunn-Elin Aa Bjørneboe, and Christian A. Drevon. "Absorption, transport and distribution of vitamin E." *the Journal of Nutrition* 120.3 (1990): 233-242.

¹² Kollack, Ingrid, et al. "HDL is the major source of vitamin E for type II pneumocytes." *Free Radical Biology and Medicine* 27.7-8 (1999): 882-890.

¹³ Bjørneboe, Anders, et al. "Transport and distribution of α -tocopherol in lymph, serum and liver cells in rats." *Biochimica et Biophysica Acta (BBA)-Molecular Cell Research* 889.3 (1986): 310-315.

¹⁴ Zhao, Yang, et al. "Analysis of multiple metabolites of tocopherols and tocotrienols in mice and humans." *Journal of agricultural and food chemistry* 58.8 (2010): 4844-4852.

¹⁵ Traber, Maret G., and Herbert J. Kayden. "Preferential incorporation of alpha-tocopherol vs gamma-tocopherol in human lipoproteins." *The American journal of clinical nutrition* 49.3 (1989): 517-526.

¹⁶ Krasavage, Walter J., and Clarence J. Terhaar. "d- α -Tocopheryl poly (ethylene glycol) 1000 succinate: acute toxicity, subchronic feeding, reproduction, and teratologic studies in the rat." *Journal of Agricultural and Food Chemistry* 25.2 (1977): 273-278.

at doses of 0, 125, 500 or 2000 mg/kg body weight daily for 13 weeks. 17/ The dose of corn oil given was 3.5 ml/kg. Additional groups of ten males and ten females were included and served as untreated controls. Deaths occurred only in males at 2000 mg/kg. Vitamin E dosing had no effect on body weight or food consumption. The liver-to-body weight ratio of females at 2000 mg/kg was significantly increased. In males, high levels of vitamin E (2000 mg/kg) caused prolongation of both prothrombin and activated partial thromboplastin (APTT) times, reticulocytosis and a decrease in haematocrit values and haemoglobin concentrations. APTT was also lengthened in females at this dose level. High levels (2000 mg/kg) caused haemorrhagic diathesis in both males and females and increased medullary erythropoiesis in the spleen of one male. The above findings indicate that vitamin E administration in excessive amounts is potentially toxic. The no observed adverse effect level (NOAEL) for these observed effects can be determined to be 125 mg/kg.

In another subchronic study, five groups of weanling rats were fed a normal level of alpha-tocopherol acetate (35 mg/kg diet) and 25, 50, 100 and 1000 times the control amount. 18/ After an 8-week feeding, rats fed the 1000x diet had significantly lower feed and protein efficiencies. Mating the animals showed that fertility and survival of pups to weaning were not affected by the diets, but that the number of pups born alive was reduced in the 1000x group. The overall results of this study indicate that dietary levels of 25 and 50 times the normal allowance of vitamin E produced no detectable adverse effects. However, the 1000x level (i.e., 35,000 mg/kg diet) was apparently detrimental to rats.

Chronic study: Groups of weanling female Wistar rats were fed diets containing 0, 25, 250, 2500, 10,000, or 25,000 IU vitamin E/kg diet for 8 and 16 months. 19/ Vitamin E depressed body-weight gain at concentrations of 10,000 and 25,000 IU/kg diet, and increased relative heart and spleen weights were seen at 8 months and 16 months, respectively. There was an increase in plasma alkaline phosphatase and a decrease in the ash content of bone after 16 months at these two dose levels. Prothrombin time was reduced at 12 months, but not at 9 or 16 months. Urinary excretion of creatine and creatinine was normal at 11 months. No histological examinations were reported.

Groups of 60 male and 60 female Charles River CD rats, initial body weight 134 g (males) or 130 g (females), were fed a diet supplemented with dl-alpha-tocopherol acetate at levels calculated to give a dose of 500, 1000, or 2000 mg/kg body weight per day. 20/ A control group received un-supplemented basal diet stated to contain 39 mg vitamin E/kg body weight and 10 mg vitamin K₃/kg body weight. Mortality due to hemorrhage in males during the first 26

17 Abdo, K. M., et al. "Thirteen-week toxicity study of d- α -tocopheryl acetate (vitamin E) in Fischer 344 rats." *Food and Chemical Toxicology* 24.10-11 (1986): 1043-1050.

18 Dymsha, H. A., and J. Park. "EXCESS DIETARY VITAMIN-E IN RATS." *FEDERATION PROCEEDINGS*. Vol. 34. No. 3. 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3998: FEDERATION AMER SOC EXP BIOL, 1975.

19 Yang NY and Desai ID (1977). Effect of high levels of dietary vitamin E on hematological indices and biochemical parameters in rats. *J Nutr* 107: 1410-1417.

20 Wheldon GH, Bhatt A, Keller P, Hummler H (1983). d,1-alpha-Tocopheryl acetate (vitamin E): a long term toxicity and carcinogenicity study in rats. *Int J Vitam Nutr Res* 53: 287-296.

weeks, maximally 10% in the high-dose group, was balanced by a similar number of deaths in control males between weeks 26 and 52, and thereafter alpha-tocopherol did not adversely affect survival. Pro-thrombin times were prolonged in males of all treatment groups at week 4 until week 13, but these returned to normal by week 26 (after initiation of vitamin K supplementation in week 24); females were unaffected. After 52 weeks of treatment, 10 rats/sex/dose were killed, necropsied, and examined histologically. The remaining animals remained on the respective diets until termination at 104 weeks. At necropsy, no macroscopic changes related to treatment were observed.

Reproductive toxicity/teratogenicity: At the end of a 90-day study on d-alpha-tocopherol (polyethylene glycol) 1000 succinate (TPGS), half the rats from each dose group were maintained on their respective diets and used for a reproduction study. 21/ The dietary concentrations of TPGS were 0, 0.002, 0.2, & 2%. The animals were mated on day 112 of treatment to produce the F_{1a} generation and on day 175 to produce the F_{1b} generation. The F₀ animals were maintained on their respective diets to 265-265 days of treatment, then sacrificed and examined histopathologically. Reproductive indices (mean gestation period, litter size, sex ratio, and mortality of pups or parents) were unaffected by treatment. Clinical chemical and haematological parameters were normal in the F₀ generation 10 days before terminal sacrifice. In another investigation on reproductive toxicity of vitamin E showed 1/91 affected mice fetuses at a daily dosage level of 0.4 ml vitamin E. The study, in the form of a letter to the journal, does not contain detailed discussion of the results. In all, the reproduction/teratology studies we reviewed did not indicate that vitamin E had adverse effects on reproductive function.

Genotoxicity: Studies reviewed show the vitamin E is not genotoxic. In investigations of the potential anticlastogenic activity in human lymphocytes *in vitro*, vitamin E did not induce chromosomal damage or sister chromatid exchange. 22/ In the *Salmonella typhimurium* assay, dl-alpha-tocopherol caused a significant decrease in point mutations induced by malonaldehyde or beta-propiolactone. 23/ In a sex-linked recessive lethal mutation assay in *Drosophila*, alpha-tocopheryl acetate in the nutrient medium at 500 IU/kg did not affect the mutation rate in irradiated males but caused a significant reduction in lethal mutations in subsequent generations bred from unirradiated females. 24/

Human studies: Farrell, P. M., & Bieri, J. G. (1975): To assess possible toxic effects of vitamin E supplementation, a group of 28 adults voluntarily ingesting 100 to 800 IU/day of tocopherol for an average of 3 years were evaluated in this study. 25/ No gross evidence of toxicity was apparent on reviewing past medical histories with the subjects. Laboratory screening for toxic

21 See *supra* note 16.

22 Gebhart, E., M. Schinzel, and K. W. Ruprecht. "Cytogenetic studies using various clastogens in two patients with Werner syndrome and control individuals." *Human genetics* 70.4 (1985): 324-327.

23 Shamberger, Raymond J., et al. "Antioxidants reduce the mutagenic effect of malonaldehyde and β-propiolactone: Part IX, antioxidants and cancer." *Mutation Research/Genetic Toxicology* 66.4 (1979): 349-355.

24 Beckman, C., R. M. Roy, and A. Sproule. "Modification of radiation-induced sex-linked recessive lethal mutation frequency by tocopherol." *Mutation research* 105.1/2 (1982): 73-77.

25 Farrell, Philip M., and John G. Bieri. "Megavitamin E supplementation in man." *The American journal of clinical nutrition* 28.12 (1975): 1381-1386.

side effects of vitamin E supplementation by performance of 20 standard clinical blood tests failed to reveal any disturbance in liver, kidney, muscle, thyroid gland, erythrocytes, leukocytes, coagulation parameters, or blood glucose. It is concluded that megavitamin E supplements in this group produced no apparent toxic side effects and that subjective claims for beneficial effects were highly variable.

Tsai, A. C., et al. (1978): A study was conducted to examine the effect of megavitamin E supplementation in healthy college student volunteers. 26/ Two hundred two subjects were randomly assigned to either of two treatment groups, one control and the other experimental. Each subject in the experimental group orally received 600 IU *dl*- α -tocopheryl acetate daily, while each subject in the control group received identical placebo tablets. The experiment was "double blind" and proceeded for a period of 4 weeks. The study indicated that under our experimental conditions, megavitamin E supplementation does not have a significant effect, beneficial or undesirable, on general health conditions, but it can cause a significant reduction of serum thyroid hormone levels and also an elevation of serum triglyceride levels in female.

Steiner, Mangfred (1991): Aggregation of platelets derived from individuals on a dietary supplementation of alpha-tocopherol ranging from 400 to 1200 IU/day showed no significant reduction. 27/ Steiner, Mangfred (1993): while the in vivo human study showed up to 1200 IU/day of vitamin E did not inhibit platelet aggregation, doses of 400 IU/day provide greater than 75% inhibition of platelet adhesion to a variety of adhesive proteins when tested at low shear rate in a laminar flow chamber (*in vitro*). 28/ The antiadhesive effect of vitamin E appears to be related to a reduction in the number and size of pseudopodia upon platelet activation.

KITAGAWA, Makoto. (1989): A study was conducted to investigate the effects of a high level of alpha-tocopherol in healthy college student volunteers. 29/ Of 19 volunteers, 14 were given daily doses of 600 mg (900 IU) of alpha-tocopherol for 12 weeks, and the remaining 5 were given identical placebo capsules. During the study, there were no changes in laboratory values for thyroid, liver, or kidney functions, and coagulation activity or immunoglobulin levels. Healthy status continued without any abnormal symptoms, and without any subjective complaints on the questionnaire. In the control group also, no changes occurred during the investigation.

Meydani et al. (1998): The authors assessed the effects of 4 month of supplementation with 60, 200, or 800 IU (55, 182, or 727 mg) alpha-tocopherol/d on general health, nutrient status, liver enzyme function, thyroid hormone concentrations, creatinine concentrations, serum autoantibodies, killing of *Candida albicans* by neutrophils, and bleeding time in 88 healthy subjects aged >65 years participating in a double-blind, placebo-controlled trial. 30/ No side

26/ Tsai, A. C., et al. "Study on the effect of megavitamin E supplementation in man." *The American journal of clinical nutrition* 31.5 (1978): 831-837.

27/ Steiner M (1991). Influence of vitamin E on platelet function in humans. *J Am Coll Nutr* 10: 466-473.

28/ Steiner M (1993). Vitamin E: more than an antioxidant. *Clin Cardiol* 16: 16-18.

29/ KITAGAWA, Makoto. "Effects of elevated d-alpha (RRR)-tocopherol dosage in man." *Journal of nutritional science and vitaminology* 35.2 (1989): 133-142.

30/ Meydani, Simin Nikbin, et al. "Assessment of the safety of supplementation with different amounts of vitamin E in healthy older adults." *The American journal of clinical nutrition* 68.2 (1998): 311-318.

effects were reported by the subjects. Vitamin E supplementation had no effect on body weight, plasma total proteins, albumin, glucose, plasma lipids or the lipoprotein profile, total bilirubin, alkaline phosphatase, serum aspartate aminotransferase, serum alanine aminotransferase, lactate dehydrogenase, serum urea nitrogen, total red blood cells, white blood cells or white blood cell differential counts, platelet number, bleeding time, hemoglobin, hematocrit, thyroid hormones, or urinary or serum creatinine concentrations. Values from all supplemented groups were within normal ranges for older adults and were not significantly different from values in the placebo group. Vitamin E supplementation had no significant effects on plasma concentrations of other antioxidant vitamins and minerals, glutathione peroxidase, superoxide dismutase, or total homocysteine. There was no significant effect of vitamin E on serum nonspecific immunoglobulin concentrations or anti-DNA and anti-thyroglobulin antibodies. The authors concluded that 4 month of supplementation with 60-800 IU vitamin E/d had no adverse effects.

In summary, the critical effect is on blood clotting and that the study by Meydani et al. (1998) provided the best basis for an evaluation of the tolerable upper intake level. The most recent systematic review conducted by EFSA on vitamin E in 2015 adopted the ULs set by SCF back in 2003. ^{31/} When compared, the highest 90th percentile intake levels among different subpopulation (i.e., 13.7 mg/day) is way below the lowest UL established based on blood clotting for different subpopulation (i.e., 100 mg/day), therefore, the intended use of vitamin E will not result in decreased blood coagulation.

- **IOM (2000) ³²**

The IOM reviewed all data relevant to vitamin E safety and selected hemorrhagic effects as the critical endpoint on which to base the UL for vitamin E for adults. However, the IOM noted the human data fail to demonstrate consistently a causal association between excess vitamin E intake in normal, apparently healthy individuals and any adverse health outcome. The risk of adverse effects resulting from excess intake of α -tocopherols from food and supplements appears to be very low at the highest intakes. The IOM established a UL for adult at 1,000 mg/day and a UL for children 1-3 years at 200 mg/day.

- **European Commission, Scientific Committee on Food (EC SCF 2003) ³³**

The EC SCF reviewed all the evidence and found no adverse effects for oral vitamin E in humans. The expert panel decided that the critical effect is on blood clotting and that the study by Meydani et al. (1998) provided the best basis for an evaluation of the tolerable upper intake level. The NOAEL established in this study was 540 mg/day. The UL for vitamin E was established as 270 mg/day for adults after applying an uncertainty factor of 2. The UL for

³¹ 2015 EFSA Report *Scientific Opinion on Dietary Reference Values for vitamin E as α -tocopherol*. *EFSA Journal*, 13(7), 4149.

³² Bendich, Adrienne. "Dietary reference intakes for vitamin C, vitamin E, selenium, and carotenoids institute of medicine washington, DC: National Academy Press, 2000 ISBN: 0-309-06935-1." *Nutrition* 17.4 (2001): 364.

³³ Scientific Committee on Food of European Commission. "Opinion of the Scientific Committee on Food on the tolerable upper intake level of vitamin E." *Bruxelles: European Commission* (2003).

children age from 1 to 3 was established as 100 mg/day. The UL for children 4-6 was set at 120 mg/day, 7-10 at 160 mg/day, 11-14 at 220 mg/day, and 15-17 at 260 mg/day.

- **Literature Search**

NutriFusion completed an independent review of the recent literature on the adverse effects of vitamin E in humans. We conducted searches in the medical literature database, PubMed, to identify studies indexed since Jan, 2000 to identify reports of human clinical trials related to adverse effects of vitamin E. We conducted the searches using keywords including “vitamin E,” “alpha-tocopherol,” “tolerable,” “safety,” or “toxicity.” We completed the search on July 10, 2018 and identified a total of 104 human studies . We carefully reviewed these studies and conclude that human safety data published subsequent to 2000 do not demonstrate any new toxicological concerns for vitamin E other than those already reported.

We also reviewed the 2015 EFSA Report *Scientific Opinion on Dietary Reference Values for vitamin E as α-tocopherol*. *EFSA Journal*, 13(7), 4149. This report discusses the risk of excess vitamin E intake on Page 10 by referencing the Maydani et al. (1998), through which a UL of 300 mg for adults was adopted. There is no discussion on any new toxicological concerns that have been identified.

6.3 Safety Conclusion

Several expert panels organized by reputable scientific and regulatory agencies including the IOM and EFSA have reviewed the available safety data on the various vitamins and established safety levels when appropriate. The intended use of the NutriFusion α-tocopherol acetate is a substitutional use given that the synthetic vitamin E is currently authorized for use with no limits other than GMPs. The current cumulative intake of vitamin E in children one to three years old, children above four, and adults are all well below the ULs set by the IOM.

Age Groups	90th Percentile Intake (Male) <u>34</u>	90th Percentile Intake (Female)	UL <u>35</u>
1-3	6.2 mg/day	5.5 mg/d	200 mg/d
4-8	7.5 mg/day	7.7 mg/d	300 mg/d
9-13	9.4 mg/day	8.5 mg/d	600 mg/d
14-18	9.9 mg/day	8.6 mg/d	800 mg/d

34 Millen, B. E., A. H. Lichtenstein, and S. Abrams. "Scientific Report of the 2015 Dietary Guidelines Advisory Committee." *Washington (DC): Department of Health and Human Services* (2015).

35 See *supra* note 32.

19-30	12.8 mg/day	9.5 mg/d	1,000 mg/d
31-50	13.7 mg/day	11 mg/d	1,000 mg/d
50 and over	12.5 mg/day	11.1 mg/d	1,000 mg/d

Vitamin E is also considered an underconsumed nutrient in the U.S. by the 2015 Dietary Guidelines Advisory Committee. The long history of consumption of fruits and vegetables as a source of vitamin E also supports its safety. In addition, the underlying safety reviews establish the safety of including the plant-based vitamin E in the diet.

Overall, the existing dietary intake from the proposed use can be considered safe. We, therefore, are of the view that there is a consensus among experts qualified by scientific training and experience to evaluate the safety that there is reasonable certainty the intended use of the NutriFusion α -tocopherol acetate product is not harmful.

In summary, due to the demonstrated safe consumption history of the fruits and vegetables that are used to make the NutriFusion α -tocopherol acetate product, as well as the expert panels opinions, we concluded that the intended use of NutriFusion α -tocopherol acetate product in foods that are otherwise authorized for the addition of vitamins can be considered GRAS through scientific procedures.

7.0 List of Supporting Data and Information

All of the following data and information are publicly available.

- USDA National Nutrient Database for Standard Reference Release 28.
- Taylor, Steve L., and Susan L. Hefle. Food allergies and other food sensitivities *Food Technology* 55.9 (2001): 68-84.
- Schmölz, Lisa, et al. "Complexity of vitamin E metabolism." *World journal of biological chemistry* 7.1 (2016): 14.
- Gallo-Torres, Hugo E. "Obligatory role of bile for the intestinal absorption of vitamin E." *Lipids* 5.4 (1970): 379-384.
- Bjørneboe, Anders, Gunn-Elin Aa Bjørneboe, and Christian A. Drevon. "Absorption, transport and distribution of vitamin E." *the Journal of Nutrition* 120.3 (1990): 233-242.
- Kolleck, Ingrid, et al. "HDL is the major source of vitamin E for type II pneumocytes." *Free Radical Biology and Medicine* 27.7-8 (1999): 882-890.
- Bjørneboe, Anders, et al. "Transport and distribution of α -tocopherol in lymph, serum and liver cells in rats." *Biochimica et Biophysica Acta (BBA)-Molecular Cell Research* 889.3 (1986): 310-315.
- Zhao, Yang, et al. "Analysis of multiple metabolites of tocopherols and tocotrienols in mice and humans." *Journal of agricultural and food chemistry* 58.8 (2010): 4844-4852.
- Traber, Maret G., and Herbert J. Kayden. "Preferential incorporation of alpha-tocopherol vs gamma-tocopherol in human lipoproteins." *The American journal of clinical nutrition* 49.3 (1989): 517-526.
- Krasavage, Walter J., and Clarence J. Terhaar. "d-. alpha.-Tocopheryl poly (ethylene glycol) 1000 succinate: acute toxicity, subchronic feeding, reproduction, and teratologic studies in the rat." *Journal of Agricultural and Food Chemistry* 25.2 (1977): 273-278.
- Abdo, K. M., et al. "Thirteen-week toxicity study of d- α -tocopheryl acetate (vitamin E) in Fischer 344 rats." *Food and Chemical Toxicology* 24.10-11 (1986): 1043-1050.
- Dymsha, H. A., and J. Park. "EXCESS DIETARY VITAMIN-E IN RATS." *FEDERATION PROCEEDINGS*. Vol. 34. No. 3. 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3998: FEDERATION AMER SOC EXP BIOL, 1975.

- Yang NY and Desai ID (1977). Effect of high levels of dietary vitamin E on hematological indices and biochemical parameters in rats. *J Nutr* 107: 1410-1417.
- Wheldon GH, Bhatt A, Keller P, Hummler H (1983). d,1-alpha-Tocopheryl acetate (vitamin E): a long term toxicity and carcinogenicity study in rats. *Int J Vitam Nutr Res* 53: 287-296.
- Gebhart, E., M. Schinzel, and K. W. Ruprecht. "Cytogenetic studies using various clastogens in two patients with Werner syndrome and control individuals." *Human genetics* 70.4 (1985): 324-327.
- Shamberger, Raymond J., et al. "Antioxidants reduce the mutagenic effect of malonaldehyde and β -propiolactone: Part IX, antioxidants and cancer." *Mutation Research/Genetic Toxicology* 66.4 (1979): 349-355.
- Beckman, C., R. M. Roy, and A. Sproule. "Modification of radiation-induced sex-linked recessive lethal mutation frequency by tocopherol." *Mutation research* 105.1/2 (1982): 73-77.
- Farrell, Philip M., and John G. Bieri. "Megavitamin E supplementation in man." *The American journal of clinical nutrition* 28.12 (1975): 1381-1386.
- Tsai, A. C., et al. "Study on the effect of megavitamin E supplementation in man." *The American journal of clinical nutrition* 31.5 (1978): 831-837.
- Steiner M (1991). Influence of vitamin E on platelet function in humans. *J Am Coll Nutr* 10: 466-473.
- Steiner M (1993). Vitamin E: more than an antioxidant. *Clin Cardiol* 16: 16-18.
- KITAGAWA, Makoto. "Effects of elevated d-alpha (RRR)-tocopherol dosage in man." *Journal of nutritional science and vitaminology* 35.2 (1989): 133-142.
- Meydani, Simin Nikbin, et al. "Assessment of the safety of supplementation with different amounts of vitamin E in healthy older adults." *The American journal of clinical nutrition* 68.2 (1998): 311-318.
- 2015 EFSA Report *Scientific Opinion on Dietary Reference Values for vitamin E as α -tocopherol*. *EFSA Journal*, 13(7), 4149.
- Bendich, Adrienne. "Dietary reference intakes for vitamin C, vitamin E, selenium, and carotenoids institute of medicine washington, DC: National Academy Press, 2000 ISBN: 0-309-06935-1." *Nutrition* 17.4 (2001): 364.

- Scientific Committee on Food of European Commission. "Opinion of the Scientific Committee on Food on the tolerable upper intake level of vitamin E." Bruxelles: European Commission (2003).
- Millen, B. E., A. H. Lichtenstein, and S. Abrams. "Scientific Report of the 2015 Dietary Guidelines Advisory Committee." Washington (DC): Department of Health and Human Services (2015).

Six pages of the following copyrighted material was removed:

AOAC Official Method 2012.09
Vitamins A and E in Infant Formula and Adult/Pediatric Nutritional Formula
HPLC with UV and Fluorescence Detection
First Action 2012

Frequently Asked Questions for Industry on Nutrition Facts Labeling Requirements

The following is one of the FAQs for industry the U.S. Food and Drug Administration has provided related to recent changes to the Nutrition Facts label.

For more FAQs, visit [Industry FAQs on the Changes to the Nutrition Facts Label](#).

What are Daily Values and where can I find them?

Daily Values are comprised of two sets of reference values for reporting nutrients in nutrition labels—the Daily Reference Values (DRVs) and the Reference Daily Intakes (RDIs). To limit consumer confusion, the single term “Daily Value” is used to designate both the DRVs and RDIs. The DVs are used to calculate the % Daily Values that consumers see on the Nutrition and Supplement Facts labels. The % Daily Value helps consumers understand how the amount of a nutrient that is present in a serving of a food fits into their total daily diet, and allows them to compare the nutritional value of food products.

RDIs - Nutrients					
Nutrient	Unit of measure	Adults and Children ≥ 4 years	¹ Infants through 12 months	Children 1 through 3 years	Pregnant women and lactating women
Vitamin A	Micrograms RAE ² (mcg)	900	500	300	1,300
Vitamin C	Milligrams (mg)	90	50	15	120
Calcium	Milligrams (mg)	1,300	260	700	1,300
Iron	Milligrams (mg)	18	11	7	27
Vitamin D	Micrograms (mcg) ³	20	10	15	15
Vitamin E	Milligrams (mg) ⁴	15	5	6	19
Vitamin K	Micrograms (mcg)	120	2.5	30	90
Thiamin	Milligrams (mg)	1.2	0.3	0.5	1.4
Riboflavin	Milligrams (mg)	1.3	0.4	0.5	1.6
Niacin	Milligrams NE ⁵ (mg)	16	4	6	18
Vitamin B ₆	Milligrams (mg)	1.7	0.3	0.5	2
Folate ⁶	Micrograms DFE ⁷ (mcg)	400	80	150	600
Vitamin B ₁₂	Micrograms (mcg)	2.4	0.5	0.9	2.8
Biotin	Micrograms (mcg)	30	6	8	35
Pantothenic acid	Milligrams (mg)	5	1.8	2	7
Phosphorus	Milligrams (mg)	1,250	275	460	1,250
Iodine	Micrograms (mcg)	150	130	90	290
Magnesium	Milligrams (mg)	420	75	80	400
Zinc	Milligrams (mg)	11	3	3	13
Selenium	Micrograms (mcg)	55	20	20	70
Copper	Milligrams (mg)	0.9	0.2	0.3	1.3
Manganese	Milligrams (mg)	2.3	0.6	1.2	2.6
Chromium	Micrograms (mcg)	35	5.5	11	45
Molybdenum	Micrograms (mcg)	45	3	17	50
Chloride	Milligrams (mg)	2,300	570	1,500	2,300
Potassium	Milligrams (mg)	4,700	700	3,000	5,100
Choline	Milligrams (mg)	550	150	200	550

Source: <https://s3.amazonaws.com/public-inspection.federalregister.gov/2016-11867.pdf> (pages 903-904)

RDIs - Nutrients					
Nutrient	Unit of measure	Adults and Children ≥ 4 years	¹ Infants through 12 months	Children 1 through 3 years	Pregnant women and lactating women
Protein	Grams (g)	N/A	11	N/A	⁸ 71

¹ RDIs are based on dietary reference intake recommendations for infants through 12 months of age.

² RAE = Retinol Activity Equivalents; 1 microgram RAE=1 microgram retinol, 2 microgram supplemental β-carotene, 12 micrograms β-carotene, or 24 micrograms α-carotene, or 24 micrograms β-cryptoxanthin.

³ The amount of vitamin D may, but is not required to, be expressed in international units (IU), in addition to the mandatory declaration in mcg. Any declaration of the amount of vitamin D in IU must appear in parentheses after the declaration of the amount of vitamin D in mcg.

⁴ 1 mg α-tocopherol (label claim) = 1 mg α-tocopherol = 1 mg RRR-α-tocopherol = 2 mg all rac-α-tocopherol.

⁵ NE = Niacin equivalents, 1 mg NE = 1 mg niacin = 60 milligrams tryptophan.

⁶ "Folate" and "Folic Acid" must be used for purposes of declaration in the labeling of conventional foods and dietary supplements. The declaration for folate must be in mcg DFE (when expressed as a quantitative amount by weight in a conventional food or a dietary supplement), and percent DV based on folate in mcg DFE. Folate may be expressed as a percent DV in conventional foods. When folic acid is added or when a claim is made about the nutrient, folic acid must be declared in parentheses, as mcg of folic acid.

⁷ DFE = Dietary Folate Equivalents; 1 DFE = 1 mcg naturally-occurring folate = 0.6 mcg folic acid.

⁸ Based on the reference caloric intake of 2,000 calories for adults and children aged 4 years and older, and for pregnant women and lactating women.

Tao, Xin

From: Sent by NCBI <nobody@ncbi.nlm.nih.gov>
Sent: Tuesday, July 10, 2018 2:50 PM
To: Chambers, Dianne L.
Subject: ("vitamin e"[Title/Abstract] OR "alpha tocerphero - PubMed

This message contains search results from the National Center for Biotechnology Information ([NCBI](#)) at the U.S. National Library of Medicine ([NLM](#)). Do not reply directly to this message

Sent on: Tue Jul 10 14:48:29 2018

Search: (("vitamin e"[Title/Abstract] OR "alpha tocerpherol"[Title/Abstract])) AND (ul[Text Word] OR tolerable[Text Word] OR safety[Text Word] OR toxicity[Text Word]) Filters: Clinical Trial, From 2000/01/01 to 2018/07/09, Humans

PubMed Results

Items 1 - 104 of 104 ([Display the 104 citations in PubMed](#))

1. Int J Dermatol. 2017 Jun;56(6):686-690. doi: 10.1111/ijd.13607. Epub 2017 Mar 30.

[A randomized, double-blind, placebo-controlled trial to determine the efficacy and safety of lactoferrin with vitamin E and zinc as an oral therapy for mild to moderate acne vulgaris.](#)

[Chan H](#)¹, [Chan G](#)¹, [Santos J](#)², [Dee K](#)², [Co JK](#)².

Author information:

1. Clinical Trial Management and Testing Associates, Inc., Alabang, Muntinlupa City, Philippines.
2. Research and Development Division, United Laboratories, Inc., Mandaluyong City, Philippines.

Abstract

Lactoferrin is an iron-binding milk-derived protein that has shown antibacterial and anti-inflammatory effects in vitro and in vivo. The objective of this study was to determine the efficacy and safety of lactoferrin, combined with vitamin E and zinc, for mild to moderate acne vulgaris. In this randomized, double-blind, placebo-controlled trial, 168 subjects aged 13-40 years old were randomly assigned to take either a capsule formulation containing lactoferrin with vitamin E and zinc or placebo twice a day for 3 months. The primary outcome measure was a reduction in the number of acne lesions compared to placebo. A total of 164 subjects completed the study per protocol. The lactoferrin group (n = 82) showed a significant median percent reduction in total lesions as early as 2 weeks (14.5%, P = 0.0120), with the maximum reduction occurring at

week 10 (28.5%, $P < 0.0001$) compared to placebo group ($n = 82$). Maximum reduction in comedones (32.5%, $P < 0.0001$) and inflammatory lesions (44%, $P < 0.0001$) was also seen at week 10 compared to placebo. Sebum scores were improved by week 12. No adverse events were observed during the trial. A twice daily regimen of lactoferrin with vitamin E and zinc significantly reduced acne lesions in people with mild to moderate acne vulgaris.

PMID: 28369875 [Indexed for MEDLINE]

[Similar articles](#)



2. Trials. 2016 Aug 12;17:400. doi: 10.1186/s13063-016-1524-9.

[Opportunities and challenges in incorporating ancillary studies into a cancer prevention randomized clinical trial.](#)

[Goodman PJ](#)¹, [Tangen CM](#)², [Darke AK](#)², [Arnold KB](#)², [Hartline J](#)³, [Yee M](#)³, [Anderson K](#)³, [Caban-Holt A](#)⁴, [Christen WG](#)⁵, [Cassano PA](#)⁶, [Lance P](#)⁷, [Klein EA](#)⁸, [Crowley JJ](#)³, [Minasian LM](#)⁹, [Meyskens FL](#)¹⁰.

Author information:

1. SWOG Statistical Center, Fred Hutchinson Cancer Research Center, 1100 Fairview Ave. N, M3-C102, Seattle, WA, 98109, USA. pgoodman@fredhutch.org.
2. SWOG Statistical Center, Fred Hutchinson Cancer Research Center, 1100 Fairview Ave. N, M3-C102, Seattle, WA, 98109, USA.
3. SWOG Statistical Center, Cancer Research and Biostatistics, Seattle, WA, USA.
4. Sanders-Brown Center on Aging, University of Kentucky, Lexington, KY, USA.
5. Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA.
6. Division of Nutritional Sciences, Cornell University, Ithaca, NY, USA.
7. Arizona Cancer Center, University of Arizona, Phoenix, AZ, USA.
8. Glickman Urological and Kidney Institute, Cleveland Clinic, Cleveland, OH, USA.
9. Division of Cancer Prevention, National Cancer Institute, Bethesda, MD, USA.
10. University of California at Irvine, Orange, CA, USA.

Abstract

BACKGROUND:

The Selenium and Vitamin E Cancer Prevention Trial (SELECT) was a randomized, double-blind, placebo-controlled, prostate cancer prevention study funded by the National Cancer Institute and conducted by SWOG (Southwest Oncology Group). A total of 35,533 men were assigned randomly to one of four treatment groups (vitamin E + placebo, selenium + placebo, vitamin E + selenium, placebo + placebo). At the time of the trial's development, NIH had invested substantial resources in evaluating the potential benefits of these antioxidants. To capitalize on the knowledge gained from following a large cohort of healthy, aging males on the effects of selenium and/or vitamin E, ancillary studies with other disease endpoints were solicited.

METHODS:

Four ancillary studies were added. Each drew from the same population but had independent objectives and an endpoint other than prostate cancer. These studies fell into two categories: those prospectively enrolling and following participants (studies of Alzheimer's disease and respiratory function) and those requiring a retrospective medical record review after a reported event (cataracts/age-related macular degeneration and colorectal screening). An examination of the challenges and opportunities of adding ancillary studies is provided. The impact of the ancillary studies on adherence to SELECT was evaluated using a Cox proportional hazards model.

RESULTS:

While the addition of ancillary studies appears to have improved participant adherence to the primary trial, this did not come without added complexity. Activation of the ancillary studies happened after the SELECT randomizations had begun resulting in accrual problems to some of the studies. Study site participation in the ancillary trials varied greatly and depended on the interest of the study site principal investigator. Procedures for each were integrated into the primary trial and all monitoring was done by the SELECT Data and Safety Monitoring Committee. The impact of the early closure of the primary trial was different for each of the ancillary trials.

CONCLUSIONS:

The ancillary studies allowed study sites to broaden the research opportunities for their participants. Their implementation was efficient because of the established infrastructure of the primary trial. Implementation of these ancillary trials took substantial planning and coordination but enriched the overall primary trial.

TRIAL REGISTRATION:

[NCT00006392](#)-S0000 : Selenium and Vitamin E in Preventing Prostate Cancer (SELECT) (4 October 2000).
[NCT00780689](#)-S0000A : Prevention of Alzheimer's Disease by Vitamin E and Selenium (PREADVISE) (25 June 2002).
[NCT00784225](#)-S0000B : Vitamin E and/or Selenium in Preventing Cataract and Age-Related Macular Degeneration in Men on SELECT SWOG-S0000 (SEE) (31 October 2008).
[NCT00706121](#)-S0000D : Effect of Vitamin E and/or Selenium on Colorectal Polyps in Men Enrolled on SELECT Trial SWOG-S0000 (ACP) (26 June 2008).
[NCT00063453](#)-S0000C : Vitamin E and/or Selenium in Preventing Loss of Lung Function in Older Men Enrolled on SELECT Clinical Trial SWOG-S0000 (26 June 2003).

PMCID: PMC4983010 [Free PMC Article](#)

PMID: 27519183 [Indexed for MEDLINE]

[Similar articles](#)



3. BMJ Open. 2016 Jul 7;6(7):e010781. doi: 10.1136/bmjopen-2015-010781.

[Migration and head penetration of Vitamin-E diffused cemented polyethylene cup compared to standard cemented cup in total hip arthroplasty: study protocol for a randomised, double-blind,](#)

controlled trial (E1 HIP).

[Sköldenberg O¹](#), [Rysinska A¹](#), [Chammout G¹](#), [Salemyr M¹](#), [Muren O¹](#), [Bodén H¹](#), [Eisler T¹](#).

Author information:

1. Department of Clinical Sciences, Danderyd Hospital, Karolinska Institutet, Stockholm, Sweden.

Abstract

INTRODUCTION:

In vitro, Vitamin-E-diffused, highly cross-linked polyethylene (PE) has been shown to have superior wear resistance and improved mechanical properties when compared to those of standard highly cross-linked PE liners used in total hip arthroplasty (THA). The aim of the study is to evaluate the safety of a new cemented acetabular cup with Vitamin-E-doped PE regarding migration, head penetration and clinical results.

METHODS AND ANALYSIS:

In this single-centre, double-blinded, randomised controlled trial, we will include 50 patients with primary hip osteoarthritis scheduled for THA and randomise them in a 1:1 ratio to a cemented cup with either argon gas-sterilised PE (control group) or Vitamin-E-diffused PE (vitamin-e group). All patients and the assessor of the primary outcome will be blinded and the same uncemented stem will be used for all participants. The primary end point will be proximal migration of the cup at 2 years after surgery measured with radiostereometry. Secondary end points include proximal migration at other follow-ups, total migration, femoral head penetration, clinical outcome scores and hip-related complications. Patients will be followed up at 3 months and at 1, 2, 5 and 10 years postoperatively.

RESULTS:

Results will be analysed using 95% CIs for the effect size. A regression model will also be used to adjust for stratification factors.

ETHICS AND DISSEMINATION:

The ethical committee at Karolinska Institutet has approved the study. The first results from the study will be disseminated to the medical community via presentations and publications in relevant medical journals when the last patient included has been followed up for 2 years.

TRIAL REGISTRATION NUMBER:

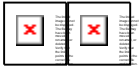
[NCT02254980](#).

Published by the BMJ Publishing Group Limited. For permission to use (where not already granted under a licence) please go to <http://www.bmj.com/company/products-services/rights-and-licensing/>

PMCID: PMC4947731 **Free PMC Article**

PMID: 27388352 [Indexed for MEDLINE]

[Similar articles](#)



Vitamin E for the treatment of E-antigen-positive chronic hepatitis B in paediatric patients: results of a randomized phase 2 controlled study.

[Fiorino S](#)^{1,2}, [Loggi E](#)¹, [Verucchi G](#)¹, [Comparcola D](#)³, [Vukotic R](#)¹, [Pavoni M](#)¹, [Grandini E](#)¹, [Cursaro C](#)¹, [Maselli S](#)⁴, [Bacchi Reggiani ML](#)⁵, [Puggioli C](#)⁴, [Badia L](#)¹, [Galli S](#)⁶, [Viale P](#)¹, [Bernardi M](#)¹, [Andreone P](#)¹.

Author information:

1. Dipartimento di Scienze Mediche e Chirurgiche, Università di Bologna, Bologna, Italy.
2. Unità Operativa di Medicina Interna, Ospedale Maggiore, AUSL Bologna, Bologna, Italy.
3. Unità Operativa Malattie Epatometaboliche, Ospedale Pediatrico del Bambin Gesù, Rome, Italy.
4. Unità Operativa di Farmacia Clinica, Azienda Ospedaliero Universitaria di Bologna, Policlinico Sant'Orsola-Malpighi, Bologna, Italy.
5. Unità Operativa Malattie Cardiovascolari, Università di Bologna, Bologna, Italy.
6. Unità Operativa di Microbiologia e Virologia, Azienda Ospedaliero Universitaria di Bologna, Policlinico Sant'Orsola-Malpighi, Bologna, Italy.

Abstract

BACKGROUND & AIMS:

The treatment of chronic hepatitis B infection (CHB) in children is still an area of great uncertainty. Vitamin E is an immunostimulating/antioxidant compound proven to be safe and effective for the treatment of adult CHB. The aim of this phase 2 controlled study was to evaluate the safety and efficacy of vitamin E for the treatment of paediatric HBeAg-positive CHB.

METHODS:

Forty-six children were randomized in a 1:1 ratio to receive vitamin E at a dose of 15 mg/kg/day (in galenic preparation) or no treatment for 12 months and were monitored for the subsequent 12 months. Clinical, biochemical, haematological and serovirological evaluations were carried out every 3 months.

RESULTS:

No significant side effects were associated with the vitamin E treatment. At the end of the study, anti-HBe seroconversion was obtained in 7 of 23 (30.4%) of vitamin E-treated versus 1 of 23 (4.3%) of the control patients ($P = 0.05$), while a virological response (≥ 2 log decrease in HBV-DNA from baseline) was observed in 9 of 23 (39.1%) vs. 2 of 23 (8.7%) respectively ($P = 0.035$).

CONCLUSIONS:

Vitamin E administration for the treatment of paediatric CHB at the tested dosage has no significant side effects and may induce anti-HBe seroconversion. Vitamin E could represent a tool for the treatment of

paediatric CHB.

© 2016 John Wiley & Sons A/S. Published by John Wiley & Sons Ltd.

PMID: 27333382 [Indexed for MEDLINE]

[Similar articles](#)



5. Cancer Chemother Pharmacol. 2016 Jul;78(1):157-65. doi: 10.1007/s00280-016-3048-0. Epub 2016 Jun 8.

Pharmacokinetics and safety of vitamin E δ -tocotrienol after single and multiple doses in healthy subjects with measurement of vitamin E metabolites.

[Mahipal A](#)¹, [Klapman J](#)¹, [Vignesh S](#)², [Yang CS](#)³, [Neuger A](#)⁴, [Chen DT](#)⁵, [Malafa MP](#)⁶.

Author information:

1. Department of Gastrointestinal Oncology, H. Lee Moffitt Cancer Center and Research Institute, 12902 Magnolia Drive FOB-2, Tampa, FL, 33612, USA.

2. Division of Gastroenterology and Hepatology, SUNY Health Sciences Center at Brooklyn, Brooklyn, NY, 11203, USA.

3. Department of Chemical Biology, Ernest Mario School of Pharmacy, Rutgers, The State University of New Jersey, Piscataway Township, NJ, USA.

4. Translational Research Core, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA.

5. Department of Biostatistics and Bioinformatics, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA.

6. Department of Gastrointestinal Oncology, H. Lee Moffitt Cancer Center and Research Institute, 12902 Magnolia Drive FOB-2, Tampa, FL, 33612, USA. mokenge.malafa@moffitt.org.

Abstract

PURPOSE:

Vitamin E delta-tocotrienol (VEDT) has demonstrated chemopreventive and antineoplastic activity in preclinical models. The aim of our study was to determine the safety and pharmacokinetics of VEDT and its metabolites after single- and multiple-dose administrations in healthy subjects.

METHODS:

Thirty-six subjects received from 100 to 1600 mg of oral VEDT as a single dose or twice daily for 14 consecutive days. A 3 + 3 dose escalation design was utilized. Pharmacokinetic data were derived from high-performance liquid chromatography (HPLC) assays. Serial blood and urine samples were collected before and during VEDT administration, with serum and urine metabolites assessed using HPLC.

RESULTS:

No drug-related adverse events were observed. Pharmacokinetic parameters for single and multiple doses were, respectively, as follows (shown as range): time to maximum concentration of 4-9.3 and 4.7-7.3 h, maximum concentration of 795.6-3742.6 and 493.3-3746 ng/mL, half-life of 1.7-5.9 and 2.3-6.9 h, and 0-12 h area under the curve of 4518.7-20,781.4 and 1987.7-22,171.2 ng h/mL. Plasma tocotrienols were significantly increased after VEDT administration, indicating oral bioavailability of VEDT in humans. Plasma and urine levels of metabolites, δ -carboxyethyl hydroxychroman, and δ -carboxymethylbutyl hydroxychroman were elevated after VEDT administration in a dose-dependent manner and were 30-60 times significantly higher than δ -tocotrienol levels. VEDT can be safely administered at doses up to 1600 mg twice daily. Plasma VEDT concentrations were comparable to those obtained in VEDT-treated mice in which tumor growth was delayed.

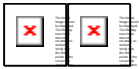
CONCLUSIONS:

Our results suggest that VEDT can be safely consumed by healthy subjects and achieve bioactive levels, supporting the investigation of VEDT for chemoprevention.

PMCID: PMC4939900 **Free PMC Article**

PMID: 27278668 [Indexed for MEDLINE]

[Similar articles](#)



6. J Hum Nutr Diet. 2016 Oct;29(5):652-61. doi: 10.1111/jhn.12381. Epub 2016 May 27.

[Maternal supplementation with a megadose of vitamin A reduces colostrum level of \$\alpha\$ -tocopherol: a randomised controlled trial.](#)

[Grilo EC](#)¹, [Medeiros WF](#)², [Silva AG](#)², [Gurgel CS](#)², [Ramalho HM](#)³, [Dimenstein R](#)².

Author information:

1. Department of Biochemistry, Biosciences Center, Federal University of Rio Grande do Norte (UFRN), Natal, Brazil. evellyn-cg@hotmail.com.

2. Department of Biochemistry, Biosciences Center, Federal University of Rio Grande do Norte (UFRN), Natal, Brazil.

3. Department of Biotechnology, School of Health, Potiguar University (UnP), Laurate International Universities, Natal, Brazil.

Abstract

BACKGROUND:

Maternal supplementation with vitamin A is one of the strategies for controlling its deficiency in the mother-child dyad, although studies with animals showed that supplementation with high doses of vitamin A reduces the levels of α -tocopherol (vitamin E) in the mother's serum and milk. The objective of the present study was

to assess the influence of maternal supplementation with vitamin A on the concentration of retinol and α -tocopherol in human milk.

METHODS:

Healthy puerperal women were randomly distributed into a control group (n = 44) and a supplemented group (n = 44). Blood and colostrum samples were collected after delivery, and mature milk samples were collected 30 days later. The supplemented group received 200 000 IU of retinyl palmitate after the first colostrum collection. The retinol and α -tocopherol levels in the samples were determined by high-performance liquid chromatography.

RESULTS:

The mean (SD) retinol and α -tocopherol levels in the maternal serum were considered adequate at 46.4 (15.9) and 1023.6 (380.4) $\mu\text{g dL}^{-1}$, respectively. The colostrum retinol levels of the supplemented group increased significantly 24 h after the intervention ($P < 0.001$). However, the retinol levels in the mature milk of both groups did not differ ($P > 0.05$). Moreover, after maternal supplementation with vitamin A, the colostrum α -tocopherol level decreased by 16.4%, which is a significant reduction ($P < 0.05$). However, vitamin A supplementation did not affect the α -tocopherol level of mature milk ($P > 0.05$).

CONCLUSIONS:

Maternal supplementation with high doses of vitamin A increased the colostrum level of this nutrient but reduced the bioavailability of α -tocopherol, which may harm the newborn's health because newborns have limited vitamin E reserves.

© 2016 The British Dietetic Association Ltd.

PMID: 27231056 [Indexed for MEDLINE]

[Similar articles](#)



7. EBioMedicine. 2015 Nov 14;2(12):1987-95. doi: 10.1016/j.ebiom.2015.11.025. eCollection 2015 Dec.

A Phase I Safety, Pharmacokinetic, and Pharmacodynamic Presurgical Trial of Vitamin E δ -tocotrienol in Patients with Pancreatic Ductal Neoplasia.

[Springett GM](#)¹, [Husain K](#)¹, [Neuger A](#)², [Centeno B](#)³, [Chen DT](#)⁴, [Hutchinson TZ](#)¹, [Lush RM](#)², [Sebti S](#)⁵, [Malafa MP](#)¹.

Author information:

1. Department of Gastrointestinal Oncology, Tampa, FL, USA.
2. Translational Research Core, Tampa, FL, USA.
3. Department of Cytopathology, Tampa, FL, USA.

4. Biostatistics Core, Tampa, FL, USA.

5. Department of Drug Discovery, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA.

Abstract

BACKGROUND:

Vitamin E δ -tocotrienol (VEDT), a natural vitamin E from plants, has shown anti-neoplastic and chemoprevention activity in preclinical models of pancreatic cancer. Here, we investigated VEDT in patients with pancreatic ductal neoplasia in a window-of-opportunity preoperative clinical trial to assess its safety, tolerability, pharmacokinetics, and apoptotic activity.

METHODS:

Patients received oral VEDT at escalating doses (from 200 to 3200 mg) daily for 13 days before surgery and one dose on the day of surgery. Dose escalation followed a three-plus-three trial design. Our primary endpoints were safety, VEDT pharmacokinetics, and monitoring of VEDT-induced neoplastic cell apoptosis (ClinicalTrials.gov number [NCT00985777](https://clinicaltrials.gov/ct2/show/study/NCT00985777)).

FINDINGS:

In 25 treated patients, no dose-limiting toxicity was encountered; thus no maximum-tolerated dose was reached. One patient had a drug-related adverse event (diarrhea) at a 3200-mg daily dose level. The effective half-life of VEDT was ~ 4 h. VEDT concentrations in plasma and exposure profiles were quite variable but reached levels that are bioactive in preclinical models. Biological activity, defined as significant induction of apoptosis in neoplastic cells as measured by increased cleaved caspase-3 levels, was seen in the majority of patients at the 400-mg to 1600-mg daily dose levels.

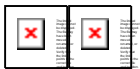
INTERPRETATION:

VEDT from 200 to 1600 mg daily taken orally for 2 weeks before pancreatic surgery was well tolerated, reached bioactive levels in blood, and significantly induced apoptosis in the neoplastic cells of patients with pancreatic ductal neoplasia. These promising results warrant further clinical investigation of VEDT for chemoprevention and/or therapy of pancreatic cancer.

PMCID: PMC4703733 [Free PMC Article](#)

PMID: 26844278 [Indexed for MEDLINE]

[Similar articles](#)



8. Minerva Ginecol. 2015 Dec;67(6):523-31.

[Hyaluronic acid and vitamins are effective in reducing vaginal atrophy in women receiving radiotherapy.](#)

Author information:

1. Department of Clinical and Molecular Medicine, La Sapienza University, Rome, Italy - mariano.bizzarri@uniroma1.it.

Abstract

AIM:

During the last decades, therapies targeting cervical cancer have been considerably improved. Surgery and radiotherapy (RT) represent the main common therapeutic approach in cervical cancer. In order to minimize the side effects of radiotherapy approach, several protocols have been developed such as brachytherapy (BRT). Among the side effects associated with RT, the vaginal atrophy is the most important and common one. Vaginal atrophy, in turn, leads to additional alterations like inflammation, associated to relevant symptoms such as itching, burning and dyspareunia. All these alterations heavily affect the quality of women's life. The aim of our study was to evaluate the toxicity induced by RT on vaginal mucosa, and the adjuvant action of a product containing LMWHA, vitamin A, and Vitamin E (Santes®, Lo.Li. Pharma, Rome, Italy). The introduction of adjuvant therapies may have likely had a relevant place in providing that result.

METHODS:

A prospective randomized study was designed. From October 2006 to October 2008, 45 women with a mean age 38 ± 6 years were enrolled. After surgery, all patients were treated with 4 weeks of RT and 4 weeks of BRT, concomitantly with chemotherapy. They were randomly assigned in two groups: 23 women were treated with two suppositories (Santes®) per day for 4 months. For the first two months the preventive treatment was simultaneous to RT and BRT. Instead the control groups for composed by 22 patients and they did not undergo any treatment during RT. To evaluate the efficacy of Santes® treatment three biopsies were performed.

RESULTS:

At the second biopsy, after the BRT therapy, the treated group showed a statistically significant improvement ($P < 0.05$ vs. control) on inflammation, cell atypia, fibrosis, mucositis and bleeding. At the third biopsy, two months after BRT, further statistically improvement were observed for all RT/BRT associated side effects. The treatment showed an efficacy also in terms of pain severity.

CONCLUSION:

Our data suggest that low molecular weight HA shows good performances in treating RT-damaged tissue and plays a key role in all steps of the healing process. Indeed the results shows that women exposed to RT treatments and simultaneously treated with Santes®, had an optimal resolution of vaginal atrophy and related symptoms.

PMID: 26788875 [Indexed for MEDLINE]

[Similar articles](#)



Randomized, controlled, double-blind clinical study evaluating the safety and efficacy of MD2011001 cream in mild-to-moderate atopic dermatitis of the face and neck in children, adolescents and adults.

[Patrizi A](#)¹, [Raone B](#)¹, [Neri I](#)¹, [Gurioli C](#)¹, [Carbonara M](#)², [Cassano N](#)³, [Vena GA](#)³.

Author information:

1. a Department of Specialized , Experimental and Diagnostic Medicine, Dermatology Unit, University of Bologna , Bologna , Italy .
2. b Regional Office of Bari, Italian Statistical Institute , Bari , Italy , and.
3. c Dermatology and Venereology Private Practice , Bari and Barletta , Italy.

Abstract

INTRODUCTION:

This mono-center randomized, controlled, double-blind study evaluates the safety and efficacy of MD2011001 cream versus placebo, in mild-to-moderate atopic dermatitis (AD). MD2011001 is a nonsteroidal topical cream containing vitamin E, epigallocatechin gallate and grape seed procyanidins.

METHODS:

Patients with AD (corresponding to an IGA score of 2 or 3), involving the face, the perioral/periorcular area and/or the neck, were enrolled. Patients were randomized 1:1 ratio to receive MD2011001 or placebo before the start of the study (D0), then evaluated after 7 days, and after 28 days. The study was approved by the Local Independent Ethics Committee and conducted according to the Declaration of Helsinki and local regulations. The statistical tests used were the Wilcoxon test and the Mann-Whitney U-test.

RESULTS:

Forty-four patients (29F and 15M) were enrolled. The IGA values showed a statistically significant reduction during the treatment period obtaining a favorable safety profile and local tolerance for both the products. The reduction in the surface area affected by AD was significantly faster with MD2011001.

DISCUSSION:

This study focuses on very sensitive areas known to be particularly susceptible to local complications.

CONCLUSIONS:

These results suggest the usefulness of an emollient treatment for mild/moderate AD.

PMID: 26652026 [Indexed for MEDLINE]

[Similar articles](#)



A new formulation of Gamma Delta Tocotrienol has superior bioavailability compared to existing Tocotrienol-Rich Fraction in healthy human subjects.

[Meganathan P](#)^{1,2,3}, [Jabir RS](#)¹, [Fuang HG](#)⁴, [Bhoo-Pathy N](#)⁵, [Choudhury RB](#)⁶, [Taib NA](#)¹, [Nesaretnam K](#)³, [Chik Z](#)².

Author information:

1. Department of Surgery, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia.
2. Department of Pharmacology, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia.
3. Malaysian Palm Oil Board (MPOB), No. 6 Persiaran Institusi, Bandar Baru Bangi, 43000 Kajang, Selangor, Malaysia.
4. Oncology Clinical Unit, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia.
5. Department of Social and Preventive Medicine (SPM), Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia.
6. Clinical Investigation Centre, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia.

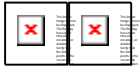
Abstract

Gamma and delta tocotrienols are isomers of Vitamin E with established potency in pre-clinical anti-cancer research. This single-dose, randomized, crossover study aimed to compare the safety and bioavailability of a new formulation of Gamma Delta Tocotrienol (GDT) in comparison with the existing Tocotrienol-rich Fraction (TRF) in terms of gamma and delta isomers in healthy volunteers. Subjects were given either two 300 mg GDT (450 mg γ -T3 and 150 mg δ -T3) capsules or four 200 mg TRF (451.2 mg γ -T3 & 102.72 mg δ -T3) capsules and blood samples were taken at several time points over 24 hours. Plasma tocotrienol concentrations were determined using HPLC method. The 90% CI for gamma and delta tocotrienols for the ratio of log-transformation of GDT/TRF for C_{max} and AUC_{0-∞} (values were anti-logged and expressed as a percentage) were beyond the bioequivalence limits (106.21-195.46, 154.11-195.93 and 52.35-99.66, 74.82-89.44 respectively). The Wilcoxon Signed Rank Test for T_{max} did not show any significant difference between GDT and TRF for both isomers ($p > 0.05$). No adverse events were reported during the entire period of study. GDT was found not bioequivalent to TRF, in terms of AUC and C_{max}. Gamma tocotrienol in GDT showed superior bioavailability whilst delta tocotrienol showed less bioavailability compared to TRF.

PMCID: PMC4555096 **Free PMC Article**

PMID: 26323969 [Indexed for MEDLINE]

[Similar articles](#)



11. Redox Biol. 2015 Dec;6:198-205. doi: 10.1016/j.redox.2015.07.012. Epub 2015 Jul 29.

Effects of N-acetylcysteine, oral glutathione (GSH) and a novel sublingual form of GSH on oxidative stress markers: A comparative crossover study.

[Schmitt B](#)¹, [Vicenzi M](#)², [Garrel C](#)³, [Denis FM](#)⁴.

Author information:

1. Centre d'Enseignement et de Recherche en Nutrition Humaine, Centre Hospitalier de Bretagne Sud, 5 Avenue De Choiseul, BP 12233, 56322 Lorient Cedex, France. Electronic address: schmitt.lorient@yahoo.fr.

2. Laboratoires Le Stum, 4 impasse de Kerhoas, 56260 Larmor Plage, France. Electronic address: innov@labo-lestum.com.

3. Unité de Biochimie Hormonale et Nutritionnelle, Département de Biochimie, Toxicologie et Pharmacologie, Institut de Biologie et de Pathologie, Centre Hospitalier Universitaire de Grenoble, CS10217, 38043 Grenoble, France. Electronic address: CGarrel@chu-grenoble.fr.

4. Laboratoires Le Stum, 4 impasse de Kerhoas, 56260 Larmor Plage, France. Electronic address: infomed@labo-lestum.com.

Abstract

Glutathione (GSH) is critical to fight against oxidative stress. Its very low bioavailability limits the interest of a supplementation. The purpose of this study was to compare the bioavailability, the effect on oxidative stress markers and the safety of a new sublingual form of GSH with two commonly used dietary supplements, N-acetylcysteine (NAC) and oral GSH. The study was a three-week randomized crossover trial. 20 Volunteers with metabolic syndrome were enrolled. GSH levels and several oxidative stress markers were determined at different times during each 21-days period. Compared to oral GSH group, an increase of total and reduced GSH levels in plasma and a higher GSH/GSSG ratio ($p=0.003$) was observed in sublingual GSH group. After 3 weeks of administration, there was a significant increase of vitamin E level in plasma only in sublingual GSH group ($0.83 \mu\text{mol/g}$; $p=0.04$). Our results demonstrate the superiority of a new sublingual form of GSH over the oral GSH form and NAC in terms of GSH supplementation.

PMCID: PMC4536296 **Free PMC Article**

PMID: 26262996 [Indexed for MEDLINE]

[Similar articles](#)



12. BMC Nephrol. 2015 Apr 11;16:52. doi: 10.1186/s12882-015-0042-4.

Trace element supplementation in hemodialysis

patients: a randomized controlled trial.

[Tonelli M](#)¹, [Wiebe N](#)², [Thompson S](#)³, [Kinniburgh D](#)⁴, [Klarenbach SW](#)⁵, [Walsh M](#)^{6,7,8}, [Bello AK](#)⁹, [Faruque L](#)¹⁰, [Field C](#)¹¹, [Manns BJ](#)¹², [Hemmelgarn BR](#)¹³; [Alberta Kidney Disease Network](#).

Author information:

1. Department of Medicine, University of Calgary, 3280 Hospital Dr NW, Calgary, AB, T2N 4Z6, Canada. tonelli.admin@ucalgary.ca.
2. Department of Medicine, University of Alberta, Edmonton, Canada. nwiebe@ualberta.ca.
3. Department of Medicine, University of Alberta, Edmonton, Canada. th11@ualberta.ca.
4. Department of Physiology & Pharmacology, Calgary, Canada. dkinnibu@ucalgary.ca.
5. Department of Medicine, University of Alberta, Edmonton, Canada. swk@ualberta.ca.
6. Department of Medicine, McMaster University, Hamilton, Canada. lastwalsh1975@gmail.com.
7. Population Health Research Institute, Hamilton Health Sciences/McMaster University, Hamilton, Canada. lastwalsh1975@gmail.com.
8. Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Canada. lastwalsh1975@gmail.com.
9. Department of Medicine, University of Alberta, Edmonton, Canada. aminul@ualberta.ca.
10. Department of Medicine, University of Alberta, Edmonton, Canada. faruque@ualberta.ca.
11. Department of Agricultural, Food & Nutritional Science, University of Alberta, Edmonton, Canada. cjfield@ualberta.ca.
12. Department of Medicine, University of Calgary, 3280 Hospital Dr NW, Calgary, AB, T2N 4Z6, Canada. Braden.Manns@albertahealthservices.ca.
13. Department of Medicine, University of Calgary, 3280 Hospital Dr NW, Calgary, AB, T2N 4Z6, Canada. Brenda.Hemmelgarn@albertahealthservices.ca.

Abstract

BACKGROUND:

People with kidney failure are often deficient in zinc and selenium, but little is known about the optimal way to correct such deficiency.

METHODS:

We did a double-blind randomized trial evaluating the effects of zinc (Zn), selenium (Se) and vitamin E added to the standard oral renal vitamin supplement (B and C vitamins) among hemodialysis patients in Alberta, Canada. We evaluated the effect of two daily doses of the new supplement (medium dose: 50 mg Zn, 75 mcg Se, 250 IU vitamin E; low dose: 25 mg Zn, 50 mcg Se, 250 IU vitamin E) compared to the standard supplement on blood concentrations of Se and Zn at 90 days (primary outcome) and 180 days (secondary outcome) as well as safety outcomes.

RESULTS:

We enrolled 150 participants. The proportion of participants with low zinc status (blood level <815 ug/L) did not differ between the control group and the two intervention groups at 90 days (control 23.9% vs combined intervention groups 23.9%, $P > 0.99$) or 180 days (18.6% vs 28.2%, $P = 0.24$). The proportion with low selenium status (blood level <121 ug/L) was similar for controls and the combined intervention groups at 90 days (32.6 vs 19.6%, $P = 0.09$) and 180 days (34.9% vs 23.5%, $P = 0.17$). There were no

significant differences in the risk of adverse events between the groups.

CONCLUSIONS:

Supplementation with low or medium doses of zinc and selenium did not correct low zinc or selenium status in hemodialysis patients. Future studies should consider higher doses of zinc (≥ 75 mg/d) and selenium (≥ 100 mcg/d) with the standard supplement.

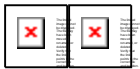
TRIAL REGISTRATION:

Registered with ClinicalTrials.gov ([NCT01473914](https://clinicaltrials.gov/ct2/show/study/NCT01473914)).

PMCID: PMC4409771 **Free PMC Article**

PMID: 25884981 [Indexed for MEDLINE]

[Similar articles](#)



13. Zhonghua Nan Ke Xue. 2014 Dec;20(12):1082-5.

[\[Efficacy and safety of vitamin D in the treatment of idiopathic oligoasthenozoospermia\].](#)

[Article in Chinese]

[Deng XL](#)¹, [Li YM](#), [Yang XY](#), [Huang JR](#), [Guo SL](#), [Song LM](#).

Author information:

1. Department of Urology, Ganzhou People's Hospital/Ganzhou Hospital affiliated to Nanchang University, Jiangxi, China. dengxiaolin@hsc.pku.edu.cn

Abstract

OBJECTIVE:

To explore the efficacy and safety of vitamin D (VD) in the treatment of idiopathic oligoasthenozoospermia.

METHODS:

This study included 86 infertile men with idiopathic oligoasthenozoospermia, who were randomized to a VD and a control group of equal number, the former given oral VD 200 IU/d and calcium 600 mg/d,qd, while the latter administered oral vitamin E 100 mg and vitamin C 100 mg, tid. After 3 months of medication, we compared the semen parameters, adverse reactions, and pregnancy rate between the two groups.

RESULTS:

After medication, the count of progressively motile sperm per ejaculate was increased from $(9.82 \pm 3.72) \times 10(6)$ to $(21.47 \pm 6.52) \times 10(6)$ ($P < 0.05$) and the proportion of progressively motile sperm from $(18.41 \pm 9.82)\%$ to $(28.27 \pm 4.47)\%$ ($P < 0.05$) in the VD group. In comparison, the count of progressively motile

sperm per ejaculate was elevated from $(9.51 \pm 6.31) \times 10^6$ to $(12.36 \pm 4.43) \times 10^6$ ($P > 0.05$) and the proportion of progressively motile sperm from $(17.79 \pm 5.25)\%$ to $(21.35 \pm 2.41)\%$ ($P > 0.05$) in the control group. Pregnancy was achieved in 7 cases (16.3%) in the VD group, but only lease (2.3%) in the control ($P < 0.05$). No adverse reactions were observed in either of the groups.

CONCLUSION:

Vitamin D, as a safe option for the treatment of idiopathic oligoasthenozoospermia, can effectively improve the semen quality, especially the progressive sperm motility of the patient.

PMID: 25597173 [Indexed for MEDLINE]

[Similar articles](#)

14. J Med Assoc Thai. 2014 Nov;97 Suppl 11:S31-40.

Effects of vitamin E on chronic hepatitis C genotype 3: a randomized, double-blind, placebo-controlled study.

[Bunchorntavakul C](#), [Wootthanant T](#), [Atsawarungrangkit A](#).

Abstract

BACKGROUND:

Hepatitis C virus (HCV) infection is associated with chronic inflammation and oxidative damage, with hepatic steatosis being common in genotype 3 cases. Vitamin E, a potent antioxidant protective against oxidative stress-induced liver damage in vitro and in vivo, has beneficial effects on alanine aminotransferase (ALT) and histological outcomes in patients with non-alcoholic steatohepatitis.

OBJECTIVE:

To assess the effect of vitamin E on ALT status in patients with HCV genotype 3.

MATERIAL AND METHOD:

This randomized, placebo-controlled, double-blind trial was conducted in a single tertiary-care hospital (Rajavithi Hospital, Bangkok) between 2010 and 2011. We included patients with HCV genotype 3 infection, unable to receive or tolerate, or did not respond to standard therapy. Responders were defined as patients exhibiting a decrease in serum ALT of at least 5% below the baseline value after 12 weeks of treatment.

RESULTS:

Thirty-seven eligible patients were randomly assigned either to receive vitamin E 400 IU twice daily ($n = 19$) or placebo ($n = 18$; 1 dropped out early) for 12 weeks. In all, 11 of 19 patients in the vitamin E group (57.8%) and 5 of 17 patients in the placebo group (29.4%) were ALT responders. Among responders, serum ALT levels were greatly decreased in the vitamin E group (reducing from 122.6 ± 80.1 IU/L to 68.4 ± 25.3 IU/L, $p = 0.016$), when compared with the placebo group (reducing from 89.2 ± 40.6 IU/L to 73.6 ± 30.6 IU/L,

p > 0.05). Vitamin E treatment was well-tolerated with no serious adverse events in the present study.

CONCLUSION:

Vitamin E treatment decreased serum ALT levels in patients with HCV genotype 3. Because of its good safety profile, vitamin E may be a worthwhile supportive therapy for patients with HCV particularly for those who were unable to achieve viral eradication by standard therapy.

PMID: 25509693 [Indexed for MEDLINE]

[Similar articles](#)

15. Trials. 2014 Sep 3;15:345. doi: 10.1186/1745-6215-15-345.

A combination of ascorbic acid and α -tocopherol to test the effectiveness and safety in the fragile X syndrome: study protocol for a phase II, randomized, placebo-controlled trial.

[de Diego-Otero Y¹](#), [Calvo-Medina R](#), [Quintero-Navarro C](#), [Sánchez-Salido L](#), [García-Guirado F](#), [del Arco-Herrera I](#), [Fernández-Carvajal I](#), [Ferrando-Lucas T](#), [Caballero-Andaluz R](#), [Pérez-Costillas L](#).

Author information:

1. Unidad de Gestión Clínica de Salud Mental, Hospital Regional Universitario de Málaga, Instituto de Investigación Biomédica de Málaga (IBIMA), Hospital Civil, Pabellón 2 bajo, Plaza del Hospital Civil S/N, 29009 Málaga, Spain. yolanda.diego.exts@juntadeandalucia.es.

Abstract

BACKGROUND:

Fragile X syndrome (FXS) is an inherited neurodevelopmental condition characterised by behavioural, learning disabilities, physical and neurological symptoms. In addition, an important degree of comorbidity with autism is also present. Considered a rare disorder affecting both genders, it first becomes apparent during childhood with displays of language delay and behavioural symptoms. Main aim: To show whether the combination of 10 mg/kg/day of ascorbic acid (vitamin C) and 10 mg/kg/day of α -tocopherol (vitamin E) reduces FXS symptoms among male patients ages 6 to 18 years compared to placebo treatment, as measured on the standardized rating scales at baseline, and after 12 and 24 weeks of treatment. Secondary aims: To assess the safety of the treatment. To describe behavioural and cognitive changes revealed by the Developmental Behaviour Checklist Short Form (DBC-P24) and the Wechsler Intelligence Scale for Children-Revised. To describe metabolic changes revealed by blood analysis. To measure treatment impact at home and in an academic environment.

METHODS/DESIGN:

A phase II randomized, double-blind pilot clinical trial.

SCOPE:

male children and adolescents diagnosed with FXS, in accordance with a standardized molecular biology test, who met all the inclusion criteria and none of the exclusion criteria.

INSTRUMENTATION:

clinical data, blood analysis, Wechsler Intelligence Scale for Children-Revised, Conners parent and teacher rating scale scores and the DBC-P24 results will be obtained at the baseline (t0). Follow up examinations will take place at 12 weeks (t1) and 24 weeks (t2) of treatment.

DISCUSSION:

A limited number of clinical trials have been carried out on children with FXS, but more are necessary as current treatment possibilities are insufficient and often provoke side effects. In the present study, we sought to overcome possible methodological problems by conducting a phase II pilot study in order to calculate the relevant statistical parameters and determine the safety of the proposed treatment. The results will provide evidence to improve hyperactivity control and reduce behavioural and learning problems using ascorbic acid (vitamin C) and α -tocopherol (vitamin E). The study protocol was approved by the Regional Government Committee for Clinical Trials in Andalusia and the Spanish agency for drugs and health products.

TRIAL REGISTRATION:

ClinicalTrials.gov Identifier: [NCT01329770](https://clinicaltrials.gov/ct2/show/study/NCT01329770) (29 March 2011).

PMCID: PMC4168067 **Free PMC Article**

PMID: 25187257 [Indexed for MEDLINE]

[Similar articles](#)



16. Invest Ophthalmol Vis Sci. 2014 Jul 11;55(8):4958-66. doi: 10.1167/iovs.14-14437.

Safety assessment of docosahexaenoic acid in X-linked retinitis pigmentosa: the 4-year DHAX trial.

[Highbanks-Wheaton DK](#)¹, [Birch DG](#)¹, [Fish GE](#)², [Spencer R](#)², [Pearson NS](#)³, [Takacs A](#)⁴, [Hoffman DR](#)¹.

Author information:

1. Retina Foundation of the Southwest, Dallas, Texas, United States Department of Ophthalmology, UT Southwestern Medical Center, Dallas, Texas, United States.
2. Texas Retina Associates, Dallas, Texas, United States.
3. Pearson Statistical Consulting & Expert Testimony, Richardson, Texas, United States.
4. Retina Foundation of the Southwest, Dallas, Texas, United States.

Abstract

PURPOSE:

Docosahexaenoic acid (DHA) continues to be evaluated and recommended as treatment and prophylaxis for

various diseases. We recently assessed efficacy of high-dose DHA supplementation to slow vision loss in patients with X-linked retinitis pigmentosa (XLRP) in a randomized clinical trial. Because DHA is a highly unsaturated fatty acid, it could serve as a target for free-radical induced oxidation, resulting in increased oxidative stress. Biosafety was monitored during the 4-year trial to determine whether DHA supplementation was associated with identifiable risks.

METHODS:

Males (n = 78; 7-31 years) meeting entry criteria were enrolled. The modified intent-to-treat cohort (DHA = 33; placebo = 27) adhered to the protocol ≥ 1 year. Participants were randomized to an oral dose of 30 mg/kg/d DHA or placebo plus a daily multivitamin. Comprehensive metabolic analyses were assessed for group differences. Treatment-emergent adverse events including blood chemistry metabolites were recorded.

RESULTS:

By year 4, supplementation elevated plasma and red blood cell-DHA 4.4- and 3.6-fold, respectively, compared with the placebo group ($P < 0.00001$). Over the trial duration, no significant differences between DHA and placebo groups were found for vitamin A, vitamin E, platelet aggregation, antioxidant activity, lipoprotein cholesterol, or oxidized LDL levels (all $P > 0.14$). Adverse events were transient and not considered severe (e.g., gastrointestinal [GI] irritability, blood chemistry alterations). One participant was unable to tolerate persistent GI discomfort.

CONCLUSIONS:

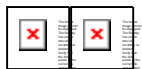
Long-term, high-dose DHA supplementation to patients with XLRP was associated with limited safety risks in this 4-year trial. Nevertheless, GI symptoms should be monitored in all patients taking high dose DHA especially those with personal or family history of GI disturbances. (ClinicalTrials.gov number, [NCT00100230](https://clinicaltrials.gov/ct2/show/study/NCT00100230)).

Copyright 2014 The Association for Research in Vision and Ophthalmology, Inc.

PMCID: PMC5963309 **Free PMC Article**

PMID: 25015354 [Indexed for MEDLINE]

[Similar articles](#)



17. JAMA Neurol. 2014 May;71(5):543-52. doi: 10.1001/jamaneurol.2014.131.

[A randomized clinical trial of high-dosage coenzyme Q10 in early Parkinson disease: no evidence of benefit.](#)

[Parkinson Study Group QE3 Investigators](#), [Beal MF](#)¹, [Oakes D](#)², [Shoulson I](#)³, [Henchcliffe C](#)¹, [Galpern WR](#)⁴, [Haas R](#)⁵, [Juncos JL](#)⁶, [Nutt JG](#)⁷, [Voss TS](#)⁸, [Ravina B](#)⁹, [Shults CM](#)¹⁰, [Helles K](#)², [Snively V](#)², [Lew MF](#)¹¹, [Griebner B](#)², [Watts A](#)¹², [Gao S](#)², [Pourcher E](#)¹³, [Bond L](#)¹³, [Kompoliti K](#)¹⁴, [Agarwal P](#)¹⁵, [Sia C](#)¹⁵, [Jog M](#)¹⁶, [Cole L](#)¹⁶, [Sultana M](#)¹⁶, [Kurlan R](#)¹⁷, [Richard I](#)¹⁸, [Deeley C](#)¹⁸, [Waters CH](#)¹⁹, [Figueroa A](#)¹⁹, [Arkun A](#)¹, [Brodsky M](#)⁷,

[Ondo WG](#)²⁰, [Hunter CB](#)²¹, [Jimenez-Shahed J](#)²¹, [Palao A](#)²¹, [Miyasaki JM](#)²², [So J](#)²², [Tetrud J](#)²³, [Reys L](#)²³, [Smith K](#)²³, [Singer C](#)²⁴, [Blenke A](#)²⁴, [Russell DS](#)²⁵, [Cotto C](#)²⁵, [Friedman JH](#)²⁶, [Lannon M](#)²⁷, [Zhang L](#)²⁸, [Drasby E](#)²⁹, [Kumar R](#)³⁰, [Subramanian T](#)³¹, [Ford DS](#)³¹, [Grimes DA](#)³², [Cote D](#)³², [Conway J](#)³², [Siderowf AD](#)³³, [Evatt ML](#)³⁴, [Sommerfeld B](#)⁶, [Lieberman AN](#)³⁵, [Okun MS](#)³⁶, [Rodriguez RL](#)³⁶, [Merritt S](#)³⁶, [Swartz CL](#)³⁶, [Martin WR](#)³⁷, [King P](#)³⁷, [Stover N](#)³⁸, [Guthrie S](#)³⁸, [Watts RL](#)³⁸, [Ahmed A](#)³⁹, [Fernandez HH](#)³⁹, [Winters A](#)³⁹, [Mari Z](#)⁴⁰, [Dawson TM](#)⁴⁰, [Dunlop B](#)⁴⁰, [Feigin AS](#)⁴¹, [Shannon B](#)⁴¹, [Nirenberg MJ](#)⁴², [Ogg M](#)¹, [Ellias SA](#)⁴³, [Thomas CA](#)⁴³, [Frei K](#)⁴⁴, [Bodis-Wollner I](#)⁴⁵, [Glazman S](#)⁴⁵, [Mayer T](#)⁴⁵, [Hauser RA](#)⁴⁶, [Pahwa R](#)⁴⁷, [Langhammer A](#)⁴⁷, [Ranawaya R](#)⁴⁸, [Derwent L](#)⁴⁸, [Sethi KD](#)⁴⁹, [Farrow B](#)⁴⁹, [Prakash R](#)⁴⁹, [Litvan I](#)⁵, [Robinson A](#)⁵⁰, [Sahay A](#)⁵¹, [Gartner M](#)⁵¹, [Hinson VK](#)⁵², [Markind S](#)⁵³, [Pelikan M](#)⁵³, [Perlmutter JS](#)⁵⁴, [Hartlein J](#)⁵⁴, [Molho E](#)⁵⁵, [Evans S](#)⁵⁵, [Adler CH](#)⁵⁶, [Duffy A](#)⁵⁶, [Lind M](#)⁵⁶, [Elmer L](#)⁵⁷, [Davis K](#)⁵⁸, [Spears J](#)⁵⁸, [Wilson S](#)⁵⁸, [Leehey MA](#)⁵⁹, [Hermanowicz N](#)⁶⁰, [Niswonger S](#)⁶⁰, [Shill HA](#)⁶¹, [Obradov S](#)⁶¹, [Rajput A](#)⁶², [Cowper M](#)⁶², [Lessig S](#)⁶³, [Song D](#)⁶³, [Fontaine D](#)⁶³, [Zadikoff C](#)⁶⁴, [Williams K](#)⁶⁴, [Blindauer KA](#)⁶⁵, [Bergholte J](#)⁶⁵, [Proptom CS](#)⁶⁵, [Stacy MA](#)⁶⁶, [Field J](#)⁶⁶, [Mihaila D](#)⁶⁷, [Chilton M](#)⁶⁷, [Uc EY](#)⁶⁸, [Sieren J](#)⁶⁸, [Simon DK](#)⁶⁹, [Kraics L](#)⁶⁹, [Silver A](#)⁶⁹, [Boyd JT](#)⁷⁰, [Hamill RW](#)⁷⁰, [Ingvoldstad C](#)⁷⁰, [Young J](#)⁷⁰, [Thomas K](#)⁷¹, [Kostyk SK](#)⁷¹, [Wojcieszek J](#)⁷², [Pfeiffer RF](#)⁷³, [Panisset M](#)⁷⁴, [Beland M](#)⁷⁴, [Reich SG](#)⁷⁵, [Cines M](#)⁷⁵, [Zappala N](#)⁷⁵, [Rivest J](#)⁷⁶, [Zweig R](#)⁷⁷, [Lumina LP](#)⁷⁷, [Hilliard CL](#)⁷⁸, [Grill S](#)⁴⁰, [Kellermann M](#)⁷⁹, [Tuite P](#)⁸⁰, [Rolandelli S](#)⁸⁰, [Kang UJ](#)⁸¹, [Young J](#)⁸¹, [Rao J](#)⁸², [Cook MM](#)⁸², [Severt L](#)⁸³, [Boyar K](#)⁸³.

Collaborators: (208)

[Oakes D](#), [Beal M](#), [Shoulson I](#), [Galpern WR](#), [Haas R](#), [Henchcliffe C](#), [Juncos JL](#), [Nutt J](#), [Ravina B](#), [Voss T](#), [Shults C](#), [Pourcher E](#), [Bond L](#), [Kompoliti K](#), [Agarwal P](#), [Sia C](#), [Jog M](#), [Cole L](#), [Sultana M](#), [Kurlan R](#), [Richard I](#), [Deeley C](#), [Waters C](#), [Figueroa A](#), [Arkun A](#), [Brodsky M](#), [Ondo W](#), [Hunter C](#), [Jimenez-Shahed J](#), [Palao A](#), [Miyasaki J](#), [So J](#), [Tetrud J](#), [Reys L](#), [Smith K](#), [Singer C](#), [Blenke A](#), [Russell D](#), [Cotto C](#), [Friedman J](#), [Lannon M](#), [Zhang L](#), [Drasby E](#), [Lannon M](#), [Kumar R](#), [Subramanian T](#), [Ford DS](#), [Grimes D](#), [Cote D](#), [Conway J](#), [Siderowf A](#), [Evatt M](#), [Sommerfeld B](#), [Lieberman A](#), [Okun MS](#), [Rodriguez R](#), [Merritt S](#), [Swartz C](#), [Martin W](#), [King P](#), [Stover N](#), [Guthrie S](#), [Watts R](#), [Ahmed A](#), [Fernandez H](#), [Winters A](#), [Mari Z](#), [Dawson T](#), [Dunlop B](#), [Feigin A](#), [Shannon B](#), [Nirenberg MJ](#), [Ogg M](#), [Ellias S](#), [Thomas CA](#), [Frei K](#), [Bodis-Wollner I](#), [Glazman S](#), [Mayer T](#), [Hauser RA](#), [Pahwa R](#), [Langhammer A](#), [Ranawaya R](#), [Derwent L](#), [Sethi K](#), [Farrow B](#), [Prakash R](#), [Litvan I](#), [Robinson A](#), [Sahay A](#), [Gartner M](#), [Hinson V](#), [Markind S](#), [Pelikan M](#), [Perlmutter JS](#), [Hartlein J](#), [Molho E](#), [Evans S](#), [Adler C](#), [Duffy A](#), [Lind M](#), [Elmer L](#), [Davis K](#), [Spears J](#), [Wilson S](#), [Leehey M](#), [Hermanowicz N](#), [Niswonger S](#), [Shill H](#), [Obradov S](#), [Rajput A](#), [Cowper M](#), [Lessig S](#), [Song D](#), [Fontaine D](#), [Zadikoff C](#), [Williams K](#), [Blindauer K](#), [Bergholte J](#), [Proptom CS](#), [Stacy M](#), [Field J](#), [Mihaila D](#), [Chilton M](#), [Uc E](#), [Sieren J](#), [Simon DK](#), [Kraics L](#), [Silver A](#), [Boyd J](#), [Hamill R](#), [Ingvoldstad C](#), [Young J](#), [Thomas K](#), [Kostyk S](#), [Wojcieszek J](#), [Pfeiffer RF](#), [Panisset M](#), [Beland M](#), [Reich S](#), [Cines M](#), [Zappala N](#), [Rivest J](#), [Zweig R](#), [Lumina L](#), [Hilliard C](#), [Grill S](#), [Kellermann M](#), [Tuite P](#), [Rolandelli S](#), [Kang UJ](#), [Young J](#), [Rao J](#), [Cook M](#), [Severt W](#), [Boyar K](#), [Oakes D](#), [McDermott M](#), [Watts A](#), [Gao S](#), [Griebner B](#), [Helles K](#), [Plumb S](#), [Snively V](#), [Lew M](#), [Voss T](#), [Gross C](#), [Albin R](#), [Bell KL](#), [Chen DT](#), [Levy DE](#), [Beimler A](#), [Doolan R](#), [Henderson S](#), [Lang L](#), [Lau G](#), [McMullen N](#), [Rothenburgh K](#), [McCoy A](#), [Dorward BJ](#), [Tran M](#), [Sombai J](#), [Quesada M](#), [Hupcey R](#), [Miracle D](#), [Altin L](#), [Weeks ML](#), [Simpson E](#), [Suelter M](#), [Scott I](#), [McMurray R](#), [Velcheva M](#), [McClain T](#), [Khavarian L](#), [Zimmerman J](#), [Zomok M](#), [Scott ME](#), [Olalde H](#), [Miller J](#), [Oesterle C](#), [Pancake P](#), [Belden J](#), [Soucy D](#), [Johnson L](#), [Kashouty R](#), [Roth L](#), [Niles L](#), [Nickels B](#).

Author information:

1. Department of Neurology, Weill Cornell Medical College, New York Hospital, New York.
2. Department of Biostatistics, University of Rochester Medical Center, Rochester, New York.
3. Department of Neurology, Georgetown University, Washington, DC.
4. National Institutes of Health, Bethesda, Maryland.
5. Department of Neurosciences, University of California, San Diego, La Jolla.
6. Department of Neurology, Emory University School of Medicine, Wesley Woods Center, Atlanta, Georgia.
7. Department of Neurology, Oregon Health and Science University, Portland.
8. Merck, New Jersey.

9. Biogen Idec, Cambridge, Massachusetts.
10. Department of Neurosciences, University of California, San Diego, La Jolla10VA Medical Center, San Diego, California.
11. Department of Neurology, Keck School of Medicine, University of Southern California, Los Angeles.
12. Department of Biostatistics, University of Rochester Medical Center, Rochester, New York12Department of Neurology, University of Rochester, Rochester, New York.
13. Québec Memory and Motor Skills Disorders Research Center, Clinique Sainte-Anne, Québec, Canada.
14. Rush University Medical Center, Chicago, Illinois.
15. Booth Gardner Parkinson's Care Center, EvergreenHealth, Kirkland, Washington.
16. London Health Sciences Centre, London, Ontario, Canada.
17. Overlook Medical Center, Atlantic Neuroscience Institute, Summit, New Jersey.
18. Department of Neurology, University of Rochester, Rochester, New York.
19. Columbia University Medical Center, Neurological Institute, New York, New York.
20. Department of Neurology, University of Texas Health Science Center at Houston.
21. Department of Neurology, Baylor College of Medicine, Houston, Texas.
22. Morton and Gloria Shulman Movement Disorders Centre, Toronto Western Hospital, University of Toronto, Toronto, Ontario, Canada.
23. The Parkinson's Institute and Clinical Center, Sunnyvale, California.
24. Department of Neurology, University of Miami School of Medicine, Miami, Florida.
25. Institute for Neurodegenerative Disorders, New Haven, Connecticut.
26. Department of Neurology, Butler Hospital, Providence, Rhode Island26Alpert Medical School, Brown University, Providence, Rhode Island.
27. Department of Neurology, Butler Hospital, Providence, Rhode Island27Port City Neurology, Inc, Scarborough, Maine.
28. Department of Neurology, University of California, Davis, School of Medicine and Sacramento VA Medical Center, Sacramento.
29. Port City Neurology, Inc, Scarborough, Maine.
30. Colorado Neurological Institute, Englewood.
31. Milton S. Hershey Medical Center, Department of Neurology, Pennsylvania State Hershey College of Medicine, Hershey.
32. Ottawa Hospital Civic Site, Ottawa, Ontario, Canada.
33. Avid Radiopharmaceuticals, Philadelphia, Pennsylvania.
34. Department of Neurology, Emory University School of Medicine, Wesley Woods Center, Atlanta, Georgia33Atlanta VA Medical Center, Atlanta, Georgia.
35. Muhammad Ali Parkinson Center, Barrow Neurological Institute, St Joseph's Hospital and Medical Center, Phoenix, Arizona.
36. Department of Neurology, University of Florida Center for Movement Disorders and Neurorestoration, Gainesville.
37. Glenrose Rehabilitation Hospital, University of Alberta, Edmonton, Alberta, Canada.
38. Department of Neurology, University of Alabama at Birmingham.
39. Center for Neurological Restoration, Department of Neurology, Cleveland Clinic, Cleveland, Ohio.
40. Department of Neurology, Johns Hopkins University, Baltimore, Maryland.
41. Feinstein Institute for Medical Research, Center for Neurosciences, Manhasset, New York.
42. Department of Neurology, New York University Langone Medical Center, New York.
43. Department of Neurology, Boston University School of Medicine, Boston, Massachusetts.
44. The Parkinson's and Movement Disorder Institute, Fountain Valley, California.
45. State University of New York, Downstate Medical Center, Brooklyn, New York.
46. Department of Neurology, University of South Florida, Tampa.
47. Department of Neurology, University of Kansas Medical Center, Kansas City.
48. Department of Clinical Neurosciences, University of Calgary, Calgary, Alberta, Canada.
49. Department of Neurology, Georgia Health Science University, Augusta.

50. Department of Neurology, University of Louisville, Kentucky.
51. University of Cincinnati College of Medicine, Cincinnati, Ohio.
52. Department of Neurology, Medical University of South Carolina, Charleston.
53. Associated Neurologists, PC, Danbury, Connecticut.
54. Department of Neurology, Washington University in St Louis, Missouri.
55. Movement Disorders Center, Albany Medical Center, Albany, New York.
56. Parkinson's Disease and Movement Disorders Center, Department of Neurology, Mayo Clinic, Scottsdale, Arizona.
57. Center for Neurological Health, University of Toledo, Toledo, Ohio.
58. Department of Neurology, Medical University of Ohio at Toledo.
59. Department of Neurology, University of Colorado Health Science Center, Denver.
60. Department of Neurology, University of California, Irvine Medical Center, Irvine.
61. Banner Sun Health Research Institute, Sun City, Arizona.
62. Department of Neurology, University of Saskatchewan, Royal University Hospital, Saskatchewan, Canada.
63. Department of Neurology, University of California, San Diego, La Jolla.
64. Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, Illinois.
65. Department of Neurology, Medical College of Wisconsin, Milwaukee.
66. Department of Neurology, Duke University, Durham, North Carolina.
67. State University of New York Upstate Medical Center and Syracuse VA Medical Center, Syracuse.
68. Department of Neurology, University of Iowa, Iowa City.
69. Department of Neurology, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Massachusetts.
70. Department of Neurology, University of Vermont College of Medicine, Burlington.
71. Department of Neurology, Ohio State University, Columbus.
72. Department of Neurology, Indiana University School of Medicine, Indianapolis.
73. Department of Neurology, University of Tennessee Health Science Center, Memphis.
74. Department of Neurology, CHUM-Hôpital Notre-Dame, Montréal, Québec, Canada.
75. Department of Neurology, University of Maryland School of Science, Baltimore.
76. Department of Neurology, University of Sherbrooke, Québec, Canada.
77. Department of Neurology, Louisiana State University Health Science Center, Shreveport.
78. Lewis Hall Singletary Oncology Center, Thomasville, Georgia.
79. Parkinson and Movement Disorders Center of Maryland, Elkridge.
80. Department of Neurology, University of Minnesota, Minneapolis.
81. Department of Neurology, University of Chicago, Chicago, Illinois.
82. Department of Neurology, Ochsner Clinic Foundation, New Orleans, Louisiana.
83. Department of Neurology, Beth Israel Medical Center, New York, New York.

Comment in

- [Targeting mitochondria for neuroprotection in Parkinson disease.](#) [JAMA Neurol. 2014]

Abstract

IMPORTANCE:

Coenzyme Q10 (CoQ10), an antioxidant that supports mitochondrial function, has been shown in preclinical Parkinson disease (PD) models to reduce the loss of dopamine neurons, and was safe and well tolerated in early-phase human studies. A previous phase II study suggested possible clinical benefit.

OBJECTIVE:

To examine whether CoQ10 could slow disease progression in early PD.

DESIGN, SETTING, AND PARTICIPANTS:

A phase III randomized, placebo-controlled, double-blind clinical trial at 67 North American sites consisting of participants 30 years of age or older who received a diagnosis of PD within 5 years and who had the following inclusion criteria: the presence of a rest tremor, bradykinesia, and rigidity; a modified Hoehn and Yahr stage of 2.5 or less; and no anticipated need for dopaminergic therapy within 3 months. Exclusion criteria included the use of any PD medication within 60 days, the use of any symptomatic PD medication for more than 90 days, atypical or drug-induced parkinsonism, a Unified Parkinson's Disease Rating Scale (UPDRS) rest tremor score of 3 or greater for any limb, a Mini-Mental State Examination score of 25 or less, a history of stroke, the use of certain supplements, and substantial recent exposure to CoQ10. Of 696 participants screened, 78 were found to be ineligible, and 18 declined participation.

INTERVENTIONS:

The remaining 600 participants were randomly assigned to receive placebo, 1200 mg/d of CoQ10, or 2400 mg/d of CoQ10; all participants received 1200 IU/d of vitamin E.

MAIN OUTCOMES AND MEASURES:

Participants were observed for 16 months or until a disability requiring dopaminergic treatment. The prospectively defined primary outcome measure was the change in total UPDRS score (Parts I-III) from baseline to final visit. The study was powered to detect a 3-point difference between an active treatment and placebo.

RESULTS:

The baseline characteristics of the participants were well balanced, the mean age was 62.5 years, 66% of participants were male, and the mean baseline total UPDRS score was 22.7. A total of 267 participants required treatment (94 received placebo, 87 received 1200 mg/d of CoQ10, and 86 received 2400 mg/d of CoQ10), and 65 participants (29 who received placebo, 19 who received 1200 mg/d of CoQ10, and 17 who received 2400 mg/d of CoQ10) withdrew prematurely. Treatments were well tolerated with no safety concerns. The study was terminated after a prespecified futility criterion was reached. At study termination, both active treatment groups showed slight adverse trends relative to placebo. Adjusted mean changes (worsening) in total UPDRS scores from baseline to final visit were 6.9 points (placebo), 7.5 points (1200 mg/d of CoQ10; $P = .49$ relative to placebo), and 8.0 points (2400 mg/d of CoQ10; $P = .21$ relative to placebo).

CONCLUSIONS AND RELEVANCE:

Coenzyme Q10 was safe and well tolerated in this population, but showed no evidence of clinical benefit.

TRIAL REGISTRATION:

clinicaltrials.gov Identifier: [NCT00740714](https://clinicaltrials.gov/ct2/show/study/NCT00740714).

PMID: 24664227 [Indexed for MEDLINE]

[Similar articles](#)



18. Environ Toxicol Pharmacol. 2014 Jan;37(1):45-54. doi: 10.1016/j.etap.2013.10.016. Epub 2013 Nov 13.

Effect of vitamin E and C supplementation on oxidative damage and total antioxidant capacity in lead-exposed workers.

[Rendón-Ramírez AL](#)¹, [Maldonado-Vega M](#)², [Quintanar-Escorza MA](#)³, [Hernández G](#)⁴, [Arévalo-Rivas BI](#)⁵, [Zentella-Dehesa A](#)⁶, [Calderón-Salinas JV](#)⁷.

Author information:

1. Biochemistry Department, Centro de Investigación y Estudios Avanzados IPN, México, DF, Mexico.
 2. CIATEC, León, GTO, Mexico.
 3. Faculty of Medicine, UJED, Durango, DGO, Mexico.
 4. Section of Methodology of Science, Centro de Investigación y Estudios Avanzados IPN, México, DF, Mexico.
 5. HRAEB, León, GTO, Mexico.
 6. Cellular Physiology Institute, UNAM, Mexico.
 7. Biochemistry Department, Centro de Investigación y Estudios Avanzados IPN, México, DF, Mexico.
- Electronic address: jcalder@cinvestav.mx.

Abstract

The molecular response of the antioxidant system and the effects of antioxidant supplementation against oxidative insult in lead-exposed workers has not been sufficiently studied. In this work, antioxidants (vitamin E 400 IU+vitamin C 1g/daily) were supplemented for one year to 15 workers exposed to lead (73 µg of lead/dl of blood) and the results were compared with those on 19 non-lead exposed workers (6.7 µg of lead/dl). Lead intoxication was accompanied by a high oxidative damage and an increment in the erythrocyte antioxidant response due to increased activity of catalase and superoxide dismutase. Antioxidant supplementations decreased significantly the oxidative damage as well as the total antioxidant capacity induced by lead intoxication with reduction of the antioxidant enzyme activities. We conclude that antioxidant supplementation is effective in reducing oxidative damage and induces modifications in the physiopathological status of the antioxidant response in lead-exposed workers.

PMID: 24560336 [Indexed for MEDLINE]

[Similar articles](#)



19. JAMA. 2014 Jan 1;311(1):33-44. doi: 10.1001/jama.2013.282834.

Effect of vitamin E and memantine on functional decline in Alzheimer disease: the TEAM-AD VA

cooperative randomized trial.

[Dysken MW](#)¹, [Sano M](#)², [Asthana S](#)³, [Vertrees JE](#)⁴, [Pallaki M](#)⁵, [Llorente M](#)⁶, [Love S](#)¹, [Schellenberg GD](#)⁷, [McCarten JR](#)¹, [Malphurs J](#)⁸, [Prieto S](#)⁸, [Chen P](#)⁵, [Loreck DJ](#)⁹, [Trapp G](#)¹⁰, [Bakshi RS](#)¹⁰, [Mintzer JE](#)¹¹, [Heidebrink JL](#)¹², [Vidal-Cardona A](#)¹³, [Arroyo LM](#)¹³, [Cruz AR](#)¹⁴, [Zachariah S](#)¹⁴, [Kowall NW](#)¹⁵, [Chopra MP](#)¹⁵, [Craft S](#)¹⁶, [Thielke S](#)¹⁶, [Turvey CL](#)¹⁷, [Woodman C](#)¹⁷, [Monnell KA](#)¹⁸, [Gordon K](#)¹⁸, [Tomaska J](#)¹, [Segal Y](#)¹, [Peduzzi PN](#)¹⁹, [Guarino PD](#)¹⁹.

Author information:

1. Minneapolis VA Health Care System, Minneapolis, Minnesota.
2. James J. Peters VA Medical Research Center, New York, New York.
3. William S. Middleton Memorial Veterans Hospital, Madison, Wisconsin.
4. Cooperative Studies Program Clinical Research Pharmacy Coordinating Center, Albuquerque, New Mexico.
5. Louis Stokes Cleveland VA Medical Center, Cleveland, Ohio6Case Western Reserve University School of Medicine, Cleveland, Ohio.
6. Washington DC VA Medical Center, Washington, DC.
7. University of Pennsylvania School of Medicine, Philadelphia.
8. Miami VA Healthcare System, Miami, Florida.
9. VA Maryland Healthcare System, Baltimore11University of Maryland Medical School, Department of Psychiatry, Baltimore.
10. VA North Texas Health Care System, Dallas.
11. Ralph H. Johnson VA Medical Center, Charleston, South Carolina14Department of Health Studies, Medical University of South Carolina, Charleston15Roper St Francis Healthcare, Charleston, South Carolina.
12. VA Ann Arbor Healthcare System, Ann Arbor, Michigan.
13. VA Caribbean Healthcare System, San Juan, Puerto Rico.
14. Bay Pines VA Healthcare System, Bay Pines, Florida.
15. VA Boston Healthcare System, Boston, Massachusetts.
16. VA Puget Sound Health Care System, Seattle, Washington21Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle.
17. Iowa City VA Medical Center, Iowa City, Iowa23University of Iowa, Iowa City.
18. W. G. (Bill) Hefner VA Medical Center, Salisbury, North Carolina.
19. Cooperative Studies Program Coordinating Center, VA Connecticut Healthcare System, West Haven26Yale University School of Public Health, New Haven, Connecticut.

Erratum in

- JAMA. 2014 Mar 19;311(11):1161.

Comment in

- [Vitamin E, memantine, and Alzheimer disease.](#) [JAMA. 2014]
- [The value of vitamin E as a treatment for Alzheimer's disease remains unproven despite functional improvement, due to a lack of established effect on cognition or other outcomes from RCTs.](#) [Evid Based Med. 2014]

Abstract

IMPORTANCE:

Although vitamin E and memantine have been shown to have beneficial effects in moderately severe Alzheimer disease (AD), evidence is limited in mild to moderate AD.

OBJECTIVE:

To determine if vitamin E (alpha tocopherol), memantine, or both slow progression of mild to moderate AD in patients taking an acetylcholinesterase inhibitor.

DESIGN, SETTING, AND PARTICIPANTS:

Double-blind, placebo-controlled, parallel-group, randomized clinical trial involving 613 patients with mild to moderate AD initiated in August 2007 and concluded in September 2012 at 14 Veterans Affairs medical centers.

INTERVENTIONS:

Participants received either 2000 IU/d of alpha tocopherol (n = 152), 20 mg/d of memantine (n = 155), the combination (n = 154), or placebo (n = 152).

MAIN OUTCOMES AND MEASURES:

Alzheimer's Disease Cooperative Study/Activities of Daily Living (ADCS-ADL) Inventory score (range, 0-78). Secondary outcomes included cognitive, neuropsychiatric, functional, and caregiver measures.

RESULTS:

Data from 561 participants were analyzed (alpha tocopherol = 140, memantine = 142, combination = 139, placebo = 140), with 52 excluded because of a lack of any follow-up data. Over the mean (SD) follow-up of 2.27 (1.22) years, ADCS-ADL Inventory scores declined by 3.15 units (95% CI, 0.92 to 5.39; adjusted P = .03) less in the alpha tocopherol group compared with the placebo group. In the memantine group, these scores declined 1.98 units less (95% CI, -0.24 to 4.20; adjusted P = .40) than the placebo group's decline. This change in the alpha tocopherol group translates into a delay in clinical progression of 19% per year compared with placebo or a delay of approximately 6.2 months over the follow-up period. Caregiver time increased least in the alpha tocopherol group. All-cause mortality and safety analyses showed a difference only on the serious adverse event of "infections or infestations," with greater frequencies in the memantine (31 events in 23 participants) and combination groups (44 events in 31 participants) compared with placebo (13 events in 11 participants).

CONCLUSIONS AND RELEVANCE:

Among patients with mild to moderate AD, 2000 IU/d of alpha tocopherol compared with placebo resulted in slower functional decline. There were no significant differences in the groups receiving memantine alone or memantine plus alpha tocopherol. These findings suggest benefit of alpha tocopherol in mild to moderate AD by slowing functional decline and decreasing caregiver burden.

TRIAL REGISTRATION:

clinicaltrials.gov Identifier: [NCT00235716](https://clinicaltrials.gov/ct2/show/study/NCT00235716).

PMCID: PMC4109898 **Free PMC Article**

PMID: 24381967 [Indexed for MEDLINE]

[Similar articles](#)



20. J Child Adolesc Psychopharmacol. 2013 Oct;23(8):558-67. doi: 10.1089/cap.2012.0098.

Nutritional and safety outcomes from an open-label micronutrient intervention for pediatric bipolar spectrum disorders.

[Frazier EA](#)¹, [Gracious B](#), [Arnold LE](#), [Failla M](#), [Chitchumroonchokchai C](#), [Habash D](#), [Fristad MA](#).

Author information:

1. Department of Psychiatry, Department of Human Nutrition, The Ohio State University, Columbus, Ohio.

Abstract

OBJECTIVE:

The purpose of this study was to report the safety, tolerability, and serum micronutrient concentrations and their correlations with mood changes from an 8 week pilot feasibility study of a 36 ingredient multinutrient supplement, EMPowerplus (EMP+), for pediatric bipolar spectrum disorders (BPSD).

METHODS:

Ten children ages 6-12 received EMP+ escalating from one to four capsules t.i.d., with four children increased to the maximum suggested dose, five capsules t.i.d. Outcome measures were micronutrient concentrations in serum and red blood cells, vital signs, body mass index (BMI), dietary intake (Food Frequency Questionnaire and 24 hour dietary recall interview), and mood and global functioning ratings.

RESULTS:

Seven children (70%) completed the study. Three (30%) terminated early for tolerability and compliance issues. Adverse effects were mild and transient, and chiefly consisted of initial insomnia or gastrointestinal (GI) upset. No differences occurred in BMI ($p = 0.310$) or waist-hip ratio (WHR; $p = 0.674$) pre- to postsupplementation. Four of the tested serum vitamin concentrations increased from pre- to postsupplementation: vitamin A-retinol, vitamin B6, vitamin E- α -tocopherol; and folate (all $p < 0.05$). The increase in serum 25-OH vitamin D approached significance ($p = 0.063$). No differences were found in dietary intake pre- to postsupplementation, suggesting that blood nutrient level increases were caused by EMP+.

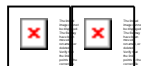
CONCLUSIONS:

In this open prospective study, short-term use of EMP+ in children with BPSD appeared safe and well-tolerated, with a side effect profile preferable to first-line psychotropic drugs for pediatric bipolar spectrum disorders. A double-blind, randomized clinical trial is feasible, appears safe, and is warranted by open-label clinical outcomes and plausible mechanisms of action, combined with documentation of increased serum concentrations of specific micronutrients.

PMCID: PMC3804335 **Free PMC Article**

PMID: 24138009 [Indexed for MEDLINE]

[Similar articles](#)



21. Clin Drug Investig. 2014 Jan;34(1):1-7. doi: 10.1007/s40261-013-0136-3.

Randomized, vitamin E-controlled trial of bicyclol plus metformin in non-alcoholic fatty liver disease patients with impaired fasting glucose.

[Han Y¹](#), [Shi JP](#), [Ma AL](#), [Xu Y](#), [Ding XD](#), [Fan JG](#).

Author information:

1. Department of Gastroenterology, Xijing Hospital of Digestive Diseases, The Fourth Military Medical University, Xi'an, 710032, China.

Abstract

BACKGROUND:

Non-alcoholic fatty liver disease (NAFLD) is associated with a high morbidity in patients with impaired fasting glucose (IFG). Bicyclol is a synthetic compound known to protect the liver against oxidation and lipid injuries.

OBJECTIVE:

The objective of this study was to evaluate the efficacy and safety of metformin and bicyclol in the treatment of NAFLD patients with IFG.

METHODS:

After lifestyle changes and metformin treatment (500 mg orally three times daily), the 248 patients enrolled with NAFLD and IFG were equally randomized to two 24-week treatment groups: bicyclol 25 mg three times daily or vitamin E (α -tocopherol) 100 mg three times daily (control). Anthropometric measurements, serum biochemistry, liver/spleen computed tomography ratio, and changes in liver histological parameters were compared before and after treatments.

RESULTS:

A total of 223 patients completed the treatment, and there were significant improvements in body mass index, waist-to-hip ratio, and biochemical parameters in both groups ($P < 0.01$). Compared with the control group, the improvement in serum alanine aminotransferase levels in the bicyclol group was statistically significant ($P < 0.01$). Liver histological assessments revealed that steatosis, inflammation, hepatocellular ballooning, and NAFLD activity scores (NAS) were all decreased in both groups after treatment ($P < 0.01$). However, decreases in inflammation and NAS in the bicyclol group were statistically significant compared with the vitamin E group ($P < 0.01$). Adverse events in the bicyclol and control groups occurred in 1.79 and 1.80 %, respectively.

CONCLUSION:

Metformin combined with bicyclol is effective and safe in the treatment of patients with NAFLD and IFG. However, further studies with a larger sample size are needed to confirm the efficacy and safety of the combination.

PMID: 24081374 [Indexed for MEDLINE]

[Similar articles](#)



22. J Pediatr Gastroenterol Nutr. 2014 Feb;58(2):177-82. doi: 10.1097/MPG.000000000000174.

[Fish Oil \(SMOFlipid\) and olive oil lipid \(Clinoleic\) in very preterm neonates.](#)

[Deshpande G¹](#), [Simmer K](#), [Deshmukh M](#), [Mori TA](#), [Croft KD](#), [Kristensen J](#).

Author information:

1. *Department of Neonatal Paediatrics, King Edward Memorial Hospital Western Australia †School of Medicine and Pharmacology, University of Western Australia ‡Department of Pharmacy, King Edward Memorial Hospital for Women, Perth, Australia.

Abstract

OBJECTIVES:

Fat emulsions used in Australia for parenteral nutrition in preterm neonates have been based on either soybean oil or olive oil (OO). OO lipid Clinoleic has a high ratio of n-6 to n-3 fatty acids (9:1); this may not be ideal for long-chain polyunsaturated fatty acids supply. Newly available SMOFlipid has an appropriate ratio of n-6 to n-3 fatty acids (2.5:1). SMOFlipid also contains OO (25%), coconut oil (30%), and soybean oil (30%). The aims of the study were to evaluate the safety of the SMOFlipid and to test the hypothesis that SMOFlipid would lead to increased omega-3 long-chain polyunsaturated fatty acid levels and reduced oxidative stress as compared with Clinoleic in preterm neonates (<30 weeks).

METHODS:

Preterm neonates (23-30 weeks) were randomised to receive Clinoleic or SMOFlipid emulsion for 7 days. Investigators and outcome assessors were masked to allocation. Plasma F2-isoprostanes (lipid peroxidation marker), red blood cell fatty acids, and vitamin E were measured before and after the study. Blood culture

positive sepsis and growth were monitored for safety.

RESULTS:

Thirty of 34 participants completed the study. Both emulsions were well tolerated without any adverse events. F2-isoprostane levels were reduced in the SMOFlipid group as compared with baseline. Eicosapentanoic acid and vitamin E levels were significantly increased in the SMOFlipid group. Oleic acid and linoleic acid levels were increased in both groups. No significant differences were noted in poststudy docosahexaenoic acid levels in both groups despite higher levels of docosahexaenoic acid in SMOFlipid.

CONCLUSIONS:

SMOFlipid was safe, well tolerated, and showed beneficial effect in terms of reduction of oxidative stress by reducing lipid peroxidation levels in high-risk preterm neonates.

PMID: 24048161 [Indexed for MEDLINE]

[Similar articles](#)



23. J Am Coll Nutr. 2013;32(1):31-40. doi: 10.1080/07315724.2013.767661.

Green tea and vitamin E enhance exercise-induced benefits in body composition, glucose homeostasis, and antioxidant status in elderly men and women.

[Narotzki B¹](#), [Reznick AZ](#), [Navot-Mintzer D](#), [Dagan B](#), [Levy Y](#).

Author information:

1. Department of Anatomy and Cell Biology, Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel.

Abstract

OBJECTIVE:

To investigate the effects of green tea plus vitamin E in addition to exercise on body composition and metabolic and antioxidant parameters in healthy elderly individuals.

DESIGN:

Interventional randomized controlled prospective trial.

METHODS:

For 12 weeks, 22 elderly men and women (age: 71.1 ± 1.2 years; body mass index: 28.3 ± 0.5 kg/m²) [mean \pm SE] undertook 30 minutes of moderately intense walking 6 d/wk. They were randomly assigned to ingest either green tea plus vitamin E (GTVE; 3 cups and 400 IU, respectively; n = 11) or placebo (n = 11).

Data on anthropometrics, fasting insulin and glucose levels, physical fitness, dietary intake, safety parameters, and biomarkers of oxidation status were recorded and analyzed at the start and end of the study.

RESULTS:

Though dietary intake was unchanged, improved exercise capacity was followed by a significant reduction in body weight and fasting insulin levels in all participants. Additional consumption of GTVE resulted in a twofold increase in serum vitamin E (from 20.4 to 40.6 $\mu\text{mol/L}$, $p < 0.001$) and a decrease of men's and women's waist circumferences (from 100.8 and 95.7 to 96.9 and 85.0 cm, $p < 0.05$ and $p < 0.01$, respectively) and fasting glucose levels (from 5.30 to 4.98 mmol/L, $p < 0.01$). Plasma protein carbonyls dropped (from 0.93 to 0.77 nmol/mg protein, $p < 0.05$), whereas erythrocyte catalase activities increased (from 26.7 to 29.7 U/g hemoglobin, $p < 0.05$) in the GTVE group only. Oral peroxidase activities were increased in both groups.

CONCLUSIONS:

A daily dose of GTVE in healthy elderly men and women may improve exercise-induced benefits in body composition and glucose tolerance and may also lower oxidative burden.

PMID: 24015697 [Indexed for MEDLINE]

[Similar articles](#)

24. Zhongguo Zhen Jiu. 2013 May;33(5):403-6.

[Efficacy observation on acupuncture and moxibustion combined with hot compress of TCM herbs for scleroderma].

[Article in Chinese]

[Yan XN](#)¹, [Zhang JR](#), [Zhang CQ](#), [Tian Q](#), [Chen L](#), [Chen L](#).

Author information:

1. Department of Dermatology, Shaanxi TCM Hospital, Xi'an 710004, China. yanxiaon2005@126.com

Abstract

OBJECTIVE:

To assess the clinical efficacy and safety of surrounding needle, moxibustion and hot compress of TCM herbs for localized scleroderma.

METHODS:

Forty-two cases of localized scleroderma were randomly divided into an acupuncture + herb group (23 cases, group A) and a heparin sodium group (19 cases, group B). Both the two groups were orally administrated with centella triterpenes tablets and vitamin E, group A was additionally treated with surrounding needle at local area, moxibustion at affected site and Hegu (LI 4), Zu sanli (ST 36) as well as hot external application of "hot compress herbs" at local location, while group B was treated with external application of heparin sodium cream. Both the two groups were treated for consecutive 6 months, and scores

of skin sclerosis, joint pain and function were compared before and after the treatment. Also the efficacy and safety of TCM syndrome were assessed.

RESULTS:

Compared with that before the treatment, the scores of skin sclerosis, joint pain and joint function in the group A after treatment were significantly decreased (all $P < 0.01$), the score of skin sclerosis in the group B was improved ($P < 0.05$), and the three types of score in the group A was obviously lower than those in the group B (both $P < 0.05$). The total effective rate was 86.4% (19/22) in the group A, which was superior to 52.6% (10/19) in the group B ($P < 0.05$).

CONCLUSION:

The surrounding needle, moxibustion and external application of "hot compress herbs" could improve skin sclerosis in patients with localized scleroderma, which has obvious efficacy and relative safety.

PMID: 23885611 [Indexed for MEDLINE]

[Similar articles](#)

25. Eur J Clin Invest. 2013 Jun;43(6):579-88. doi: 10.1111/eci.12085. Epub 2013 Apr 17.

[Baseline comorbidities in a skin cancer prevention trial in Bangladesh.](#)

[Argos M¹](#), [Rahman M](#), [Parvez F](#), [Dignam J](#), [Islam T](#), [Quasem I](#), [K Hore S](#), [T Haider A](#), [Hossain Z](#), [I Patwary T](#), [Rakibuz-Zaman M](#), [Sarwar G](#), [La Porte P](#), [Harjes J](#), [Anton K](#), [Kibriya MG](#), [Jasmine F](#), [Khan R](#), [Kamal M](#), [Shea CR](#), [Yunus M](#), [Baron JA](#), [Ahsan H](#).

Author information:

1. Department of Health Studies, The University of Chicago, Chicago, IL 60637, USA.

Abstract

BACKGROUND:

Epidemiologic research suggests that increased cancer risk due to chronic arsenic exposure persists for several decades even after the exposure has terminated. Observational studies suggest that antioxidants exert a protective effect on arsenical skin lesions and cancers among those chronically exposed to arsenic through drinking water. This study reports on the design, methods and baseline analyses from the Bangladesh Vitamin E and Selenium Trial (BEST), a population-based chemoprevention study conducted among adults in Bangladesh with visible arsenic toxicity.

MATERIALS AND METHODS:

Bangladesh Vitamin E and Selenium Trial is a 2×2 full factorial, double-blind, randomized controlled trial of 7000 adults having manifest arsenical skin lesions evaluating the efficacy of 6-year supplementation with alpha-tocopherol (100 mg daily) and L-selenomethionine (200 μg daily) for the prevention of nonmelanoma skin cancer.

RESULTS:

In cross-sectional analyses, we observed significant associations of skin lesion severity with male gender (female prevalence odds ratio (POR) = 0.87; 95% CI = 0.79-0.96), older age (aged 36-45 years, POR = 1.27; 95% CI = 1.13-1.42; aged 46-55 years, POR = 1.44; 95% CI = 1.27-1.64 and aged 56-65 years, POR = 1.50; 95% CI = 1.26-1.78 compared with aged 25-35 years), hypertension (POR = 1.29; 95% CI = 1.08-1.55), diabetes (POR = 2.13; 95% CI = 1.32-3.46), asthma (POR = 1.55; 95% CI = 1.03-2.32) and peptic ulcer disease (POR = 1.20; 95% CI = 1.07-1.35).

CONCLUSIONS:

We report novel associations between arsenical skin lesions with several common chronic diseases. With the rapidly increasing burden of preventable cancers in developing countries, efficient and feasible chemoprevention study designs and approaches, such as employed in BEST, may prove both timely and potentially beneficial in conceiving cancer chemoprevention trials in Bangladesh and beyond.

© 2013 Stichting European Society for Clinical Investigation Journal Foundation. Published by John Wiley & Sons Ltd.

PMCID: PMC3953314 **Free PMC Article**

PMID: 23590571 [Indexed for MEDLINE]

[Similar articles](#)



26. *Alzheimers Dement.* 2014 Jan;10(1):36-44. doi: 10.1016/j.jalz.2013.01.014. Epub 2013 Apr 11.

[Vitamin E and memantine in Alzheimer's disease: clinical trial methods and baseline data.](#)

[Dysken MW](#)¹, [Guarino PD](#)², [Vertrees JE](#)³, [Asthana S](#)⁴, [Sano M](#)⁵, [Llorente M](#)⁶, [Pallaki M](#)⁷, [Love S](#)⁸, [Schellenberg GD](#)⁹, [McCarten JR](#)⁸, [Malphurs J](#)¹⁰, [Prieto S](#)¹⁰, [Chen P](#)⁷, [Loreck DJ](#)¹¹, [Carney S](#)¹², [Trapp G](#)¹³, [Bakshi RS](#)¹³, [Mintzer JE](#)¹⁴, [Heidebrink JL](#)¹⁵, [Vidal-Cardona A](#)¹⁶, [Arroyo LM](#)¹⁶, [Cruz AR](#)¹⁷, [Kowall NW](#)¹⁸, [Chopra MP](#)¹⁸, [Craft S](#)¹⁹, [Thielke S](#)¹⁹, [Turvey CL](#)²⁰, [Woodman C](#)²⁰, [Monnell KA](#)²¹, [Gordon K](#)²¹, [Tomaska J](#)⁸, [Vatassery G](#)⁸.

Author information:

1. VA Minneapolis Health Care System, Minneapolis, MN, USA. Electronic address: maurice.dysken@va.gov.
2. Cooperative Studies Program Coordinating Center, VA Connecticut Healthcare System, West Haven, CT, USA.
3. VA Cooperative Studies Program Clinical Research Pharmacy Coordinating Center, Albuquerque, NM, USA.
4. William S. Middleton Memorial Veterans Hospital, Madison, WI, USA.
5. Bronx Veterans Medical Research Center, New York, NY, USA.
6. VAMC, Washington, DC, USA.
7. Louis Stokes Cleveland VAMC, Cleveland, OH, USA.
8. VA Minneapolis Health Care System, Minneapolis, MN, USA.

9. University of Pennsylvania School of Medicine, Philadelphia, PA, USA.
10. VA Miami Healthcare System, Miami, FL, USA.
11. VA Maryland Healthcare System, University of Maryland Medical School, Department of Psychiatry, Baltimore, MD, USA.
12. VA Maryland Healthcare System, Baltimore, MD, USA.
13. VA North Texas Healthcare System, Dallas, TX, USA.
14. Ralph H. Johnson VAMC, Medical University of South Carolina, Charleston, SC, USA.
15. VA Ann Arbor Healthcare System, Ann Arbor, MI, USA.
16. VA Caribbean Healthcare System, San Juan, PR.
17. Bay Pines VA Healthcare System, Bay Pines, FL, USA.
18. VA Boston Healthcare System, Boston, MA, USA.
19. VA Puget Sound Healthcare System, Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, WA, USA.
20. Iowa City VAMC, University of Iowa, Iowa City, IA, USA.
21. W.G. (Bill) Hefner VAMC, Salisbury, NC, USA.

Abstract

BACKGROUND:

Alzheimer's disease (AD) has been associated with both oxidative stress and excessive glutamate activity. A clinical trial was designed to compare the effectiveness of (i) alpha-tocopherol, a vitamin E antioxidant; (ii) memantine (Namenda), an N-methyl-D-aspartate antagonist; (iii) their combination; and (iv) placebo in delaying clinical progression in AD.

METHODS:

The Veterans Affairs Cooperative Studies Program initiated a multicenter, randomized, double-blind, placebo-controlled trial in August 2007, with enrollment through March 2012 and follow-up continuing through September 2012. Participants with mild-to-moderate AD who were taking an acetylcholinesterase inhibitor were assigned randomly to 2000 IU/day of alpha-tocopherol, 20 mg/day memantine, 2000 IU/day alpha-tocopherol plus 20 mg/day memantine, or placebo. The primary outcome for the study is the Alzheimer's Disease Cooperative Study/Activities of Daily Living Inventory. Secondary outcome measures include the Mini-Mental State Examination; the Alzheimer's Disease Assessment Scale, cognitive portion; the Dependence Scale; the Neuropsychiatric Inventory; and the Caregiver Activity Survey. Patient follow-up ranged from 6 months to 4 years.

RESULTS:

A total of 613 participants were randomized. The majority of the patients were male (97%) and white (86%), with a mean age of 79 years. The mean Alzheimer's Disease Cooperative Study/Activities of Daily Living Inventory score at entry was 57 and the mean Mini-Mental State Examination score at entry was 21.

CONCLUSION:

This large multicenter trial will address the unanswered question of the long-term safety and effectiveness of alpha-tocopherol, memantine, and their combination in patients with mild-to-moderate AD taking an acetylcholinesterase inhibitor. The results are expected in early 2013.

Published by Elsevier Inc.

PMCID: PMC4128187 **Free PMC Article**

PMID: 23583234 [Indexed for MEDLINE]

[Similar articles](#)



27. Sao Paulo Med J. 2013;131(1):35-8.

Vitamin E for prevention of oxaliplatin-induced peripheral neuropathy: a pilot randomized clinical trial.

[Afonseca SO¹](#), [Cruz FM](#), [Cubero Dde I](#), [Lera AT](#), [Schindler F](#), [Okawara M](#), [Souza LF](#), [Rodrigues NP](#), [Giglio Ad](#).

Author information:

1. Department of Hematology and Oncology, Faculdade de Medicina do ABC, Fundação ABC, Santo André, São Paulo, Brazil.

Abstract

CONTEXT AND OBJECTIVE Oxaliplatin is one of the chemotherapy regimens most used for treating colorectal cancer. One of the main limitations to its use is induction of peripheral neuropathy. Previous studies have shown that vitamin E can reduce the incidence of peripheral neuropathy by 50%. This study aimed to assess the effectiveness of vitamin E for prevention of oxaliplatin-induced peripheral neuropathy. **DESIGN AND SETTING** Prospective, phase II, randomized pilot study developed at a university hospital in the Greater ABC region. **METHODS** Patients were randomized five days before starting oxaliplatin treatment, to receive either vitamin E or placebo until the end of the chemotherapy regimen. The outcome was evaluated using the Common Terminology Criteria for Adverse Events (CTCAE), version 3, and specific gradation scales for oxaliplatin-induced peripheral neuropathy. Patients with colorectal and gastric cancer who had been scheduled to receive oxaliplatin-based chemotherapy were included. Both groups received calcium and magnesium supplementation before and after oxaliplatin infusions. **RESULTS** Eighteen patients were randomized to the vitamin E group and 16 to the placebo group. Cumulative incidence of 83% with peripheral neuropathy grades 1/2 was observed in the vitamin E group, versus 68% in the placebo group ($P = 0.45$). A trend towards more diarrhea was observed among patients who received vitamin E (55.6% vs. 18.8%; $P = 0.06$). There were no other significant differences in toxicity between the groups. **CONCLUSIONS** No significant decrease in the incidence of acute oxaliplatin-induced peripheral neuropathy was demonstrated through vitamin E use.

TRIAL REGISTRATION:

ClinicalTrials.gov [NCT01523574](#).

Free Article

PMID: 23538593 [Indexed for MEDLINE]



Evaluation of the effect of vitamin E on pelvic pain reduction in women suffering from primary dysmenorrhea.

[Kashanian M¹](#), [Lakeh MM](#), [Ghasemi A](#), [Noori S](#).

Author information:

1. Department of Obstetrics and Gynecology, Tehran University of Medical Sciences, Akbarabadi Teaching Hospital, Tehran, Iran. maryamkashanian@yahoo.com

Abstract

OBJECTIVE:

To evaluate the effect of vitamin E on the reduction of pelvic pain in women with primary dysmenorrhea and to compare its effect with placebo.

STUDY DESIGN:

A double-blind randomized clinical trial was performed on 120 women suffering from primary dysmenorrhea. They were randomly assigned into 2 groups, and 94 women finished the study. In the study group (n = 42) 400 IU/day of vitamin E was prescribed starting 2 days before the beginning of menstruation and continuing for a total of 5 days, for 2 consecutive cycles. In the control group (n = 52) a placebo was prescribed. Pain severity was evaluated using the Visual Analogue Scale for 1 month before the study and during the 2 months of study.

RESULTS:

Pain severity during the first month of the study was 5.41 +/- 2.4 in the study group and 5.76 +/- 2.08 in the control group and 4.73 +/- 1.89 and 5.35 +/- 2.05 in the study and control groups, respectively, during the second month of the study. Pain severity during the first and second months of treatment with vitamin E and placebo was lower than the pain severity before treatment. The mean reduction of pain in the study group (-2.7 +/- 2.1) was greater than that in the control group (-1.8 +/- 2.4) during the second month of the study.

CONCLUSION:

Both vitamin E and placebo may reduce the pelvic pain of dysmenorrhea, but vitamin E seems to cause a more significant reduction in pain. With regard to its safety, the study indicates it can be a simple and safe option for the treatment of dysmenorrhea.

PMID: 23447916 [Indexed for MEDLINE]

[Similar articles](#)

[Vitamin E, \$\gamma\$ -tocopherol, reduces airway neutrophil recruitment after inhaled endotoxin challenge in rats and in healthy volunteers.](#)

[Hernandez ML](#)¹, [Wagner JG](#), [Kala A](#), [Mills K](#), [Wells HB](#), [Alexis NE](#), [Lay JC](#), [Jiang Q](#), [Zhang H](#), [Zhou H](#), [Peden DB](#).

Author information:

1. Center for Environmental Medicine, Asthma, & Lung Biology, The University of North Carolina at Chapel Hill, Chapel Hill, NC 27516, USA. Michelle_Hernandez@med.unc.edu

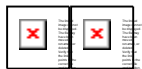
Abstract

Epidemiologic studies suggest that dietary vitamin E is an important candidate intervention for asthma. Our group has shown that daily consumption of vitamin E (γ -tocopherol, γ T) has anti-inflammatory actions in both rodent and human phase I studies. The objective of this study was to test whether γ T supplementation could mitigate a model of neutrophilic airway inflammation in rats and in healthy human volunteers. F344/N rats were randomized to oral gavage with γ T versus placebo, followed by intranasal LPS (20 μ g) challenge. Bronchoalveolar lavage fluid and lung histology were used to assess airway neutrophil recruitment. In a phase IIa clinical study, 13 nonasthmatic subjects completed a double-blinded, placebo-controlled crossover study in which they consumed either a γ T-enriched capsule or a sunflower oil placebo capsule. After 7 days of daily supplementation, they underwent an inhaled LPS challenge. Induced sputum was assessed for neutrophils 6 h after inhaled LPS. The effect of γ T compared to placebo on airway neutrophils post-LPS was compared using a repeated-measures analysis of variance. In rats, oral γ T supplementation significantly reduced tissue infiltration ($p < 0.05$) and accumulation of airway neutrophils ($p < 0.05$) that are elicited by intranasal LPS challenge compared to control rats. In human volunteers, γ T treatment significantly decreased induced sputum neutrophils ($p = 0.03$) compared to placebo. Oral supplementation with γ T reduced airway neutrophil recruitment in both rat and human models of inhaled LPS challenge. These results suggest that γ T is a potential therapeutic candidate for prevention or treatment of neutrophilic airway inflammation in diseased populations.

PMCID: PMC3654053 **Free PMC Article**

PMID: 23402870 [Indexed for MEDLINE]

[Similar articles](#)



[Effect of high-dose vs standard-dose multivitamin supplementation at the initiation of HAART on HIV disease progression and mortality in](#)

Tanzania: a randomized controlled trial.

[Isanaka S¹](#), [Mugusi F](#), [Hawkins C](#), [Spiegelman D](#), [Okuma J](#), [Aboud S](#), [Guerino C](#), [Fawzi WW](#).

Author information:

1. Departments of Nutrition, Harvard School of Public Health, Boston, Massachusetts 02115, USA.
sisanaka@hsph.harvard.edu

Comment in

- [Standard-dose vs high-dose multivitamin supplements for HIV](#). [JAMA. 2013]
- [Standard-dose vs high-dose multivitamin supplements for HIV--reply](#). [JAMA. 2013]

Abstract

CONTEXT:

Large randomized trials have previously shown that high-dose micronutrient supplementation can increase CD4 counts and reduce human immunodeficiency virus (HIV) disease progression and mortality among individuals not receiving highly active antiretroviral therapy (HAART); however, the safety and efficacy of such supplementation has not been established in the context of HAART.

OBJECTIVE:

To test the hypothesis that high-dose multivitamin supplementation vs standard-dose multivitamin supplementation decreases the risk of HIV disease progression or death and improves immunological, virological, and nutritional parameters in patients with HIV initiating HAART.

DESIGN, SETTING, AND PARTICIPANTS:

A randomized, double-blind, controlled trial of high-dose vs standard-dose multivitamin supplementation for 24 months in 3418 patients with HIV initiating HAART between November 2006 and November 2008 in 7 clinics in Dar es Salaam, Tanzania. INTERVENTION The provision of daily oral supplements of vitamin B complex, vitamin C, and vitamin E at high levels or standard levels of the recommended dietary allowance.

MAIN OUTCOME MEASURE:

The composite of HIV disease progression or death from any cause.

RESULTS:

The study was stopped early in March 2009 because of evidence of increased levels of alanine transaminase (ALT) in patients receiving the high-dose multivitamin supplement. At the time of stopping, 3418 patients were enrolled (median follow-up, 15 months), and there were 2374 HIV disease progression events and 453 observed deaths (2460 total combined events). Compared with standard-dose multivitamin supplementation, high-dose supplementation did not reduce the risk of HIV disease progression or death. The absolute risk of HIV progression or death was 72% in the high-dose group vs 72% in the standard-dose group (risk ratio [RR], 1.00; 95% CI, 0.96-1.04). High-dose supplementation had no effect on CD4 count, plasma viral load,

body mass index, or hemoglobin level concentration, but increased the risk of ALT elevations (1239 events per 1215 person-years vs 879 events per 1236 person-years; RR, 1.44; 95% CI, 1.11-1.87) vs standard-dose supplementation. **CONCLUSION** In adults receiving HAART, use of high-dose multivitamin supplements compared with standard-dose multivitamin supplements did not result in a decrease in HIV disease progression or death but may have resulted in an increase in ALT levels.

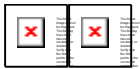
TRIAL REGISTRATION:

Clinicaltrials.gov Identifier: [NCT00383669](https://clinicaltrials.gov/ct2/show/study/NCT00383669).

PMCID: PMC3811009 **Free PMC Article**

PMID: 23073950 [Indexed for MEDLINE]

[Similar articles](#)



31. Clin Trials. 2013 Feb;10(1):131-42. doi: 10.1177/1740774512460345. Epub 2012 Oct 12.

Moving a randomized clinical trial into an observational cohort.

[Goodman PJ](#)¹, [Hartline JA](#), [Tangen CM](#), [Crowley JJ](#), [Minasian LM](#), [Klein EA](#), [Cook ED](#), [Darke AK](#), [Arnold KB](#), [Anderson K](#), [Yee M](#), [Meyskens FL](#), [Baker LH](#).

Author information:

1. SWOG Statistical Center, Fred Hutchinson Cancer Research Center, Seattle, WA 98109, USA.
pgoodman@fhcrc.org

Abstract

BACKGROUND:

The Selenium and Vitamin E Cancer Prevention Trial (SELECT) was a randomized, double-blind, placebo-controlled prostate cancer prevention study funded by the National Cancer Institute (NCI) and conducted by the Southwest Oncology Group (SWOG). A total of 35,533 men were assigned randomly to one of the four treatment groups (vitamin E + placebo, selenium + placebo, vitamin E + selenium, and placebo + placebo). The independent Data and Safety Monitoring Committee (DSMC) recommended the discontinuation of study supplements because of the lack of efficacy for risk reduction and because futility analyses demonstrated no possibility of benefit of the supplements to the anticipated degree (25% reduction in prostate cancer incidence) with additional follow-up. Study leadership agreed that the randomized trial should be terminated but believed that the cohort should be maintained and followed as the additional follow-up would contribute important information to the understanding of the biologic consequences of the intervention. Since the participants no longer needed to be seen in person to assess acute toxicities or to be given study supplements, it was determined that the most efficient and cost-effective way to follow them was via a central coordinated effort.

PURPOSE:

A number of changes were necessary at the local Study Sites and SELECT Statistical Center to transition to following participants via a Central Coordinating Center. We describe the transition process from a randomized clinical trial to the observational Centralized Follow-Up (CFU) study.

METHODS:

The process of transitioning SELECT, implemented at more than 400 Study Sites across the United States, Canada, and Puerto Rico, entailed many critical decisions and actions including updates to online documents such as the SELECT Workbench and Study Manual, a protocol amendment, reorganization of the Statistical Center, creation of a Transition Committee, development of materials for SELECT Study Sites, development of procedures to close Study Sites, and revision of data collection procedures and the process by which to contact participants.

RESULTS:

At the time of the publication of the primary SELECT results in December 2008, there were 32,569 men alive and currently active in the trial. As of 31 December 2011, 17,761 participants had been registered to the CFU study. This number is less than had been anticipated due to unforeseen difficulties with local Study Site institutional review boards (IRBs). However, from this cohort, we estimate that an additional 580 prostate cancer cases and 215 Gleason 7 or higher grade cancers will be identified. Over 109,000 individual items have been mailed to participants. Active SELECT ancillary studies have continued. The substantial SELECT biorepository is available to researchers; requests to use the specimens are reviewed for feasibility and scientific merit. As of April 2012, 12 proposals had been approved.

LIMITATIONS:

The accrual goal of the follow-up study was not met, limiting our power to address the study objectives satisfactorily. The CFU study is also dependent on a number of factors including continued funding, continued interest of investigators in the biorepository, and the continued contribution of the participants. Our experience may be less pertinent to investigators who wish to follow participants in a treatment trial or participants in prevention trials in other medical areas.

CONCLUSIONS:

Extended follow-up of participants in prevention research is important to study the long-term effects of the interventions, such as those used in SELECT. The approach taken by SELECT investigators was to continue to follow participants centrally via an annual questionnaire and with a web-based option. The participants enrolled in the CFU study represent a large, well-characterized, generally healthy cohort. The CFU has enabled us to collect additional prostate and other cancer endpoints and longer follow-up on the almost 18,000 participants enrolled. The utility of the extensive biorepository that was developed during the course of the SELECT is enhanced by longer follow-up.

TRIAL REGISTRATION:

ClinicalTrials.gov [NCT00006392](https://clinicaltrials.gov/ct2/show/study/NCT00006392).

PMCID: PMC3636982 **Free PMC Article**

PMID: 23064404 [Indexed for MEDLINE]

[Similar articles](#)



Four-week parenteral nutrition using a third generation lipid emulsion (SMOFlipid)--a double-blind, randomised, multicentre study in adults.

[Klek S¹](#), [Chambrier C](#), [Singer P](#), [Rubin M](#), [Bowling T](#), [Staun M](#), [Joly F](#), [Rasmussen H](#), [Strauss BJ](#), [Wanten G](#), [Smith R](#), [Abraham A](#), [Szczepanek K](#), [Shaffer J](#).

Author information:

1. Jagiellonian University Medical College, Krakow, Poland.

Abstract

PRECIS:

The aim of this study was to evaluate the safety and tolerance of a soybean/MCT/olive/fish oil emulsion in intestinal failure patients on long-term parenteral nutrition. 73 patients took part in a randomized, double-blind, multi-centre study. The study demonstrates that the lipid emulsion containing four different types of oils is safe and well tolerated in long-term PN.

BACKGROUND & AIM:

Long-term safety and efficacy of a lipid emulsion containing soybean oil, medium-chain triglycerides (MCT), olive oil and fish oil and enriched in vitamin E have not yet been evaluated in adult patients requiring long-term parenteral nutrition (PN).

METHODS:

Randomised, controlled, double-blind, multicentre study in 73 patients with stable intestinal failure, requiring PN with either soybean/MCT/olive/fish emulsion (SMOFlipid, n = 34) or soybean emulsion (Intralipid, control n = 39) for 4 weeks. Safety and tolerance were monitored with standard clinical laboratory parameters, adverse events (AEs, according to the Common Terminology Criteria for Adverse Events (CTCAE) classification v 3.0) and vital signs. Fatty acid pattern in red blood cell phospholipids and plasma lipoproteins, serum Vitamin E, Interleukin (IL)-6, and soluble tumour necrosis (s-TNF)-receptor(R)II were also evaluated.

RESULTS:

Mean concentrations of alanine transaminase (ALT), aspartate transaminase (AST) and total bilirubin, whilst remaining within the reference range, were significantly lower with soybean/MCT/olive/fish (SMOF) oil emulsion after the treatment period compared to control. Eicosapentaenoic acid, docosahexaenoic acid and n-3/n-6 fatty acid ratio increased in the SMOF group, while they remained unchanged in the control in plasma and RBC. Serum α -tocopherol concentrations significantly increased in the study group compared to control (p = 0.0004). IL-6 and sTNF-RII levels did not change during the study period. Grade 4 (serious)

adverse events occurred in 2 SMOF patients and in 8 control patients ($p = 0.03$).

CONCLUSIONS:

Soybean/MCT/olive/fish emulsion was safe and well tolerated over 4 weeks and leads to positive change in fatty acids profile.

Copyright © 2012 Elsevier Ltd and European Society for Clinical Nutrition and Metabolism. All rights reserved.

PMID: 22796064 [Indexed for MEDLINE]

[Similar articles](#)



33. Cell Biochem Funct. 2012 Oct;30(7):552-7. doi: 10.1002/cbf.2830. Epub 2012 Apr 20.

[Isotretinoin treatment induces oxidative toxicity in blood of patients with acne vulgaris: a clinical pilot study.](#)

[Erturan İ¹](#), [Naziroğlu M](#), [Akkaya VB](#).

Author information:

1. Department of Dermatology, Faculty of Medicine, Suleyman Demirel University, Isparta, Turkey.

Abstract

Acne vulgaris is the one of the most common skin diseases. Although isotretinoin (13-cis-retinoic acid) is an effective and well-tolerated medication, it has a wide range of side effects. Because the effects of isotretinoin on oxidant and antioxidant systems have not yet been clarified, we investigated plasma and erythrocyte antioxidant vitamins, lipid peroxidation (LP), reduced glutathione (GSH) and glutathione peroxidase (GSH-Px) values in patients with acne vulgaris before and after isotretinoin treatment. The study was performed on the blood plasma and erythrocytes of 31 acne vulgaris patients. Blood samples were taken from the patients before treatment and after isotretinoin (oral and 0.5-0.7 mg·kg⁻¹) treatment for 2 months. Plasma antioxidant vitamins, erythrocyte malondialdehyde, GSH and GSH-Px levels were measured. Plasma vitamin E ($p < 0.001$), lipid peroxidation (LP) and serum high-density lipoprotein cholesterol ($p < 0.001$) values were significantly lower in the treatment group than in the pre-treatment group, although erythrocyte LP ($p < 0.001$), GSH ($p < 0.01$) and GSH-Px ($p < 0.001$), aspartate aminotransferase ($p < 0.05$), alanine aminotransferase ($p < 0.05$), density lipoprotein cholesterol ($p < 0.001$) and total cholesterol ($p < 0.01$) levels were significantly higher in the treatment group than in the pre-treatment group. Vitamins A, C and β -carotene concentrations did not change significantly between the two groups. In conclusion, the results of the current study indicate that isotretinoin treatment induces oxidative stress and liver damage by decreasing plasma vitamin E and increasing erythrocytes GSH-Px, GSH and liver enzyme values.

PMID: 22517509 [Indexed for MEDLINE]

[Similar articles](#)

34. Arch Neurol. 2012 Jul;69(7):836-41.

Antioxidants for Alzheimer disease: a randomized clinical trial with cerebrospinal fluid biomarker measures.

[Galasko DR¹](#), [Peskind E](#), [Clark CM](#), [Quinn JF](#), [Ringman JM](#), [Jicha GA](#), [Cotman C](#), [Cottrell B](#), [Montine TJ](#), [Thomas RG](#), [Aisen P](#); [Alzheimer's Disease Cooperative Study](#).

Collaborators: (20)

[Weisman D](#), [Pay MM](#), [Lerner A](#), [Ziol E](#), [Quinn J](#), [Mulnard R](#), [McAdams-Ortiz C](#), [Ringman J](#), [Bardens J](#), [Jicha G](#), [Clark CM](#), [Pham C](#), [Peskind E](#), [Mandelco L](#), [Walker A](#), [Kirbach S](#), [DeKosky S](#), [Mishler-Rickard C](#), [Kittur S](#), [Mirje S](#).

Author information:

1. Department of Neurosciences, University of California, San Diego, 92093, USA. dgalasko@ucsd.edu

Abstract

OBJECTIVE:

To evaluate whether antioxidant supplements presumed to target specific cellular compartments affected cerebrospinal fluid (CSF) biomarkers.

DESIGN:

Double-blind, placebo-controlled clinical trial.

SETTING:

Academic medical centers.

PARTICIPANTS:

Subjects with mild to moderate Alzheimer disease.

INTERVENTION:

Random assignment to treatment for 16 weeks with 800 IU/d of vitamin E (α -tocopherol) plus 500 mg/d of vitamin C plus 900 mg/d of α -lipoic acid (E/C/ALA); 400 mg of coenzyme Q 3 times/d; or placebo.

MAIN OUTCOME MEASURES:

Changes from baseline to 16 weeks in CSF biomarkers related to Alzheimer disease and oxidative stress, cognition (Mini-Mental State Examination), and function (Alzheimer's Disease Cooperative Study Activities of Daily Living Scale).

RESULTS:

Seventy-eight subjects were randomized; 66 provided serial CSF specimens adequate for biochemical analyses. Study drugs were well tolerated, but accelerated decline in Mini-Mental State Examination scores occurred in the E/C/ALA group, a potential safety concern. Changes in CSF A β 42, tau, and P-tau(181) levels did not differ between the 3 groups. Cerebrospinal fluid F2-isoprostane levels, an oxidative stress biomarker, decreased on average by 19% from baseline to week 16 in the E/C/ALA group but were unchanged in the other groups.

CONCLUSIONS:

Antioxidants did not influence CSF biomarkers related to amyloid or tau pathology. Lowering of CSF F2-isoprostane levels in the E/C/ALA group suggests reduction of oxidative stress in the brain. However, this treatment raised the caution of faster cognitive decline, which would need careful assessment if longer-term clinical trials are conducted.

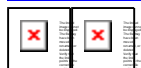
TRIAL REGISTRATION:

clinicaltrials.gov Identifier: [NCT00117403](https://clinicaltrials.gov/ct2/show/study/NCT00117403).

PMCID: PMC3661272 **Free PMC Article**

PMID: 22431837 [Indexed for MEDLINE]

[Similar articles](#)



35. J BUON. 2011 Oct-Dec;16(4):759-64.

[Hand-foot syndrome due to sorafenib in hepatocellular carcinoma treated with vitamin E without dose modification; a preliminary clinical study.](#)

[Bozkurt Duman B](#)¹, [Kara B](#), [Oguz Kara I](#), [Demiryurek H](#), [Aksungur E](#).

Author information:

1. Cukurova University Medical Faculty, Department of Medical Oncology, Adana, Turkey.
berboz@hotmail.com

Abstract

PURPOSE:

Sorafenib has been found to have significant clinical activity against hepatocellular carcinoma (HCC). Hand-foot skin syndrome (HFS) has been described with the usage of sorafenib. It is a dose-limiting toxicity and may lead to compromised efficacy because of dose reduction.

METHODS:

From 14 patients diagnosed with HCC 10 who developed HFS while on treatment with sorafenib were included in this study. Sorafenib was administered orally at a dose of 400 mg twice daily vitamin E usage can be effective in HFS due to sorafenib, therefore vitamin E 300 mg/day was started when HFS occurred. HFS was graded according to the National Cancer Institute (NCI) criteria.

RESULTS:

Grade 2-3 HFS was found in 10 of 14 patients. Vitamin E was started to all patients without using topical agents. Mean time to the appearance of HFS was 15 ± 3 days (range 10-22) after starting sorafenib. Grade was 3 in 4 patients, 2 in 4 patients and 1 in 2 patients. Vitamin E administration had a marked effect after 10-12 days of its initiation. Skin lesions disappeared without any dose modification.

CONCLUSION:

Sorafenib is the gold standard for HCC treatment. Dose modification due to HFS decreases the effectiveness of this agent. Adding vitamin E to sorafenib is effective in HFS without dose reduction or treatment interruption. This is the first clinical study to report resolution of HFS with vitamin E due to sorafenib therapy.

PMID: 22331734 [Indexed for MEDLINE]

[Similar articles](#)

36. Clin Nutr. 2012 Apr;31(2):176-82. doi: 10.1016/j.clnu.2011.10.005. Epub 2011 Nov 1.

Randomized phase III clinical trial of a combined treatment with carnitine + celecoxib ± megestrol acetate for patients with cancer-related anorexia/cachexia syndrome.

[Madeddu C](#)¹, [Dessi M](#), [Panzone F](#), [Serpe R](#), [Antoni G](#), [Cau MC](#), [Montaldo L](#), [Mela Q](#), [Mura M](#), [Astara G](#), [Tanca FM](#), [Macciò A](#), [Mantovani G](#).

Author information:

1. Department of Medical Oncology, University of Cagliari, Cagliari, Italy.

Abstract

BACKGROUND & AIMS:

A phase III, randomized non-inferiority study was carried out to compare a two-drug combination (including nutraceuticals, i.e. antioxidants) with carnitine + celecoxib ± megestrol acetate for the treatment of cancer-related anorexia/cachexia syndrome (CACS): the primary endpoints were increase of lean body mass (LBM) and improvement of total daily physical activity. Secondary endpoint was: increase of physical performance tested by grip strength and 6-min walk test.

METHODS:

Sixty eligible patients were randomly assigned to: arm 1, L-carnitine 4 g/day + Celecoxib 300 mg/day or arm 2, L-carnitine 4 g/day + celecoxib 300 mg/day + megestrol acetate 320 mg/day, all orally. All patients received as basic treatment polyphenols 300 mg/day, lipoic acid 300 mg/day, carbocysteine 2.7 g/day, Vitamin E, A, C. Treatment duration was 4 months. Planned sample size was 60 patients.

RESULTS:

The results did not show a significant difference between the treatment arms in both primary and secondary endpoints. Analysis of changes from baseline showed that LBM (by dual-energy X-ray absorptiometry and by L3 computed tomography) increased significantly in both arms as well as physical performance assessed by 6MWT. Toxicity was quite negligible and comparable between arms.

CONCLUSIONS:

The results of the present study showed a non-inferiority of arm 1 (two-drug combination) vs arm 2 (two-drug combination + megestrol acetate). Therefore, this simple, feasible, effective, safe, low cost with favorable cost-benefit profile, two-drug approach could be suggested in the clinical practice to implement CACS treatment.

Copyright © 2011 Elsevier Ltd and European Society for Clinical Nutrition and Metabolism. All rights reserved.

PMID: 22047681 [Indexed for MEDLINE]

[Similar articles](#)



37. Psychopharmacology (Berl). 2012 Mar;220(2):351-65. doi: 10.1007/s00213-011-2481-3. Epub 2011 Oct 18.

[Memory improvements in elderly women following 16 weeks treatment with a combined multivitamin, mineral and herbal supplement: A randomized controlled trial.](#)

[Macpherson H¹](#), [Ellis KA](#), [Sali A](#), [Pipingas A](#).

Author information:

1. Centre for Human Psychopharmacology, NICM Collaborative Centre for Neurocognition, Swinburne University of Technology, 427-451 Burwood Road, Hawthorn, Melbourne, VIC, 3122, Australia.
hmacpherson@swin.edu.au

Abstract

RATIONALE:

There is potential for multivitamin supplementation to improve cognition in the elderly. This randomized, double-blind, placebo-controlled trial was conducted to investigate the effects of 16 weeks multivitamin supplementation (Swisse Women's 50+ Ultivite ®) on cognition in elderly women.

METHODS:

Participants in this study were 56 community dwelling, elderly women, with subjective complaints of memory loss. Cognition was assessed using a computerized battery of memory and attention tasks designed to be sensitive to age-related declines to fluid intelligence, and a measure of verbal recall. Biochemical measures of selected nutrients, homocysteine, markers of inflammation, oxidative stress, and blood safety parameters were also collected. All cognitive and haematological parameters were assessed at baseline and 16 weeks post-treatment.

RESULTS:

The multivitamin improved speed of response on a measure of spatial working memory, however benefits to other cognitive processes were not observed. Multivitamin supplementation decreased levels of homocysteine and increased levels of vitamin B(6) and B(12), with a trend for vitamin E to increase. There were no hepatotoxic effects of the multivitamin formula indicating this supplement was safe for everyday usage in the elderly.

CONCLUSION:

Sixteen weeks supplementation with a combined multivitamin, mineral and herbal formula may benefit working memory in elderly women at risk of cognitive decline.

PMID: 22006207 [Indexed for MEDLINE]

[Similar articles](#)



38. Int J Radiat Oncol Biol Phys. 2012 Mar 15;82(4):1454-62. doi: 10.1016/j.ijrobp.2011.04.022. Epub 2011 Jun 2.

Predictors of severe acute and late toxicities in patients with localized head-and-neck cancer treated with radiation therapy.

[Meyer F¹](#), [Fortin A](#), [Wang CS](#), [Liu G](#), [Bairati I](#).

Author information:

1. Laval University Cancer Research Center, Centre Hospitalier Universitaire de Québec - L'Hôtel-Dieu de Québec, Quebec, Canada. francois.meyer@chuq.qc.ca

Abstract

PURPOSE:

Radiation therapy (RT) causes acute and late toxicities that affect various organs and functions. In a large cohort of patients treated with RT for localized head and neck cancer (HNC), we prospectively assessed the occurrence of RT-induced acute and late toxicities and identified characteristics that predicted these toxicities.

METHODS AND MATERIALS:

We conducted a randomized trial among 540 patients treated with RT for localized HNC to assess whether vitamin E supplementation could improve disease outcomes. Adverse effects of RT were assessed using the Radiation Therapy Oncology Group Acute Radiation Morbidity Criteria during RT and one month after RT, and the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer Late Radiation Morbidity Scoring Scheme at six and 12 months after RT. The most severe adverse effect among the organs/tissues was selected as an overall measure of either acute or late toxicity. Grade 3 and 4 toxicities were considered as severe. Stepwise multivariate logistic regression models were used to identify all independent predictors ($p < 0.05$) of acute or late toxicity and to estimate odds ratios (OR) for severe toxicity with their 95% confidence intervals (CI).

RESULTS:

Grade 3 or 4 toxicity was observed in 23% and 4% of patients, respectively, for acute and late toxicity. Four independent predictors of severe acute toxicity were identified: sex (female vs. male: OR = 1.72, 95% confidence interval [CI]: 1.06-2.80), Karnofsky Performance Status (OR = 0.67 for a 10-point increment, 95% CI: 0.52-0.88), body mass index (above 25 vs. below: OR = 1.88, 95% CI: 1.22-2.90), TNM stage (Stage II vs. I: OR = 1.91, 95% CI: 1.25-2.92). Two independent predictors were found for severe late toxicity: female sex (OR = 3.96, 95% CI: 1.41-11.08) and weight loss during RT (OR = 1.26 for a 1 kg increment, 95% CI: 1.12-1.41).

CONCLUSIONS:

Knowledge of these predictors easily collected in a clinical setting could help tailoring therapies to reduce toxicities among patients treated with RT for HNC.

Copyright © 2012 Elsevier Inc. All rights reserved.

PMID: 21640495 [Indexed for MEDLINE]

[Similar articles](#)



39. J Pharm Sci. 2011 Oct;100(10):4536-45. doi: 10.1002/jps.22645. Epub 2011 May 31.

Pharmacokinetics of SN2310, an injectable emulsion that incorporates a new derivative of SN-38 in patients with advanced solid tumors.

[Marier JF¹](#), [Pheng L](#), [Trinh MM](#), [Burris HA 3rd](#), [Jones S](#), [Anderson K](#), [Warner S](#), [Porubek D](#).

Author information:

1. Pharsight, A Certara Company, Montreal, Quebec, Canada.

Abstract

SN2310 is an injectable emulsion composed of vitamin E, a succinate derivative, as well as 7-ethyl-10-hydroxycamptothecin (SN-38), the active metabolite of irinotecan. Single intravenous doses of 15, 20, 25, and 30 mg/m² of SN2310 emulsion were administered in a total of 26 patients with advanced solid malignancies. Serial blood samples were collected and concentrations of SN2310, SN-38, and SN-38 glucuronide were assayed. Mean systemic clearance of SN2310 ranged between 1.91 and 2.02 L/h/m². Peak concentrations of SN-38 were observed at the end of infusion, suggesting a fast metabolic conversion of SN2310 to its active form, SN-38. Mean t_{1/2} values of SN-38 across the 20-30 mg/m² dose levels (131-199 h) were 33-55-fold longer than those observed for SN2310. The systemic exposure of SN-38 increased in a proportional manner over the dose range studied. SN2310 emulsion displayed an improved safety profile as compared with irinotecan. The most significant safety risk was neutropenia. Considering the rapid formation of SN-38, the proportional increase in exposure levels, and its longer elimination half-life, less frequent dosing of SN2310 emulsion may be considered for the treatment of patients with advanced solid malignancies.

PMID: 21630281 [Indexed for MEDLINE]

[Similar articles](#)



40. Saudi J Gastroenterol. 2011 May-Jun;17(3):174-9. doi: 10.4103/1319-3767.80379.

Safety and efficacy of vitamin-based antioxidant therapy in patients with severe acute pancreatitis: a randomized controlled trial.

[Bansal D¹](#), [Bhalla A](#), [Bhasin DK](#), [Pandhi P](#), [Sharma N](#), [Rana S](#), [Malhotra S](#).

Author information:

1. Department of Pharmacology, Postgraduate Institute of Medical Education and Research, Chandigarh, India.

Abstract

BACKGROUND/AIM:

Oxidative stress plays a major role in the pathogenesis of pancreatitis. Antioxidant therapy in the form of high-dose vitamin has been used for the treatment of severe acute pancreatitis with equivocal results. We wished to evaluate the efficacy and safety of antioxidant (vitamin A, vitamin C, vitamin E) therapy in patients with severe acute pancreatitis.

SETTING AND DESIGN:

This was a single-center, prospective, randomized, open-label with blinded endpoint assessment study of

antioxidant therapy, conducted in the emergency department attached to our hospital.

MATERIALS AND METHODS:

Thirty-nine patients with severe acute pancreatitis were randomly assigned to antioxidant treatment group (n=19) or a control group (n=20) within 96 hours of developing symptoms. Patients in the antioxidant group received antioxidants (vitamin A, vitamin E, vitamin C) in addition to the standard treatment provided to both the groups for a period of 14 days. The primary outcome variable was presence of organ dysfunction at day 7. The secondary outcome variables were length of hospital stay, multiorgan dysfunction (MODS) at day 7, recovery at the end of 4 weeks, complications, and mortality. The change in markers of oxidative stress from baseline was also measured.

RESULTS:

We demonstrated no significant difference in organ dysfunction (P=1.0), MODS (P=0.8), and length of hospital stay (P=0.29) between the two groups. All the patients survived in the antioxidant-treated group, whereas two patients died in the control group. The change in the levels of malondialdehyde, superoxide dismutase, and reduced glutathione were not significantly different in the two groups at day 7. Univariate analysis showed marginal benefit with antioxidant treatment (P=0.034) in patients with severe acute pancreatitis.

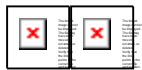
CONCLUSIONS:

This randomized study demonstrates that there is no significant benefit from antioxidant therapy in patients with established severe acute pancreatitis.

PMCID: PMC3122086 **Free PMC Article**

PMID: 21546719 [Indexed for MEDLINE]

[Similar articles](#)



41. J Clin Pharmacol. 2012 Jan;52(1):65-77. doi: 10.1177/0091270010390807. Epub 2011 Feb 22.

Use of an adaptive study design in single ascending-dose pharmacokinetics of A0001 (α -tocopherylquinone) in healthy male subjects.

Hawi A¹, Heald S, Sciascia T.

Author information:

1. Penwest Pharmaceuticals Co., Patterson, NY 12563, USA. amale.hawi@penwest.com

Abstract

A0001 (α -tocopherylquinone) is a potent antioxidant currently in development for the treatment of symptoms associated with inherited mitochondrial disorders. A0001 pharmacokinetics were studied in a

single-blind, adaptive design study following a single daily oral dose of placebo (n = 2) or ascending doses of A0001 (n = 8) at 0.25 and 0.5 g under a fasted state or a 0.5- to 6-g dose with a high-fat meal. Dose escalation was based on safety assessment, and proceeding dose levels were selected based on interim pharmacokinetic analyses. A0001 plasma concentration-time profiles were similar across doses, reaching peak concentration within 4 to 6 hours, with concentrations returning to baseline within 24 hours. Exposure was highly dependent on food and dosing frequency. Exposure was nearly 60-fold higher with food but increased subproportionally above 1-g dose; however, the nonproportionality was offset by administering A0001 in divided doses (0.735 g, 3 times per day). The potential for an A0001:vitamin E interaction was also explored, as vitamin E use is prevalent in this patient population, and suggested that a clinically significant pharmacokinetic interaction is not likely. A0001 was well tolerated with no serious adverse events or dose-limiting toxicities. These findings suggest that A0001 has a favorable pharmacokinetic profile when administered orally with food.

PMID: 21343342 [Indexed for MEDLINE]

[Similar articles](#)



42. Support Care Cancer. 2011 Nov;19(11):1769-77. doi: 10.1007/s00520-010-1018-3. Epub 2010 Oct 9.

[The use of vitamin E for the prevention of chemotherapy-induced peripheral neuropathy: results of a randomized phase III clinical trial.](#)

[Kottschade LA](#)¹, [Sloan JA](#), [Mazurczak MA](#), [Johnson DB](#), [Murphy BP](#), [Rowland KM](#), [Smith DA](#), [Berg AR](#), [Stella PJ](#), [Loprinzi CL](#).

Author information:

1. Mayo Clinic, Rochester, MN 55905, USA. kottschade.lisa@mayo.edu

Comment in

- [Neuroprotective strategies in the prevention of chemotherapy-induced neuropathies.](#) [Support Care Cancer. 2013]
- [Second response to the letter to the editor referencing the manuscript the "use of vitamin E for the prevention of chemotherapy-induced peripheral neuropathy: results of a randomized phase III clinical trial".](#) [Support Care Cancer. 2013]

Abstract

BACKGROUND:

Chemotherapy-induced peripheral neuropathy (CIPN) continues to be a substantial problem for many cancer patients. Pursuant to promising appearing pilot data, the current study evaluated the use of vitamin E for the prevention of CIPN.

METHODS:

A phase III, randomized, double-blind, placebo-controlled study was conducted in patients undergoing therapy with neurotoxic chemotherapy, utilizing twice daily dosing of vitamin E (400 mg)/placebo. The primary endpoint was the incidence of grade 2+ sensory neuropathy (SN) toxicity (CTCAE v 3.0) in each treatment arm, analyzed by chi-square testing. Planned sample size was 100 patients per arm to provide 80% power to detect a difference in incidence of grade 2+ SN toxicity from 25% in the placebo group to 10% in the vitamin E group.

RESULTS:

Two-hundred seven patients were enrolled between December 1, 2006 and December 14, 2007, producing 189 evaluable cases for analysis. Cytotoxic agents included taxanes (109), cisplatin (8), carboplatin (2), oxaliplatin (50), or combination (20). There was no difference in the incidence of grade 2+ SN between the two arms (34%-vitamin E, 29%-placebo; $P = 0.43$). There were no significant differences between treatment arms for time to onset of neuropathy ($P = 0.58$), for chemotherapy dose reductions due to neuropathy ($P = 0.21$), or for secondary endpoints derived from patient-reported neuropathy symptom assessments. The treatment was well tolerated overall.

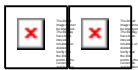
CONCLUSIONS:

Vitamin E did not appear to reduce the incidence of sensory neuropathy in the studied group of patients receiving neurotoxic chemotherapy.

PMCID: PMC3329941 [Free PMC Article](#)

PMID: 20936417 [Indexed for MEDLINE]

[Similar articles](#)



43. Arch Neurol. 2011 Jan;68(1):45-50. doi: 10.1001/archneurol.2010.229. Epub 2010 Sep 13.

[A randomized pilot clinical trial of the safety of pioglitazone in treatment of patients with Alzheimer disease.](#)

[Geldmacher DS](#)¹, [Fritsch T](#), [McClendon MJ](#), [Landreth G](#).

Author information:

1. Department of Neurology, University of Virginia Health System, Charlottesville, USA.
dsg8n@virginia.edu

Comment in

- [Targets of the peroxisome proliferator-activated receptor \$\gamma\$ agonist trials for the prevention of Alzheimer disease.](#) [Arch Neurol. 2011]

Abstract

OBJECTIVES:

To evaluate the safety of the peroxisome proliferator-activated receptor gamma agonist pioglitazone in nondiabetic patients with Alzheimer disease (AD) and to explore treatment effect sizes on clinical outcomes.

DESIGN:

Double-blind, placebo-controlled randomized controlled trial of 18-month duration.

SETTING:

Two academic medical center outpatient clinics.

PATIENTS:

Nondiabetic patients meeting research criteria for probable AD were enrolled. Twenty-five of 29 subjects completed the study; no withdrawals were attributable to adverse effects.

INTERVENTION:

Subjects received pioglitazone (Actos), titrated to 45 mg daily, or matching placebo, and 200 IU of vitamin E daily. Patients maintained treatment with cholinesterase inhibitors and could begin memantine therapy when it became available during the study.

MAIN OUTCOME MEASURES:

The primary outcome was frequency of reported adverse effects (AEs). Secondary outcomes were measures of cognition, activities of daily living, neuropsychiatric symptoms, and global function.

RESULTS:

Peripheral edema was the principal AE occurring more frequently in subjects taking pioglitazone than placebo (28.6% vs 0%). This is consistent with the known AE profile of pioglitazone. No group differences in laboratory measures were identified. No significant treatment effect was observed on exploratory analysis of clinical efficacy.

CONCLUSIONS:

Pioglitazone was generally well tolerated in this pilot study. There were no serious or unanticipated adverse events or clinical laboratory changes attributable to pioglitazone over a long-term exposure in nondiabetic patients with AD. The tolerability of pioglitazone in this population and peroxisome proliferator-activated receptor gamma effects in laboratory models of AD support further study of this drug class in earlier disease stages.

TRIAL REGISTRATION:

clinicaltrials.gov Identifier: [NCT00982202](https://clinicaltrials.gov/ct2/show/study/NCT00982202).

PMID: 20837824 [Indexed for MEDLINE]

[Similar articles](#)



Safety and efficacy of a lipid emulsion containing a mixture of soybean oil, medium-chain triglycerides, olive oil, and fish oil: a randomised, double-blind clinical trial in premature infants requiring parenteral nutrition.

[Tomsits E¹](#), [Pataki M](#), [Tölgyesi A](#), [Fekete G](#), [Rischak K](#), [Szollár L](#).

Author information:

1. 2nd Department of Paediatrics, Semmelweis University, Budapest, Hungary. tomeri2@gyer2.sote.hu

Abstract

OBJECTIVES:

Safety, tolerability, and efficacy of a novel lipid emulsion containing a mixture of soybean oil, medium-chain triglycerides, olive oil, and fish oil (SMOFlipid 20%) with reduced n-6 fatty acids (FA), increased monounsaturated and n-3 FA, and enriched in vitamin E were evaluated in premature infants compared with a soybean oil-based emulsion.

PATIENTS AND METHODS:

Sixty (30/30) premature neonates (age 3-7 days, gestational age \leq 34 weeks, birth weights 1000-2500 g) received parenteral nutrition (PN) with either SMOFlipid 20% (study group) or a conventional lipid emulsion (Intralipid 20%, control group) for a minimum of 7 up to 14 days. Lipid supply started at $0.5 \text{ g} \cdot \text{kg} \text{ body weight}^{-1} \cdot \text{day}^{-1}$ on day 1 and increased stepwise (by $0.5 \text{ g} \cdot \text{kg} \text{ body weight}^{-1} \cdot \text{day}^{-1}$) on days 4 to 14. Safety and efficacy parameters were assessed on days 0, 8, and 15 if PN was continued.

RESULTS:

Adverse events, serum triglycerides, vital signs, local tolerance, and clinical laboratory did not show noticeable group differences, confirming the safety of study treatment. At study end, γ -glutamyl transferase was lower in the study versus the control group (107.8 ± 81.7 vs 188.8 ± 176.7 IU/L, $P < 0.05$). The relative increase in body weight (day 8 vs baseline) was $5.0\% \pm 6.5\%$ versus $5.1\% \pm 6.6\%$ (study vs control, not significant). In the study group, an increase in n-3 FA in red blood cell phospholipids and n-3:n-6 FA ratio was observed. Plasma α -tocopherol (study vs control) was increased versus baseline on day 8 (26.35 ± 10.03 vs 3.67 ± 8.06 $\mu\text{mol/L}$, $P < 0.05$) and at study termination (26.97 ± 18.32 vs 8.73 ± 11.41 $\mu\text{mol/L}$, $P < 0.05$).

CONCLUSIONS:

Parenteral infusion of SMOFlipid was safe and well tolerated and showed a potential beneficial influence on

cholestasis, n-3 FA, and vitamin E status in premature infants requiring PN.

PMID: 20531018 [Indexed for MEDLINE]

[Similar articles](#)



45. Biol Trace Elem Res. 2011 Jun;141(1-3):16-25. doi: 10.1007/s12011-010-8712-3. Epub 2010 May 13.

[Effects of vitamin C and E combination on element and oxidative stress levels in the blood of operative patients under desflurane anesthesia.](#)

[Ceylan BG¹](#), [Nazıroğlu M](#), [Uğuz AC](#), [Barak C](#), [Erdem B](#), [Yavuz L](#).

Author information:

1. Department of Anesthesiology and Reanimation, Medical Faculty, Suleyman Demirel University, Isparta, Turkey.

Abstract

We investigated effects of vitamin C and E (VCE) administration on desflurane-induced oxidative toxicity and element changes in the blood of operative patients under desflurane general anesthesia. Forty American Society of Anesthesiologists I or II Physical Status adult patients were scheduled for elective surgery. The patients were randomly divided into two groups. Control and VCE group was introduced to anesthesia with desflurane. VCE was administered to patients in the control and VCE group before 1 hour of anesthesia with desflurane. Baseline (preoperative) and postoperative (at the 1(st), the 24(th), and 72(th) h), blood samples were taken from the first and second groups. Erythrocyte and plasma lipid peroxidation levels at the 1(st), 24(th), and 72(th) hours were higher in the control than in baseline group, although their levels at the same periods were lower in the VCE group than in the control. Vitamin E levels at the postoperative 1(st) and 24(th) hours and erythrocyte glutathione peroxidase (GSH-Px) activity at the postoperative 1(st), 24(th), and 72(th) hours was lower than in baseline values. Erythrocyte GSH-Px activity and plasma vitamins A, C, and E levels at the postoperative 1(st), 24(th), and 72(th) hours were higher in the VCE group than in the control group. Erythrocyte and plasma reduced glutathione, plasma β -carotene, and serum copper, while zinc, selenium, aluminum, iron, magnesium, and calcium levels did not differ between preoperative and postoperative periods in both groups. In conclusion, VCE combination prevented the desflurane-induced vitamin E and GSH-Px consumptions to strengthen the antioxidant levels in the blood of operative patients.

PMID: 20464539 [Indexed for MEDLINE]

[Similar articles](#)



46. Support Care Cancer. 2011 Jan;19(1):57-65. doi: 10.1007/s00520-009-0788-y. Epub 2009 Dec 9.

[Radiodermatitis prevention with sucralfate in](#)

breast cancer: fundamental and clinical studies.

[Falkowski S¹](#), [Trouillas P](#), [Duroux JL](#), [Bonnetblanc JM](#), [Clavère P](#).

Author information:

1. Service de Radiothérapie, Centre Hospitalier Universitaire, 2 rue du Docteur Marcland, 87025, Limoges, France.

Abstract

BACKGROUND:

Acute radiodermatitis induced by radiotherapy may affect the quality of life and in some cases requires withholding treatment. The present study concerns the protective effect of a 1% sucralfate lotion. We propose joint fundamental and clinical points of view.

METHODS:

The free radical scavenging capacity of sucralfate was measured with electron spin resonance and was supported by theoretical calculations. The clinical effects of sucralfate lotion were evaluated on 21 women treated for breast cancer. Breast skin response was evaluated at 0, 10, 20, 30, 40, and 50 Gy, according to (1) the radiation therapy oncology group (RTOG) acute toxicity scale and (2) spectrophotometry data obtained with X-Rite SP60.

RESULTS AND CONCLUSIONS:

Sucralfate appeared as a relatively poor free radical scavenger (compared to reference compounds such as vitamin E). The sucralfate-containing lotion used in the present study did not provide systematic radiodermatitis prevention. Spectrophotometric evaluation of the skin response to irradiation appeared to be a very effective and more sensitive technique than the RTOG scale. Its use should be recommended to study cutaneous radioprotective action.

PMID: 19998046 [Indexed for MEDLINE]

[Similar articles](#)



47. Contemp Clin Trials. 2010 Jan;31(1):62-70. doi: 10.1016/j.cct.2009.09.001. Epub 2009 Sep 15.

Treatment of nonalcoholic fatty liver disease in children: TONIC trial design.

[Lavine JE¹](#), [Schwimmer JB](#), [Molleston JP](#), [Scheimann AO](#), [Murray KF](#), [Abrams SH](#), [Rosenthal P](#), [Sanyal AJ](#), [Robuck PR](#), [Brunt EM](#), [Unalp A](#), [Tonascia J](#); [Nonalcoholic Steatohepatitis Clinical Research Network Research Group](#).

Collaborators: (106)

[Bringman D](#), [Dasarathy S](#), [Feldstein A](#), [Hawkins C](#), [Liu YC](#), [McCullough A](#), [Sargent R](#), [Stager M](#), [Abdelmalek M](#), [Diehl AM](#), [Gottfried M](#), [Guy C](#), [Killenberg P](#), [Kwan S](#), [Pan YP](#), [Piercy D](#), [Smith M](#), [Pfeifer](#)

[K](#), [Scheimann AO](#), [Torbensohn M](#), [Bhimalli P](#), [Byam E](#), [Chalasanani N](#), [Cummings OW](#), [Klipsch A](#), [Lee L](#), [Molleston JP](#), [Ragozzino L](#), [Subbarao G](#), [Vuppalanchi R](#), [Barlow S](#), [Brunt EM](#), [Derdoy J](#), [Hoffmann J](#), [King D](#), [Siegner J](#), [Stewart S](#), [Neuschwander-Tetri BA](#), [Thompson J](#), [Abrams SH](#), [Arceo D](#), [Espinosa D](#), [Fairly LA](#), [Behling C](#), [Clark L](#), [Durelle J](#), [Hassanein T](#), [Lavine JE](#), [Mendoza S](#), [Parman Z](#), [Patton H](#), [Schwimmer JB](#), [Sirlin C](#), [Stein T](#), [Palomares Z](#), [Bambha K](#), [Bass NM](#), [Ferrell LD](#), [Filipowski D](#), [Merriman R](#), [Pabst M](#), [Rosenthal M](#), [Rosenthal P](#), [Steel T](#), [Coffey M](#), [Kowdley KV](#), [Mooney J](#), [Murray KF](#), [Nelson J](#), [Saunders C](#), [Yeh M](#), [Young M](#), [Boyett S](#), [Bryan D](#), [Contos MJ](#), [Fuchs M](#), [Jones A](#), [Luketic VA](#), [Sandhu B](#), [Sanyal AJ](#), [Sargeant C](#), [White M](#), [Mohan P](#), [Kleiner DE](#), [Doo E](#), [Hoofnagle J](#), [Robuck PR](#), [Huang TT](#), [Belt P](#), [Brancati F](#), [Clark J](#), [Colvin R](#), [Donithan M](#), [Green M](#), [Hollick R](#), [Isaacson M](#), [Kim W](#), [Lydecker A](#), [Mann P](#), [Miriell L](#), [Sternberg A](#), [Tonascia J](#), [Unalp-Arida A](#), [Van Natta M](#), [Wilson L](#), [Yates K](#).

Author information:

1. University of California San Diego, La Jolla, CA, USA.

Abstract

BACKGROUND:

Nonalcoholic fatty liver disease (NAFLD) in children can lead to steatohepatitis, cirrhosis, and end-stage liver disease. The cause of NAFLD is unknown, but it is commonly associated with obesity, insulin resistance, and dyslipidemia.

OBJECTIVES:

TONIC is conducted to test whether treatment with metformin, an insulin sensitizer, or vitamin E, a naturally available antioxidant, will lead to improvements in biochemical and histological features of nondiabetic children with biopsy-proven NAFLD.

DESIGN:

TONIC is a randomized, multicenter, double-masked, placebo-controlled trial of 96 weeks of treatment with metformin or vitamin E. The primary outcome measure chosen for the trial is improvement in serum alanine aminotransferase (ALT) levels with treatment as compared to placebo. An improvement in ALT is defined as reduction in serum ALT levels to below 50% of the baseline values or into the normal range (40 U/L or less) during the last 48 weeks of treatment. Histological improvement is defined by changes in liver histology between a baseline and end-of-treatment liver biopsy in regards to (1) steatohepatitis, (2) NAFLD Activity Score, consisting of scores for steatosis, lobular inflammation, and hepatocellular injury (ballooning), and (3) fibrosis score.

METHODS:

Between September 2005 and September 2007, 173 children were enrolled into TONIC at 10 clinical centers in the United States. Participants were randomized to receive either metformin (500 mg b.i.d.), vitamin E (400 IU b.i.d.), or placebo for 96 weeks. This protocol was approved by all participating center Institutional Review Boards (IRBs) and an independent Data and Safety Monitoring Board (DSMB). (ClinicalTrials.gov number, [NCT00063635](#)).

Copyright (c) 2009 Elsevier Inc. All rights reserved.

PMCID: PMC2936451 **Free PMC Article**



Parenteral lipid emulsions based on olive oil compared with soybean oil in preterm (<28 weeks' gestation) neonates: a randomised controlled trial.

[Deshpande GC¹](#), [Simmer K](#), [Mori T](#), [Croft K](#).

Author information:

1. Department of Neonatal Paediatrics, King Edward Memorial Hospital for Women, Perth, Australia.
girish.deshpande@health.wa.gov.au

Abstract

BACKGROUND:

: New olive oil-based (OL) lipid emulsions (olive:soy oil = 4:1) have lower polyunsaturated fatty acid (PUFA) (20% vs 60%) and higher vitamin E content (an antioxidant) compared with traditional soybean oil (SO) emulsions.

OBJECTIVE:

: Compare efficacy and safety of OL with SO emulsions in preterm neonates (<28 weeks) at high risk for oxidative stress.

PATIENTS AND METHODS:

: Preterm neonates (gestation 23-<28 weeks) were randomised to receive OL or SO emulsion for 5 days using a standard protocol in a tertiary perinatal centre (King Edward Memorial Hospital for Women, Perth, Western Australia). Investigators and outcome assessors were masked to allocation. Plasma F2-isoprostanes (lipid peroxidation marker), plasma, and red blood cell fatty acids were measured before and after the study. Safety was monitored by liver function tests.

RESULTS:

: Forty-four of 50 participants (OL-23, SO-21) completed the study. Both emulsions were well tolerated with no significant adverse events. F2-isoprostane levels were comparable at baseline and study end. Oleic and linoleic acid levels were significantly high on day 6 in OL and SO groups, respectively. Long-chain PUFA levels were similar between groups despite the lower PUFA content of OL. The olive oil-based group had significantly higher levels of C18:4n-3, suggesting Delta6-desaturase enzyme inhibition in the SO group.

CONCLUSIONS:

: Olive oil-based emulsion was safe and well tolerated by preterm neonates. Similar long-chain PUFA levels were achieved in the OL group despite significantly lower amount of PUFA content; however, there was no difference in lipid peroxidation (F2-isoprostane levels). Large trials are needed to confirm these benefits.

PMID: 19644398 [Indexed for MEDLINE]

[Similar articles](#)



49. Cell Biochem Funct. 2009 Oct;27(7):424-9. doi: 10.1002/cbf.1589.

Vitamin C and E combination modulates oxidative stress induced by X-ray in blood of smoker and nonsmoker radiology technicians.

[Kayan M](#)¹, [Naziroğlu M](#), [Celik O](#), [Yalman K](#), [Köylü H](#).

Author information:

1. Department of Radiology, Isparta State Hospital, Isparta, Turkey.

Abstract

X-ray radiation is detrimental to human cells and may lead to development of life-threatening diseases. Cigarette smoke contains about 500 chemicals that include organic and oxidant compounds whereas vitamin C and E (VCE) have scavenger effects on the compounds. We investigated effects of VCE administration on X-ray-induced oxidative toxicity in blood of smoker and nonsmoker X-ray technicians. Twenty technicians and 30 healthy age-matched subjects control were used in the study. Ten of the X-ray technicians and 15 of the control were smokers. Blood samples were taken from the control. Oral vitamin C (500 mg) and vitamin E (150 mg) were daily supplemented to the smoker and nonsmoker X-ray technicians for 5 weeks. Blood samples were taken from the X-ray technicians after and before 5 weeks. Plasma and erythrocytes lipid peroxidation (LP), reduced glutathione (GSH) levels, erythrocytes glutathione peroxidase (GSH-Px), and plasma antioxidant vitamin concentrations were investigated in control and X-ray technicians with smoker and nonsmoker. Plasma and erythrocytes LP levels were higher in the total X-ray group and smoker X-ray group than in control and nonsmoker X-ray group, respectively although the LP level was decreased by the VCE treatment. The plasma vitamin C, vitamin A, vitamin E, and beta-carotene concentrations were lower in the X-ray group than in control although their concentrations were increased by the treatment. The erythrocytes GSH level and GSH-Px activity were found to be higher in the treatment group than in the X-ray group. Plasma GSH level was not found to be different in all group. Reactive oxygen species may play role in the mechanism that has been proposed to explain the biological side effect of X-ray radiation and smoke. VCE prevents the smoke and X-ray-induced oxidative stress to strengthen antioxidant vitamin concentrations in the blood of the technicians.

PMID: 19637207 [Indexed for MEDLINE]

[Similar articles](#)

50. Clin Nutr. 2009 Dec;28(6):631-5. doi: 10.1016/j.clnu.2009.04.021. Epub 2009 Jun 3.

Olive oil-based intravenous lipid emulsion in pediatric patients undergoing bone marrow transplantation: a short-term prospective controlled trial.

[Hartman C¹](#), [Ben-Artzi E](#), [Berkowitz D](#), [Elhasid R](#), [Lajterer N](#), [Postovski S](#), [Hadad S](#), [Shamir R](#).

Author information:

1. Institute of Gastroenterology, Nutrition, and Liver Diseases, Schneider Children's Medical Center of Israel, Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel. corinahartman@gmail.com

Abstract

BACKGROUND & AIMS:

Parenteral nutrition (PN) is an important component of the supportive care of children undergoing bone marrow transplantation (BMT). The study aimed to assess short-term safety and metabolic effects of an olive oil-based (OO) lipid emulsion compared with a MCT/LCT (M/L) emulsion in the clinical setting of pediatric BMT.

METHODS:

Twenty-eight pediatric BMT patients (age 1-18 years) expected to need PN support for at least 2 weeks, were prospectively enrolled and randomly assigned to receive either OO or M/L lipid emulsions within PN. Clinical and routine laboratory parameters, plasma fatty acids profile, vitamin E and peroxidation status were recorded at baseline and after 14 days of PN.

RESULTS:

No significant differences were found for hematological parameters, liver enzymes, vitamins, plasma peroxidation status, percentage and time to engraftment. Taking into consideration the baseline fatty acids levels, the OO group showed higher oleic acid ($p=0.012$), linoleic ($p=0.012$) and arachidonic acid ($p=0.002$) enrichment but similar eicosapentanoic and docosahexanoic acids levels compared to the M/L group at day 14. Cholesterol levels decreased significantly in the OO group after 14 days on PN ($p=0.017$).

CONCLUSIONS:

OO lipid emulsion was well tolerated, maintained essential fatty acids and peroxidation status, and generated a favorable plasma lipid profile. In this study short-term use of OO intravenous lipid emulsions was safe in children who needed PN support during BMT.

PMID: 19497646 [Indexed for MEDLINE]

[Similar articles](#)



Pentoxifylline in association with vitamin E reduces cutaneous fibrosis in systemic sclerosis.

[de Souza RB](#)¹, [Macedo AR](#), [Kuruma KA](#), [Macedo PA](#), [Borges CT](#).

Author information:

1. Rheumatology Division, Medical School, University of São Paulo, Av. Dr. Arnaldo 455, 30 andar, São Paulo, SP, 01246-903, Brazil. romy.souza@gmail.com

Abstract

Systemic sclerosis (SSc) is a disorder characterized by skin thickness and vasculopathy. The objective of the study was to evaluate the therapeutic effect and safety of the association of pentoxifylline and vitamin E in SSc patients. Twelve SSc patients (American College of Rheumatology criteria) enrolled this 24-week open-label study. Patients received daily 800 mg of pentoxifylline and 800 UI of vitamin E and were evaluated at 4-week interval. The primary efficacy endpoint was the change in Modified Rodnan Skin Score (MRSS) at week 24. Nine diffuse SSc patients treated 6 months with cyclophosphamide were used as a historical control group. The mean age of the treated group was 43.6 years, and ten of 12 (84%) patients were women. Their mean MRSS reduced from 25.7 to 18.7 ($p = 0.03$) at 16th week and remained significantly reduced throughout the study. In contrast, only a trend of MRSS reduction was observed in the historical control group ($p = 0.06$). Two patients started the study with active ischemic ulcers and ended with a complete healing of them. No serious side effects were reported. Pentoxifylline and vitamin E might be an alternative therapeutic approach in SSc patients.

PMID: 19468787 [Indexed for MEDLINE]

[Similar articles](#)



Vitamin E levels during early iron supplementation in preterm infants.

[Arnon S](#)¹, [Regev RH](#), [Bauer S](#), [Shainkin-Kestenbaum R](#), [Shiff Y](#), [Bental Y](#), [Dolfin T](#), [Litmanovitz I](#).

Author information:

1. Department of Neonatology, Meir Medical Center, Kfar Saba, Israel.

Abstract

On the basis of preliminary data, this larger bi-institutional continuation trial evaluating the efficacy and safety of early iron supplementation in preterm infants calls attention to the levels of vitamin E, a marker of antioxidant activity, during iron treatment. A total of 116 preterm infants were randomly assigned to receive at 2 or 4 weeks of age ($N = 62$, $N = 54$, respectively) 5 mg/kg/d of nonionic iron polymaltose complex

concomitantly with a daily dose of 25 IU vitamin E (as dl-alpha-tocopherol acetate) from 2 weeks of age. Vitamin E (alpha-tocopherol) levels, iron, ferritin, hemoglobin concentration, and reticulocyte count were recorded from 2 to 8 weeks of age. The morbidities of prematurity associated with free radicals formation were also documented. A gradual increase of alpha-tocopherol levels within physiological range (0.8 to 3.5 mg/dL) was found in the 2-week and 4-week groups during the study period with no difference among the groups ($P > 0.05$ for all comparisons). At 8 weeks of age, iron and ferritin levels, hemoglobin concentration, and reticulocyte count were higher in the 2-week group. No correlation was observed between timing of both iron and vitamin E supplement and hemolysis or morbidities associated with prematurity. Thus, treatment of iron with vitamin E supplement at 2 weeks of age is, in our experience, an efficacious and safe treatment for improving anemia in preterm infants.

PMID: 19263337 [Indexed for MEDLINE]

[Similar articles](#)



53. Eur Rev Med Pharmacol Sci. 2008 Nov-Dec;12(6):411-6.

[Effectiveness and safety of vaginal suppositories for the treatment of the vaginal atrophy in postmenopausal women: an open, non-controlled clinical trial.](#)

[Costantino D](#)¹, [Guaraldi C](#).

Author information:

1. Centro Salute Donna, Azienda USL, Ferrara, Italy. kostin@alice.it

Abstract

Menopause, due to the physiological decrease in the estrogens levels, is often associated with many symptoms related to vaginal atrophy such vaginal dryness, dyspareunia, burning, itching, decreasing in libido and therefore a worsening of the quality of life and in particular of the sexual activity. There are many pharmacological remedies to solve these events, first of all hormone replacement therapy (HRT) that up to the 90s was the therapy of choice for the care of the menopause symptoms. This hormonal therapy, however, has been re-considered due to its side effects. As alternative, a clinical trial has been performed to investigate the efficacy and safety, in postmenopausal women with urogenital atrophy, of the use of suppositories for vaginal use, containing hyaluronic acid, vitamin E and vitamin A. The trial, according to an open, non-controlled design, was performed on 150 postmenopausal women, 1 vaginal suppository per day, for the first 14 days and then a vaginal suppository, day in and day out, for other 14 days. The primary endpoint was the evaluation of vaginal dryness assessed by a Visual Analogue Scale (VAS) both by the investigator and the patient. The secondary endpoints were the evaluation of all the other symptoms and signs associated with the vaginal atrophy (itching, burning, dyspareunia, vaginal inflammation or swelling, irritation, assessed by a 4-point scale, presence of vaginal abrasions and irritation), and the recording of the adverse events occurring during the trial. The patients have not reported adverse effects during the treatment, and the results in terms of effectiveness on the vaginal atrophy symptoms were markedly positive. A high level of compliance was registered. The product tested can therefore be considered a safe and effective

alternative for the treatment of vaginal atrophy symptoms in postmenopausal women, especially when HRT is not recommended.

PMID: 19146203 [Indexed for MEDLINE]

[Similar articles](#)

54. World J Gastroenterol. 2008 Dec 21;14(47):7208-13.

Vitamin E treatment for children with chronic hepatitis B: a randomized placebo controlled trial.

[Gerner P¹](#), [Posselt HG](#), [Krahl A](#), [Ballauff A](#), [Innerhofer A](#), [Binder C](#), [Wenzl TG](#), [Zense M](#), [Hector A](#), [Dockter G](#), [Adam R](#), [Neubert J](#), [Classen M](#), [van Gemmern R](#), [Wirth S](#).

Author information:

1. Children's Hospital, Duisburg-Essen University, Klinik 2, Essen 45122, Germany. patrick.gerner@uk-essen.de

Abstract

AIM:

To evaluate the safety and efficacy of Vitamin E in children with chronic hepatitis B.

METHODS:

We randomly assigned patients with chronic hepatitis B, positive for hepatitis B e antigen (HBeAg), to receive either Vitamin E or placebo once daily for 6 mo in a 3:1 ratio and double-blind manner. The primary end point was HBeAg seroconversion, defined as the loss of HBeAg, undetectable levels of serum hepatitis B virus DNA, and the appearance of antibodies against HBeAg 12 mo after therapy.

RESULTS:

At baseline visit, 49 patients had normal and 43 had increased serum aminotransferase levels. Twenty-nine patients did not respond to previous treatment with interferon-alpha or lamivudine. Seventy-six children completed the study; 16 were non-compliant (n = 7), lost to follow-up (n = 7), or started another antiviral treatment (n = 3). Intention-to-treat analysis showed HBeAg seroconversion in 16 children (23.2%) treated with Vitamin E and two (8.7%) in the placebo group (P = 0.13). Vitamin E was well tolerated.

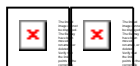
CONCLUSION:

There is only a tendency that Vitamin E may promote HBeAg seroconversion. Therefore larger studies are needed to clarify the role of antioxidants in the therapy of chronic hepatitis B.

PMCID: PMC2776878 **Free PMC Article**

PMID: 19084935 [Indexed for MEDLINE]

[Similar articles](#)



Effect of selenium and vitamin E on risk of prostate cancer and other cancers: the Selenium and Vitamin E Cancer Prevention Trial (SELECT).

[Lippman SM](#)¹, [Klein EA](#), [Goodman PJ](#), [Lucia MS](#), [Thompson IM](#), [Ford LG](#), [Parnes HL](#), [Minasian LM](#), [Gaziano JM](#), [Hartline JA](#), [Parsons JK](#), [Bearden JD 3rd](#), [Crawford ED](#), [Goodman GE](#), [Claudio J](#), [Winkquist E](#), [Cook ED](#), [Karp DD](#), [Walther P](#), [Lieber MM](#), [Kristal AR](#), [Darke AK](#), [Arnold KB](#), [Ganz PA](#), [Santella RM](#), [Albanes D](#), [Taylor PR](#), [Probstfield JL](#), [Jagpal TJ](#), [Crowley JJ](#), [Meyskens FL Jr](#), [Baker LH](#), [Coltman CA Jr](#).

Author information:

1. Division of Cancer Medicine, University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030, USA. slippman@mdanderson.org

Comment in

- [ACP Journal Club. Selenium and vitamin E, alone or together, did not prevent prostate cancer.](#) [Ann Intern Med. 2009]
- [Randomized trials of antioxidant supplementation for cancer prevention: first bias, now chance--next, cause.](#) [JAMA. 2009]
- [Selenium and vitamin E supplementation for cancer prevention.](#) [JAMA. 2009]
- [Selenium and vitamin E supplementation for cancer prevention.](#) [JAMA. 2009]
- [Early results of the selenium and vitamin E prostate cancer prevention study.](#) [Curr Urol Rep. 2009]
-

Abstract

CONTEXT:

Secondary analyses of 2 randomized controlled trials and supportive epidemiologic and preclinical data indicated the potential of selenium and vitamin E for preventing prostate cancer.

OBJECTIVE:

To determine whether selenium, vitamin E, or both could prevent prostate cancer and other diseases with little or no toxicity in relatively healthy men.

DESIGN, SETTING, AND PARTICIPANTS:

A randomized, placebo-controlled trial (Selenium and Vitamin E Cancer Prevention Trial [SELECT]) of 35,533 men from 427 participating sites in the United States, Canada, and Puerto Rico randomly assigned to 4 groups (selenium, vitamin E, selenium + vitamin E, and placebo) in a double-blind fashion between August 22, 2001, and June 24, 2004. Baseline eligibility included age 50 years or older (African American men) or 55 years or older (all other men), a serum prostate-specific antigen level of 4 ng/mL or less, and a

digital rectal examination not suspicious for prostate cancer.

INTERVENTIONS:

Oral selenium (200 microg/d from L-selenomethionine) and matched vitamin E placebo, vitamin E (400 IU/d of all rac-alpha-tocopheryl acetate) and matched selenium placebo, selenium + vitamin E, or placebo + placebo for a planned follow-up of minimum of 7 years and a maximum of 12 years.

MAIN OUTCOME MEASURES:

Prostate cancer and prespecified secondary outcomes, including lung, colorectal, and overall primary cancer.

RESULTS:

As of October 23, 2008, median overall follow-up was 5.46 years (range, 4.17-7.33 years). Hazard ratios (99% confidence intervals [CIs]) for prostate cancer were 1.13 (99% CI, 0.95-1.35; n = 473) for vitamin E, 1.04 (99% CI, 0.87-1.24; n = 432) for selenium, and 1.05 (99% CI, 0.88-1.25; n = 437) for selenium + vitamin E vs 1.00 (n = 416) for placebo. There were no significant differences (all $P > .15$) in any other prespecified cancer end points. There were statistically nonsignificant increased risks of prostate cancer in the vitamin E group ($P = .06$) and type 2 diabetes mellitus in the selenium group (relative risk, 1.07; 99% CI, 0.94-1.22; $P = .16$) but not in the selenium + vitamin E group.

CONCLUSION:

Selenium or vitamin E, alone or in combination at the doses and formulations used, did not prevent prostate cancer in this population of relatively healthy men.

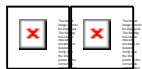
TRIAL REGISTRATION:

clinicaltrials.gov identifier: [NCT00006392](https://clinicaltrials.gov/ct2/show/study/NCT00006392).

PMCID: PMC3682779 **Free PMC Article**

PMID: 19066370 [Indexed for MEDLINE]

[Similar articles](#)



56. Contemp Clin Trials. 2009 Jan;30(1):88-96. doi: 10.1016/j.cct.2008.09.003. Epub 2008 Sep 10.

Pioglitazone versus vitamin E versus placebo for the treatment of non-diabetic patients with non-alcoholic steatohepatitis: PIVENS trial design.

[Chalasani NP](#)¹, [Sanyal AJ](#), [Kowdley KV](#), [Robuck PR](#), [Hoofnagle J](#), [Kleiner DE](#), [Unalp A](#), [Tonascia J](#); NASH CRN Research Group.

Author information:

1. Indiana University School of Medicine, Indianapolis, IN, United States.

Abstract

BACKGROUND:

Non-alcoholic steatohepatitis (NASH) is a common liver disease associated with obesity and diabetes. NASH is a progressive disorder that can lead to cirrhosis and liver failure. Insulin resistance and oxidative stress are thought to play important roles in its pathogenesis. There is no definitive treatment for NASH.

OBJECTIVES:

PIVENS is conducted to test the hypotheses that treatment with pioglitazone, a thiazolidinedione insulin sensitizer, or vitamin E, a naturally available antioxidant, will lead to improvement in hepatic histology in non-diabetic adults with biopsy proven NASH.

DESIGN:

PIVENS is a randomized, multicenter, double-masked, placebo-controlled trial to evaluate whether 96 weeks of treatment with pioglitazone or vitamin E improves hepatic histology in non-diabetic adults with NASH compared to treatment with placebo. Before and post-treatment liver biopsies are read centrally in a masked fashion for an assessment of steatohepatitis and a NAFLD Activity Score (NAS) consisting of steatosis, lobular inflammation, and hepatocyte ballooning. The primary outcome measure is defined as either an improvement in NAS by 2 or more in at least two NAS features, or a post-treatment NAS of 3 or less, and improvement in hepatocyte ballooning by 1 or more, and no worsening of fibrosis.

METHODS:

PIVENS enrollment started in January 2005 and ended in January 2007 with 247 patients randomized to receive either pioglitazone (30 mg q.d.), vitamin E (800 IU q.d.), or placebo for 96 weeks. Participants will be followed for an additional 24 weeks after stopping the treatment. The study protocol incorporates the use of several validated questionnaires and specimen banking. This protocol was approved by all participating center Institutional Review Boards (IRBs) and an independent Data and Safety Monitoring Board (DSMB) which was established for monitoring the accumulated interim data as the trial progresses to ensure patient safety and to review efficacy as well as the quality of data collection and overall study management. (ClinicalTrials.gov number, [NCT00063622](https://clinicaltrials.gov/ct2/show/study/NCT00063622)).

PMCID: PMC2929909 **Free PMC Article**

PMID: 18804555 [Indexed for MEDLINE]

[Similar articles](#)



57. Food Addit Contam Part A Chem Anal Control Expo Risk Assess. 2008 Jul;25(7):872-84. doi: 10.1080/02652030701854758.

[NovaSil clay does not affect the concentrations of vitamins A and E and nutrient minerals in serum](#)

samples from Ghanaians at high risk for aflatoxicosis.

[Afriyie-Gyawu E¹](#), [Wang Z](#), [Ankrah NA](#), [Xu L](#), [Johnson NM](#), [Tang L](#), [Guan H](#), [Huebner HJ](#), [Jolly PE](#), [Ellis WO](#), [Taylor R](#), [Brattin B](#), [Ofori-Adjei D](#), [Williams JH](#), [Wang JS](#), [Phillips TD](#).

Author information:

1. Department of Veterinary Integrative Biosciences, Texas A&M University, College Station, TX, USA.

Abstract

To assess the potential interference of NovaSil (NS) clay with micronutrients in humans, vitamins A and E and minerals (15 nutrient and 15 non-nutrient minerals) were measured in serum samples from a 3-month intervention trial with NS. Participants (n = 177) were randomly divided into three groups that received 3.0 g NS day(-1) (high dose, HD), 1.5 g NS day(-1) (low dose, LD), or placebo (PL). Levels of vitamins A and E in serum were comparable among the three study groups at baseline, 1 month and 3 months of NS intervention. Gender-stratified non-parametric mixed-effect model analysis showed no significant effects of dose and dose-time interaction for levels of vitamins A and E. A significant time effect was detected; however, it was limited to an increase in vitamin E in the male participants over the course of the study. No significant differences were found in levels of the nutrient and non-nutrient minerals between the HD and PL groups at baseline and 3 months of NS intervention, except for strontium levels. Strontium was significantly increased (p < 0.001) in the HD group (male = 113.65 +/- 28.00 microg l(-1); female = 116.40 +/- 24.26 microg l(-1)) compared with the PL group (male = 83.55 +/- 39.90 microg l(-1); female = 90.47 +/- 25.68 microg l(-1)) following the 3-month intervention with NS. These results, combined with safety and efficacy data, confirm that NS clay is highly effective in reducing aflatoxin exposure and acts as a selective enterosorbent that does not affect the serum concentrations of important vitamins and nutrient minerals in humans.

PMID: 18569006 [Indexed for MEDLINE]

[Similar articles](#)



58. J Am Coll Nutr. 2008 Feb;27(1):22-30.

Safety aspects and cholesterol-lowering efficacy of chitosan tablets.

[Tapola NS¹](#), [Lyyra ML](#), [Kolehmainen RM](#), [Sarkkinen ES](#), [Schauss AG](#).

Author information:

1. Oy Foodfiles Ltd, Neulaniementie, Finland.

Abstract

OBJECTIVE:

The purpose of this study was to determine the effect of two different doses of chitosan on serum fat-soluble vitamin concentrations, cholesterol concentrations, and other safety parameters.

METHODS:

A total of 65 men and women consumed 0, 4.5, 6.75 g per day of chitosan or 6.75 g per day glucomannan for eight weeks in a parallel, placebo-controlled, single-blind study. Altogether, 56 participants completed the study.

RESULTS:

No differences were detected among the treatments in serum vitamins (vitamin A, vitamin E, 25-hydroxyvitamin D), carotenes (alpha- and beta-carotene), clinical chemistry or hematology measurements. The changes in the total and LDL-cholesterol concentrations among the study groups were not statistically significant.

CONCLUSION:

In the present study, the consumption of chitosan tablets was found to be safe, but there was no significant effect on cholesterol concentration.

PMID: 18460478 [Indexed for MEDLINE]

[Similar articles](#)

59. Nutr Cancer. 2008;60(1):55-60. doi: 10.1080/01635580701761282.

Effect of selenium and vitamin e supplementation on plasma protein carbonyl levels in patients with arsenic-related skin lesions.

[Mahata J¹](#), [Argos M](#), [Verret W](#), [Kibriya MG](#), [Santella RM](#), [Ahsan H](#).

Author information:

1. Department of Environmental Health Sciences, Mailman School of Public Health, Columbia University, New York, NY, USA.

Abstract

An estimated 35 million people in Bangladesh have been chronically exposed to arsenic in drinking water and are at risk of an array of adverse health conditions. The mechanisms of arsenic toxicity have not been well established; however, oxidative stress has been one commonly proposed pathway. In this study, we evaluated the effect of antioxidant supplementation on plasma protein oxidation among patients with arsenical skin lesions participating in a randomized double-blinded placebo-controlled trial of vitamin E and selenium. Subjects were randomized to 1 of 4 treatments arms (vitamin E, selenium, combination, or placebo) and were treated for a 6-mo period. We observed a dose-dependent increase in adjusted protein carbonyl levels by arsenic exposure status in the pretreatment samples, although trends were not statistically significant. Following the 6-mo intervention, there was a decrease in protein carbonyl levels in each treatment group, although no resultant decrease was significantly different from that seen in the placebo group. Although we did not see a notable effect of selenium or vitamin E supplementation on changes in

protein carbonyl levels, these preliminary data demonstrate a feasible methodological approach for the assessment of plasma protein carbonyls in relation to environmental toxicants in a human population and their potential use as endpoints in intervention trials.

PMID: 18444136 [Indexed for MEDLINE]

[Similar articles](#)

60. Crit Care Med. 2008 Jan;36(1):131-44.

Early enteral supplementation with key pharmaconutrients improves Sequential Organ Failure Assessment score in critically ill patients with sepsis: outcome of a randomized, controlled, double-blind trial.

[Beale RJ¹](#), [Sherry T](#), [Lei K](#), [Campbell-Stephen L](#), [McCook J](#), [Smith J](#), [Venetz W](#), [Alteheld B](#), [Stehle P](#), [Schneider H](#).

Author information:

1. Department of Adult Critical Care Medicine, Guy's and St. Thomas' Hospital, London, United Kingdom.
richard.beale@gstt.nhs.uk

Comment in

- [Separating pharmaconutrition from classic nutrition goals: a necessary step.](#) [Crit Care Med. 2008]

Abstract

OBJECTIVE:

To assess the safety and efficacy of an early enteral pharmaconutrition supplement containing glutamine dipeptides, antioxidative vitamins and trace elements, and butyrate in critically ill, septic patients.

DESIGN:

A prospective, randomized, controlled, double-blind clinical trial.

SETTING:

Adult intensive care unit in a university hospital.

PATIENTS:

Fifty-five critically ill, septic patients requiring enteral feeding.

INTERVENTIONS:

Patients received either an enteral supplement (500 mL of Intestamin, Fresenius Kabi) containing conditionally essential nutrients or a control solution via the nasogastric route for up to 10 days. Inclusion occurred within 24 hrs of intensive care unit admission. Additionally, patients received enteral feeding with an immunonutrition formula (experimental group) or standard formula (control group) initiated within 48 hrs after enrollment.

MEASUREMENTS AND MAIN RESULTS:

Organ dysfunction was assessed by daily total Sequential Organ Failure Assessment (SOFA) score over the 10-day study period in both patient groups. Patients receiving the experimental supplement showed a significantly faster decline in the regression slopes of delta daily total SOFA score over time compared with control. The difference between the regression coefficients of the two slopes was significant irrespective of the level of analysis: intent to treat -0.32 vs. -0.14, $p < .0001$; per protocol -0.34 vs. -0.14, $p < .0001$; and completers (patients receiving $\geq 80\%$ of the calculated caloric target over a period of 6 days), -0.26 vs. -0.16, $p = .0005$. Vitamin C, as a marker of supplement absorption, increased from 10.6 (1.9-159.4) micromol/L (normal range 20-50 micromol/L) on day 1 to 58.7 (5.4-189.9) micromol/L by day 3 ($p = .002$) in the intervention group but remained below the normal range in the control group 17.0 (2.8-78.5) on day 1 and 14.3 (2.4-179.6) on day 3. Serum levels of glycine, serine, arginine, ornithine, vitamin E, and beta-carotene all increased significantly with treatment in the supplementation group.

CONCLUSIONS:

In medical patients with sepsis, early enteral pharmaconutrition with glutamine dipeptides, vitamin C and E, beta-carotene, selenium, zinc, and butyrate in combination with an immunonutrition formula results in significantly faster recovery of organ function compared with control.

PMID: 18007263 [Indexed for MEDLINE]

[Similar articles](#)



61. Med Oncol. 2007;24(3):308-11.

[Pentoxifylline and alpha-tocopherol in prevention of radiation-induced lung toxicity in patients with lung cancer.](#)

[Misirlioglu CH¹](#), [Demirkasimoglu T](#), [Kucukplakci B](#), [Sanri E](#), [Altundag K](#).

Author information:

1. Department of Radiation Oncology, Ankara Oncology Hospital, Ankara, Turkey.

Abstract

Combined use of pentoxifylline and vitamin E is reported to reduce radiation-induced toxicity in normal tissues at molecular level. We plan to evaluate the role of combined use of pentoxifylline (PTX) and alpha-tocopherol (vitamin E; Vit E) for minimizing radiation-induced lung toxicity. A total of 91 lung cancer patients were randomized. Among them, 44 received PTX (400 mg three times a day orally and Vit E 300

mg twice a day orally during the entire period of radiotherapy. PTX and Vit E were further administered at doses of 400 mg once a day and 300 mg once a day, respectively for 3 months after radiotherapy. A total of 47 patients were assigned as a control group. Radiation related acute and late toxicities are evaluated by radiation RTOG/EORTC toxicity scale. Median age was 59 (range, 41-75). Median follow-up was 13 months (range, 3-28 months). Radiation-induced lung toxicity was more frequent in control group for all phases than in pentoxifylline and alpha-tocopherol group (acute phase, $P = 0.042$, subacute phase $P = 0.0001$, late phase $P = 0.256$). PTX and Vit E combination might be considered especially in patients with lung cancer who receive concurrent chemo-radiotherapy, or have a poor respiratory function tests.

PMID: 17873306 [Indexed for MEDLINE]

[Similar articles](#)

62.J Urol. 2007 Oct;178(4 Pt 1):1398-403; discussion 1403. Epub 2007 Aug 16.

Comparison of vitamin E and propionyl-L-carnitine, separately or in combination, in patients with early chronic Peyronie's disease: a double-blind, placebo controlled, randomized study.

[Safarinejad MR](#)¹, [Hosseini SY](#), [Kolahi AA](#).

Author information:

1. Urology and Nephrology Research Center, Faculty of Medicine, Shaheed Beheshti University of Medical Sciences, Tehran, Iran. safarinejad@urologist.md

Abstract

PURPOSE:

We compared the efficacy and safety of oral vitamin E and propionyl-L-carnitine, separately or in combination, for the treatment of Peyronie's disease.

MATERIALS AND METHODS:

A total of 236 men (mean age 43.4 years) with Peyronie's disease were randomly assigned to 4 groups. Group 1 (58 men) received 300 mg vitamin E orally twice daily. Group 2 (59) received 1 gm propionyl-L-carnitine orally twice daily, and group 3 (60) received 300 mg vitamin E and 1 gm propionyl-L-carnitine orally twice daily. Group 4 (control group, 59 men) received a similar regimen of placebo during the 6-month treatment period. The efficacy of the 4 treatments was assessed using responses to the International Index of Erectile Function, visual analog scale for pain evaluation, mean intercourse satisfaction domain, mean weekly coitus episodes, penile curvature, plaque size and adverse drug effects.

RESULTS:

Pain decreased in 60.4%, 63%, 62.3% and 59.2% of the patients treated with vitamin E, propionyl-L-carnitine, vitamin E plus propionyl-L-carnitine and placebo, respectively ($p = 0.1$). After therapy a reduction in penile curvature was observed by 18.9%, 20.4%, 22.6% and 18.4% of the patients in groups 1, 2, 3 and 4, respectively ($p = 0.09$), and a decrease in plaque size was noted in 11.3%, 12.9%, 13.2% and 11.1%,

respectively ($p = 0.1$).

CONCLUSIONS:

This study did not show significant improvement in pain, curvature or plaque size in patients with PD treated with vitamin E, propionyl-L-carnitine, or vitamin E plus propionyl-L-carnitine compared with those treated with placebo.

PMID: 17706714 [Indexed for MEDLINE]

[Similar articles](#)



63. Ann Pharm Fr. 2006 Nov;64(6):397-401.

[\[The SU.VI.MAX study, a randomized, placebo-controlled trial on the effects of antioxidant vitamins and minerals on health\].](#)

[Article in French]

[Herberg S¹](#).

Author information:

1. U 557 Inserm (UMR Inserm/Inra/Cnam), Centre De Recherche En Nutrition Humaine d'Ile-de-France, Paris 13/Bobigny, Cnam, 5, rue du Vertbois, F 75003 Paris, France.

Abstract

The SU.VI.MAX study is a double blind, randomized, placebo-controlled trial testing, for 7,5 years, the effect of a combination of antioxidant vitamins and minerals, at doses considered to be nutritional (120 mg vitamin C, 30 mg vitamin E, 6 mg beta-carotene, 100 microg selenium and 20 mg zinc) in reducing cancer and ischemic vascular disease incidence in a general population (12.741 middle-aged). After 7.5 years, low-dose antioxidant supplementation had no effect on vascular disease incidence. This dose lowered, however, total cancer incidence in men, but not in women. With regard to contradictory results of observational and interventional studies published for the last decades, we can consider that the effect of antioxidants on cancer may depend on the doses (nutritional versus pharmacological), baseline antioxidant status (different between gender and/or nutritional status) and health status of subjects (healthy versus cancer high-risk subjects). Antioxidant supplementation may have a beneficial effect on cancer incidence only in healthy subjects who are not exposed to cancer risk, and with a particularly low baseline status. Finally, antioxidants as well as free radicals appear to be ambiguous nutrients with a wide range of benefits and toxicity. High doses of antioxidant supplements may be deleterious in high-risk subjects without any clinical symptoms in whom the initial phase of cancer development has already started.

PMID: 17119469 [Indexed for MEDLINE]

[Similar articles](#)



64. J Pain Symptom Manage. 2006 Sep;32(3):237-44.

Preventing paclitaxel-induced peripheral neuropathy: a phase II trial of vitamin E supplementation.

[Argyriou AA](#)¹, [Chroni E](#), [Koutras A](#), [Iconomou G](#), [Papapetropoulos S](#), [Polychronopoulos P](#), [Kalofonos HP](#).

Author information:

1. EMG Laboratory, Department of Neurology, University of Patras Medical School, Rion-Patras, Greece.
andargyriou@yahoo.gr

Abstract

A randomized, controlled trial was performed to assess the efficacy and safety of vitamin E supplementation for prophylaxis against paclitaxel-induced peripheral neuropathy (PIPN). Thirty-two patients undergoing six courses of paclitaxel-based chemotherapy were randomly assigned to receive either chemotherapy with vitamin E (300 mg twice a day, Group I) or chemotherapy without vitamin E supplementation (Group II). A detailed neurological examination and electrophysiological study was performed during and 3 months after chemotherapy. The severity of PIPN was summarized by means of a modified Peripheral Neuropathy (PNP) score. The incidence of neurotoxicity differed significantly between groups, occurring in 3/16 (18.7%) patients assigned to the vitamin E supplementation group and in 10/16 (62.5%) controls (P=0.03). The relative risk (RR) of developing PIPN was significantly higher in controls than in vitamin E group patients (RR=0.3, 95% confidence interval (CI)=0.1-0.9). Mean PNP scores were 2.25±5.1 (range 0-15) for patients in Group I and 11±11.63 (range 0-32) for those in Group II (P=0.01). Vitamin E supplementation was well tolerated and showed an excellent safety profile. This study shows that vitamin E effectively and safely protects patients with cancer from the occurrence of paclitaxel-induced peripheral nerve damage. A double-blind, placebo-controlled trial is needed to confirm these results.

PMID: 16939848 [Indexed for MEDLINE]

[Similar articles](#)



65. Free Radic Biol Med. 2006 May 15;40(10):1702-12.

Vitamin supplementation does not protect against symptoms in ozone-responsive subjects.

[Mudway IS](#)¹, [Behndig AF](#), [Helleday R](#), [Pourazar J](#), [Frew AJ](#), [Kelly FJ](#), [Blomberg A](#).

Author information:

1. Lung Biology, Pharmaceutical Sciences Research Division, Franklin-Wilkins Building, Kings' College London, London, UK.

Comment in

- [Combating oxidative stress at respiratory tract biosurfaces: challenges yet to be resolved, a commentary on "Vitamin supplementation does not protect against symptoms in ozone-responsive subjects". \[Free Radic Biol Med. 2006\]](#)

Abstract

Vitamin supplements have been reported to reduce the magnitude of symptoms in subjects exposed to oxidant air pollution. To confirm whether supplementation with vitamins C and E could reduce lung function decrements, airway inflammation, and epithelial injury in subjects sensitive to ozone, a double-blinded, crossover control study was performed. Fourteen ozone-responsive subjects were randomly exposed to both air and ozone (0.2 ppm for 2 h) after 7 days of either placebo treatment or supplementation with vitamin C (500 mg/day) and E (100 mg/day). Lung function was assessed pre- and immediately postexposure and blood samples were taken at set intervals. Inflammatory, tissue injury, and antioxidant responses were examined in lavage fluid obtained by bronchoscopy 6 h postexposure. Exposure to ozone resulted in significant ($P < 0.01$) decrements in FEV1 with no protection observed following vitamin supplementation (-8.5%) versus placebo (-7.3%) treatment. Similarly, ozone-induced neutrophilia were of a similar magnitude after both treatments ($P < 0.05$). This lack of protection was observed despite elevated plasma vitamin C (+60.1%) and vitamin E (+51.4%) concentrations following supplementation, and increased vitamin C concentrations in the airways after supplementation following ozone exposure. These data do not therefore support the contention that acute ozone-induced symptoms can be attenuated through the use of dietary antioxidants in well-nourished individuals.

PMID: 16767844 [Indexed for MEDLINE]

[Similar articles](#)



66. J Obstet Gynaecol. 2006 May;26(4):344-7.

[Effect of a compound containing isoflavones, primrose oil and vitamin E in two different doses on climacteric symptoms.](#)

[Cancelo Hidalgo MJ](#)¹, [Castelo-Branco C](#), [Blumel JE](#), [Lanchares Pérez JL](#), [Alvarez De Los Heros JJ](#); [Isona Study Group](#).

Author information:

1. Hospital Universitario de Guadalajara, Universidad de Alcalá de Henares, Madrid, Spain.

Abstract

The object of this study was to evaluate the effect of different doses of a compound containing isoflavones 60 mg, primrose oil 440 mg and vitamin E 10 mg. (IOVE) on menopausal complaints. This was an open, multicentre, randomised, group comparative, efficacy and safety trial. A total of 1,080 postmenopausal women, with climacteric symptoms, were allocated into one of two treatment groups to receive one (Group 1; n = 562) or two IOVE capsules (Group 2; n = 518) per day. The Blatt - Kupperman scale and safety parameters including weight, body mass index, blood pressure and adverse effects were assessed at the first visit before initiating the treatment, and 3 - 6 months thereafter. In addition, cholesterol, high density

lipoprotein (HDL), low-density lipoprotein (LDL) and triglyceride levels were measured at baseline and at the 6th month visit. Finally, at the end of follow-up, the patient's satisfaction was assessed. No differences between groups at the beginning of the study and during the follow-up were observed. A significant reduction in Blatt - Kupperman scores were observed in the two groups. In addition, the reduction of the symptoms was more intense in the first 3 months. Increasing doses of IOVE add no beneficial effects since both studied doses were equally effective in the reduction of climacteric complaints.

PMID: 16753687 [Indexed for MEDLINE]

[Similar articles](#)



67. Int Arch Occup Environ Health. 2006 Nov;80(2):154-9. Epub 2006 May 19.

The role of antioxidant supplementation in occupational exposure to waste anaesthetic gases.

[Sardas S¹](#), [Izdes S](#), [Ozcagli E](#), [Kanbak O](#), [Kadioglu E](#).

Author information:

1. Department of Toxicology, Faculty of Pharmacy, Gazi University, Ankara, Turkey.
semrasardas@superonline.com

Abstract

OBJECTIVES:

Although the genotoxicity related to waste anaesthetic gases is controversial, a consistent number of observations have provided evidence for an increased level of DNA strand breaks. The goal of the research was to investigate this hypothesis and estimate the genoprotective role of antioxidant supplementation in technical anaesthesiology staff working in operating theatres.

METHODS:

Heparinized venous blood samples were collected from 17 exposed technical anaesthesiology staff (mean age 34.3 +/- 3.5 years) and non-exposed control group (mean age 32.2 +/- 3.4 years) and examined in the alkaline comet assay for DNA strand breakage. Vitamin E (300 mg/day) plus vitamin C (500 mg/day) were supplemented to the technical anaesthesiology staff for 12 weeks and blood samples were retaken and evaluated by comet assay.

RESULTS:

The DNA breakage observed in the lymphocytes of the technical anaesthesiology staff was 21.5 +/- 5.0, as calculated by total comet score (TCS). This score was significantly higher (P<0.001) than in the controls (8.6 +/- 4.7) before antioxidant treatment. Supplementation of vitamins E plus C significantly (P<0.01) reduced the mean TCS as 14.2 +/- 6.1.

CONCLUSION:

The results of our study indicate that occupational exposure to anaesthetic gases induces oxidative DNA damage. Supplementation of the diet for 12 weeks with vitamin C and vitamin E resulted in a significant decrease in the DNA damage.

PMID: 16710711 [Indexed for MEDLINE]

[Similar articles](#)



68. Cancer Epidemiol Biomarkers Prev. 2006 May;15(5):1030-4.

A phase II study with antioxidants, both in the diet and supplemented, pharmaconutritional support, progestagen, and anti-cyclooxygenase-2 showing efficacy and safety in patients with cancer-related anorexia/cachexia and oxidative stress.

[Mantovani G¹](#), [Macciò A](#), [Madeddu C](#), [Gramignano G](#), [Lusso MR](#), [Serpe R](#), [Massa E](#), [Astara G](#), [Deiana L](#).

Author information:

1. Cattedra e Divisione di Oncologia Medica, Università di Cagliari, Policlinico Universitario, Presidio di Monserrato, SS 554, KM 4.500, 09042 Monserrato, Cagliari, Italy. mantovan@pacs.unica.it

Abstract

PURPOSE:

To test the efficacy and safety of an integrated treatment based on a pharmaconutritional support, antioxidants, and drugs, all given orally, in a population of advanced cancer patients with cancer-related anorexia/cachexia and oxidative stress.

PATIENTS AND METHODS:

An open early-phase II study was designed according to the Simon two-stage design. The integrated treatment consisted of diet with high polyphenols content (400 mg), antioxidant treatment (300 mg/d alpha-lipoic acid + 2.7 g/d carbocysteine lysine salt + 400 mg/d vitamin E + 30,000 IU/d vitamin A + 500 mg/d vitamin C), and pharmaconutritional support enriched with 2 cans per day (n-3)-PUFA (eicosapentaenoic acid and docosahexaenoic acid), 500 mg/d medroxyprogesterone acetate, and 200 mg/d selective cyclooxygenase-2 inhibitor celecoxib. The treatment duration was 4 months. The following variables were evaluated: (a) clinical (Eastern Cooperative Oncology Group performance status); (b) nutritional [lean body mass (LBM), appetite, and resting energy expenditure]; (c) laboratory [proinflammatory cytokines and leptin, reactive oxygen species (ROS) and antioxidant enzymes]; (d) quality of life (European Organization for Research and Treatment of Cancer QLQ-C30, Euro QL-5D, and MFSI-SF).

RESULTS:

From July 2002 to January 2005, 44 patients were enrolled. Of these, 39 completed the treatment and were assessable. Body weight increased significantly from baseline as did LBM and appetite. There was an important decrease of proinflammatory cytokines interleukin-6 (IL-6) and tumor necrosis factor-alpha, and a negative relationship worthy of note was only found between LBM and IL-6 changes. As for quality of life evaluation, there was a marked improvement in the European Organization for Research and Treatment of Cancer QLQ-C30, Euro QL-5D(VAS), and multidimensional fatigue symptom inventory-short form scores. At the end of the study, 22 of the 39 patients were "responders" or "high responders." The minimum required was 21; therefore, the treatment was effective and more importantly was shown to be safe.

CONCLUSION:

The efficacy and safety of the treatment have been shown by the study; therefore, a randomized phase III study is warranted.

Free Article

PMID: 16702388 [Indexed for MEDLINE]

[Similar articles](#)



69. Support Care Cancer. 2006 Nov;14(11):1134-40. Epub 2006 Apr 19.

[A randomized controlled trial evaluating the efficacy and safety of vitamin E supplementation for protection against cisplatin-induced peripheral neuropathy: final results.](#)

[Argyriou AA](#)¹, [Chroni E](#), [Koutras A](#), [Iconomou G](#), [Papapetropoulos S](#), [Polychronopoulos P](#), [Kalofonos HP](#).

Author information:

1. EMG/ENG Laboratory, Department of Neurology, University of Patras Medical School, Rion-Patras, Greece.

Abstract

AIM:

A randomized, open label with blind assessment, controlled trial was performed to assess efficacy and adverse-event profile of vitamin E, given as supplementation for prophylaxis against cisplatin-induced peripheral neuropathy (CIPN).

PATIENTS AND METHODS:

A total of 30 patients scheduled to receive six courses of cumulative cisplatin-based regimens were randomly allocated to treatment and control groups and were then studied by means of neurological examination and electrophysiological study. Patients assigned to group I (n=14) orally received vitamin E at

a daily dose of 600 mg/day during chemotherapy and 3 months after its cessation were compared to patients of group II (n=16), who received no vitamin E supplementation and served as controls. The severity of neurotoxicity was summarized by means of a modified Peripheral Neuropathy (PNP) score.

RESULTS:

The incidence of neurotoxicity differed significantly between groups, occurring in 3/14 (21.4%) of patients assigned to the vitamin E supplementation group and in 11/16 (68.5%) of controls (p=0.026). The relative risk (RR) of developing neurotoxicity was significantly higher in case of controls, RR=2.51, 95% C.I.=1.16-5.47. Mean PNP scores were 4.99+/-1.33 for patients of group I and 10.47+/-10.62 for controls, (p=0.023). None of the adverse events or deaths occurred, were judged as likely to be related to the vitamin E supplementation.

CONCLUSION:

Vitamin E effectively and safely protects patients with cancer from occurrence of cisplatin neurotoxicity.

PMID: 16622646 [Indexed for MEDLINE]

[Similar articles](#)



70. Arzneimittelforschung. 2006;56(3):230-8.

[Open, non-controlled clinical studies to assess the efficacy and safety of a medical device in form of gel topically and intravaginally used in postmenopausal women with genital atrophy.](#)

[Morali G](#)¹, [Polatti F](#), [Metelitsa EN](#), [Mascarucci P](#), [Magnani P](#), [Marrè GB](#).

Author information:

1. Department of Gynecology and Obstetrics, Scassi Hospital, Genoa, Italy.

Abstract

Menopause is often associated with vaginal atrophy and related symptoms, such as vaginal dryness, burning, itching, and dyspareunia, decrease in libido and in general a decrease in the quality of life. The common treatment up to the 1990's has been the oral hormone replacement therapy (HRT), but this treatment has been consequently re-considered due to its adverse effects. Topical estrogenic products have been subsequently developed to minimize the systemic adverse effects of the oral HRT, but they are still considered at risk in case of prolonged use. As an alternative, two clinical trials were performed to investigate the effects of a medical device in the form of a gel, containing hyaluronic acid, liposomes, phytoestrogens from *Humulus lupulus* extract, and Vitamin E, with the aim of testing its safety and efficacy in post-menopausal women with urogenital atrophy. The first pilot study confirmed in 10 women the good safety profile, both locally and systemically, of the device applied on the external genitals at the dose of 1-2 g/day for 30 days. The second study was carried out, according to a multicenter, open, non-controlled

design, in 100 post-menopausal women assigned to the vaginal application of 2.5 g of gel/day for 1 week followed by two applications/week for 11 weeks. The primary end-point was the evaluation of vaginal dryness assessed by a Visual Analogue Scale both by the investigator and the subject. Secondary endpoints were the evaluation of all other symptoms and signs associated with atrophic vaginitis (itching, burning, dyspareunia, vaginal inflammation/oedema and rash assessed by a 4-point scale and presence of vaginal abrasions and disepithelialisation), and the recording of adverse events during the study. At the end of the treatment, an overall judgment on the efficacy and safety of the device was made by the investigator and a judgment on the acceptability of the treatment was made by the subjects. The results showed a marked effect of the tested product on the vaginal dryness and on all other symptoms and signs with statistically significant reductions since the first week of treatment. No treatment-related adverse events were complained by the subjects and the treatment course showed a high level of acceptability by the subjects. This device could be considered an effective and safe alternative treatment of genital atrophy in post-menopausal women, especially when HRT is not recommended.

PMID: 16618016 [Indexed for MEDLINE]

[Similar articles](#)



71. Urology. 2006 May;67(5):1038-42. Epub 2006 Apr 11.

Effect of intralesional interferon-alpha 2b combined with oral vitamin E for treatment of early stage Peyronie's disease: a randomized and prospective study.

[Inal T¹](#), [Tokatli Z](#), [Akand M](#), [Ozdiler E](#), [Yaman O](#).

Author information:

1. Department of Urology, University of Ankara School of Medicine, Ankara, Turkey.

Abstract

OBJECTIVES:

To compare the efficacy and safety of intralesional interferon-alpha 2b combined with oral vitamin E or intralesional interferon-alpha 2b alone or oral vitamin E alone for the treatment of Peyronie's disease.

METHODS:

From January 2000 to March 2002, a total of 30 consecutive men with Peyronie's disease were randomized prospectively into three different treatment groups. All the patients were assessed objectively with penile duplex Doppler ultrasonography for plaque size, location, and presence of calcification before and after treatment. Subjective data were obtained by querying about the improvement in penile pain and by using the "global efficacy question" for the assessment of the quality of sexual intercourse at the end of the study. A total of 5.0 x 10(6) U of interferon-alpha 2b was given once per week directly into the plaque for a period of

12 weeks. Patients received 400 IU of vitamin E orally twice daily for 6 months.

RESULTS:

At the 6-month follow-up visit, we did not find any statistically significant changes in the objective parameters when compared with the initial findings in each group or among the three groups ($P > 0.05$). We did not observe any clinically significant improvement in the subjective parameters among the three groups ($P > 0.05$). However, all patients who were treated with interferon-alpha 2b experienced brief flu-like side effects.

CONCLUSIONS:

Our findings indicate that 5 million units of intralesional interferon-alpha 2b injection therapy either alone or in combination with vitamin E does not appear to be clinically effective in the management of early stage Peyronie's disease compared with only oral vitamin E.

PMID: 16581113 [Indexed for MEDLINE]

[Similar articles](#)



72. Am J Ophthalmol. 2006 Jan;141(1):193-4.

Vitamin E in the treatment of uveitis-associated macular edema.

[Nussenblatt RB¹](#), [Kim J](#), [Thompson DJ](#), [Davis MD](#), [Chew E](#), [Ferris FL](#), [Buggage R](#).

Author information:

1. Laboratory of Immunology, National Eye Institute, National Institutes of Health, Building 10, Rm. 10S219, 10 Center Drive, Bethesda, MD 20892, USA. drbob@nei.nih.gov

Abstract

PURPOSE:

To investigate whether high-dose alpha-tocopherol (vitamin E) could reduce vision loss and retinal thickening associated with uveitis-associated cystoid macular edema.

DESIGN:

A double-masked, randomized study.

METHODS:

Uveitis patients with macular edema seen at the NIH were randomized and received either 1600 IU/day of vitamin E or placebo for 4 months. Visual acuity and retinal thickening were collected for the efficacy and the safety of the high dose of vitamin E.

RESULTS:

Changes in visual acuity and retinal thickening.

CONCLUSIONS:

Four-month oral supplementation with 1600 IU/d of vitamin E had no apparent effect on uveitis-associated macular edema or visual acuity in this small study.

PMID: 16386999 [Indexed for MEDLINE]

[Similar articles](#)



73. Clin Ther. 2005 Nov;27(11):1764-73.

Effects of antioxidant supplementation on postprandial oxidative stress and endothelial dysfunction: a single-blind, 15-day clinical trial in patients with untreated type 2 diabetes, subjects with impaired glucose tolerance, and healthy controls.

[Neri S¹](#), [Signorelli SS](#), [Torrise B](#), [Pulvirenti D](#), [Mauceri B](#), [Abate G](#), [Ignaccolo L](#), [Bordonaro F](#), [Cilio D](#), [Calvagno S](#), [Leotta C](#).

Author information:

1. Department of Internal Medicine and Systemic Disease, University of Catania, Via S. Sofia 86, 95123 Catania, Italy. sergio.neri4@tin.it

Abstract

BACKGROUND:

Increased generation of reactive oxygen species (ROS) and oxidative stress may be of crucial importance in the pathogenesis of endothelial damage. Furthermore, there is understood to be a relationship between endothelial damage, glycemic control, disorders of lipid metabolism, and coagulative hemostatic disorders.

OBJECTIVE:

This study investigated within- and between-group changes in various circulating markers of oxidation-reduction balance and endothelial function after a balanced moderate-fat meal with and without antioxidant supplementation in patients with early-stage, untreated type 2 diabetes mellitus; subjects with impaired glucose tolerance (IGT); and healthy controls.

METHODS:

In this single-blind, controlled clinical study, groups of patients with type 2 diabetes and subjects with IGT were identified and compared with a group of healthy controls. All groups followed a controlled, well-balanced diet for 10 days before and throughout the study. Before and after consumption of a standardized moderate-fat meal, plasma levels of oxidants (malondialdehyde, 4-hydroxynonenal, oxidized low-density lipoprotein), the antioxidant glutathione peroxidase, and markers of endothelial function (NO, endothelin-1, von Willebrand factor [vWF], vascular cell adhesion molecule-1 [VCAM-1]) were determined. These measures were then reassessed after 15 days of standard antioxidant treatment consisting of a thiol-containing antioxidant (N-acetylcysteine 600 g/d), a bound antioxidant (vitamin E 300 g/d), and an aqueous phase antioxidant (vitamin C 250 mg/d). The efficacy of antioxidant treatment in reversing abnormalities in oxidation-reduction balance after a moderate-fat meal was assessed by evaluating changes in plasma levels of ROS on the morning of the 16th day following an overnight fast. Safety was monitored in terms of adverse events, vital signs, physical findings, and laboratory values.

RESULTS:

The study included 46 patients with type 2 diabetes (23 men, 23 women; mean [SD] age, 41 [3] years; mean body mass index [BMI], 24 [2] kg/m²), 46 with IGT (23 men, 23 women; mean age, 39 [3] years; mean BMI, 23 [3] kg/m²), and 46 control subjects (23 men, 23 women; mean age, 40 [1] years; mean BMI, 22 [1] kg/m²). Before supplementation, all 3 groups had significantly increased levels of oxidants, vWF, and VCAM-1 (all, $P < 0.001$) and significantly decreased levels of antioxidants and NO (both, $P < 0.001$) after consumption of a moderate-fat meal. After 15 days of antioxidant treatment, significant improvements in these measures were seen in all groups ($P < 0.05$).

CONCLUSIONS:

This study showed changes in oxidation-reduction balance, NO bioavailability, and nonthrombogenic endothelial factors after a moderate-fat meal in patients with type 2 diabetes and those with IGT, but these postprandial changes were reverse in all subjects after 15 days of standard antioxidant supplementation. These findings suggest that the use of anti-oxidants may have decreased oxidative stress in these subjects. PMID: 16368447 [Indexed for MEDLINE]

[Similar articles](#)



74. Zhonghua Nan Ke Xue. 2005 Oct;11(10):761-4.

[\[A controlled randomized trial of the use of combined L-carnitine and acetyl-L-carnitine treatment in men with oligoasthenozoospermia\].](#)

[Article in Chinese]

[Li Z¹](#), [Chen GW](#), [Shang XJ](#), [Bai WJ](#), [Han YF](#), [Chen B](#), [Teng XM](#), [Meng FH](#), [Zhang B](#), [Chen DN](#), [Liu JH](#), [Zheng XM](#), [Cao XR](#), [Liu Y](#), [Zhu XB](#), [Wang YX](#).

Author information:

Abstract

OBJECTIVE:

To determine the efficacy and safety of combined L-carnitine and acetyl-L-carnitine therapy in infertile males with oligoasthenozoospermia.

METHODS:

One hundred fifty patients with oligoasthenozoospermia were randomized selected into treatment and control groups. The treatment group with 90 patients were given L-carnitine (2 g/d) and acetyl-L-carnitine (1 g/d) orally, twice a day. The patients in control group were given Vitamin E 100 mg plus Vitamin C 100 mg, tid. The oral therapy lasted three months and patients accepted sperm analysis every one month. The L-carnitine level in seminal plasma was examined by high performance liquid chromatography (HPLC). Side effects as well as pregnant rate were observed.

RESULTS:

In the treatment group, 85 patients out of 90 finished the three month treatment. Female spouses of 10 patients (11.6%) achieved pregnancy. Moreover, their forward motile sperm per ejaculation, total motile sperm, as well as the concentration of L-carnitine in seminal plasma were increased significantly ($P < 0.01$). In control group, 53 patients out of 60 completed three months therapy. Two pregnancy (3.7%) was observed. Though some increase was seen in number of forward motile sperm and total motile sperm per ejaculation, the changes were not statistically significant ($P > 0.05$). The difference of the pregnant rate between two groups was statistically significant. No side effects were found.

CONCLUSION:

Combined treatment with L-carnitine and acetyl-L-carnitine can be an effective and safe option for treating oligoasthenozoospermia by means of significantly improving forward motile sperm and total motile sperm per ejaculation, as well as increasing pregnant rates.

PMID: 16281510 [Indexed for MEDLINE]

[Similar articles](#)

75. Eur J Clin Nutr. 2005 Nov;59(11):1282-90.

Effects of vitamin E on the toxicity of oxidized LDL on endothelial cells in vitro in smokers vs nonsmokers on diets rich in fish.

[Seppo L¹](#), [Lähteenmäki T](#), [Tikkanen MJ](#), [Vanhanen H](#), [Korpela R](#), [Vapaatalo H](#).

Author information:

1. Institute of Biomedicine, Pharmacology, University of Helsinki, Finland.

Abstract

OBJECTIVE:

To clarify whether supplementation of vitamin E can alter the low density lipoprotein (LDL) oxidation properties and thereby affect endothelial cell function and prostacyclin production in smokers compared to nonsmokers on diets rich in fish in a pilot study.

DESIGN:

The LDL of six smokers and six nonsmokers on habitual high fish diet was isolated before and after an 8-week supplementation of vitamin E (800 IU/day). LDL was oxidized by incubation with CuSO₄. Cytotoxicity of LDL oxidized to different degrees on endothelial cells was investigated in vitro in these two groups.

SETTING:

Helsinki University Central Hospital; Institute of Biomedicine, Pharmacology, University of Helsinki.

RESULTS:

At baseline, the rate of oxidation was higher in nonsmokers than in smokers. The lag phase increased significantly after the supplementation of vitamin E both in smokers and nonsmokers. Native LDL dose dependently tended to reduce the viability of endothelial cells in vitro more markedly when isolated from smokers than from nonsmokers. Vitamin E supplementation had no beneficial effect on the cytotoxicity of oxidized LDLs in endothelial cell culture. On the other hand, simultaneous administration of Trolox, the water-soluble analogue of vitamin E, attenuated the LDL cytotoxicity on endothelial cells. The vitamin E supplementation to LDL donors attenuated the increase in prostacyclin production both in smokers and nonsmokers.

CONCLUSION:

Supplementation of LDL donors (healthy male volunteers on habitual fish diet) with vitamin E increased the lag phase of LDL oxidation, but, on the other hand, did not influence in vitro cytotoxicity of LDL, or prostacyclin production.

PMID: 16047029 [Indexed for MEDLINE]

[Similar articles](#)



76. J Ren Nutr. 2005 Jul;15(3):318-31.

[An anti-inflammatory and antioxidant nutritional supplement for hypoalbuminemic hemodialysis patients: a pilot/feasibility study.](#)

[Kalantar-Zadeh K¹](#), [Braglia A](#), [Chow J](#), [Kwon O](#), [Kuwaie N](#), [Colman S](#), [Cockram DB](#), [Kopple JD](#).

Author information:

1. Division of Nephrology and Hypertension, Los Angeles Biomedical Institute at Harbor-UCLA Medical Center, Torrance, CA 90509-2910, USA. kamkal@ucla.edu

Abstract

BACKGROUND:

A low serum albumin concentration < 3.8 g/dL, a marker of malnutrition-inflammation complex syndrome, is observed in approximately half of all maintenance hemodialysis (MHD) patients in the United States and is strongly associated with increased mortality.

OBJECTIVES:

We hypothesized that a novel oral nutritional intervention with anti-inflammatory and antioxidant properties taken during routine dialysis sessions is well tolerated and corrects hypoalbuminemia in MHD patients.

DESIGN:

Controlled clinical study.

SETTING:

An outpatient dialysis facility affiliated with a tertiary care community medical center with six equally distributed hemodialysis shifts and 163 MHD patients.

PATIENTS:

Among all MHD outpatients of three selected HD shifts ($n = 81$ patients), 21 subjects had a serum albumin level < 3.8 g/dL. One patient who was hospitalized before the intervention was excluded. The other three dialysis shifts, with 82 MHD outpatients including 20 hypoalbuminemic subjects, were observed as concurrent controls.

INTERVENTION:

The nutritional intervention included one can of Oxepa and one can of Nepro to be taken together orally during each routine hemodialysis session for 4 weeks. Each can contains 237 mL fluid. Oxepa provides 355 calories and 14.8 g protein per can, includes maltodextrin, medium-chain triglycerides, borage oil, and refined and deodorized fish oil, and is designed for critically ill patients with inflammation and oxidative stress. Each can of Oxepa includes 1,020 mg gamma-linolenic acid, 3,100 mg caprylic acid, 1,080 mg eicosapentaenoic acid, 75 mg taurine, 2,840 IU vitamin A activity, 75 IU vitamin E, and 200 mg vitamin C. Nepro provides 475 calories and 16.7 g protein per can; includes high-oleic safflower oil, corn syrup solids, and fructo-oligosaccharides; and is tailored for the nutritional needs of MHD patients. Oxepa and Nepro also contain L-carnitine, 43 mg and 62 mg, respectively.

MAIN OUTCOME MEASURES:

Serum albumin pretrial and posttrial.

RESULTS:

Studied outpatients (12 men and 8 women) were aged 60.4 +/- 13.0 (SD) years. Three patients had started MHD treatment between 1.5 and 3 months before the intervention. Nine patients were diabetic. Preintervention serum albumin, 3.44 +/- 0.34 g/dL (mean +/- SD) increased to 3.68 +/- 0.34 g/dL (P = .001) 4 weeks after the start of the intervention. In 16 patients, serum albumin level increased by 0.2 to 1.3 g/dL, whereas in 4 patients the serum albumin level decreased by 0.2 to 0.6 g/dL. Three patients reported diarrhea, and one diabetic patient had increased serum glucose values. No other side effects were noted. In 20 control outpatients not receiving nutritional intervention, serum albumin did not change from 3.46 +/- 0.20 to 3.47 +/- 0.44 g/dL (P = .47).

CONCLUSIONS:

In hypoalbuminemic MHD patients, a short-term in-center nutritional intervention with one can of Nepro and one can of Oxepa during HD is practical, convenient, well-tolerated, and associated with a significant increase in serum albumin level. Well-designed randomized placebo-controlled clinical trials are needed to verify the safety and effectiveness of this nutritional intervention and its impact on clinical outcome in hypoalbuminemic MHD patients.

PMID: 16007562 [Indexed for MEDLINE]

[Similar articles](#)



77. Int J Dermatol. 2005 Mar;44(3):248-51.

Vitamin E does not reduce the side-effects of isotretinoin in the treatment of acne vulgaris.

[Kus S¹](#), [Gün D](#), [Demirçay Z](#), [Sur H](#).

Author information:

1. Department of Dermatology, Marmara University School of Medicine, Altunizade, Turkey.

Abstract

BACKGROUND:

Isotretinoin is widely used in the treatment of severe, recalcitrant, nodular acne. Mucocutaneous side-effects are seen in the great majority of patients and some of them have elevations in their serum lipid and liver enzyme profiles. Recently, it has been shown that addition of vitamin E decreased the toxicity of high-dose retinoids.

OBJECTIVE:

The purpose of this investigator-blinded, randomized study was to assess whether vitamin E would reduce the side-effects of isotretinoin in the treatment of acne vulgaris.

METHODS:

Eighty two patients were randomly assigned to one of two treatment groups with isotretinoin (1 mg/kg/day) alone or combined with vitamin E (800 IU/day). The treatment duration was 16 weeks. Mucocutaneous side-effects such as facial erythema, facial dryness, cheilitis and serum lipid and liver enzyme profiles were assessed.

RESULTS:

There was no difference in the incidence and severity of side-effects related to isotretinoin between the two treatment groups.

CONCLUSION:

Eight hundred IU/day vitamin E did not improve the side-effects of 1 mg/kg/day of isotretinoin in the treatment of acne vulgaris.

PMID: 15807739 [Indexed for MEDLINE]

[Similar articles](#)



78. Int Braz J Urol. 2004 May-Jun;30(3):199-204; discussion 204.

An alternative non-invasive treatment for Peyronie's disease.

[Claro JA¹](#), [Passerotti CC](#), [Figueiredo Neto AC](#), [Nardoza A Jr](#), [Ortiz V](#), [Srougi M](#).

Author information:

1. Division of Urology, Paulista School of Medicine, Federal University of São Paulo, UNIFESP, São Paulo, SP, Brazil. joaquimclaro@hotmail.com

Abstract

OBJECTIVE:

Surgical correction of the deformity and plaque caused by Peyronie's disease has some important disadvantages and extracorporeal shockwave therapy (ESWT) emerged as a new promising therapy. We evaluated prospectively the efficacy and safety of the association of high dose vitamin E and ESWT as a non-invasive treatment for the disease.

MATERIALS AND METHODS:

Twenty-five patients 42 to 68 years old (mean = 54) presenting penile deviation and sexual distress caused by Peyronie's disease were treated in a non-invasive manner. The time of penile deviation ranged from 16 to 52 months (mean = 30). All patients had previous unsuccessful treatment for Peyronie's disease. The angulation's deformity of the penis was assessed by photography at home. The patients received vitamin E (1.200 mg daily) during 3 months and underwent 3 to 6 sessions (mean = 3) of ESWT (3,000 to 4,000

shockwaves) at a power level of 1 to 2 at 1-week intervals.

RESULTS:

From 25 patients treated, 16 (64%) reported an improvement in penile angulation, with a mean reduction of 21 degrees (10 to 40). Eight patients reported improvement in their spontaneous erections. Overall, the patients presented only minimal bruising at the site of treatment and skin hematoma. Four patients presented urethral bleeding. The mean angulation after treatment in the control group was 48.67 degrees (30 - 70) and in the study group was 24.42 degrees (0 - 70), statistically significant.

CONCLUSION:

Considering the common complications and the unsatisfactory outcome of the surgical correction for Peyronie's disease, the association of high dose vitamin E and ESWT represents a good option for a non-invasive, effective and safe treatment of the penile deformity.

Free Article

PMID: 15689246 [Indexed for MEDLINE]

[Similar articles](#)



79. J Am Coll Nutr. 2005 Feb;24(1):16-21.

[Chemotherapy alone vs. chemotherapy plus high dose multiple antioxidants in patients with advanced non small cell lung cancer.](#)

[Pathak AK¹](#), [Bhutani M](#), [Guleria R](#), [Bal S](#), [Mohan A](#), [Mohanti BK](#), [Sharma A](#), [Pathak R](#), [Bhardwaj NK](#), [Prasad KN](#), [Kochupillai V](#).

Author information:

1. Department of Medical Oncology, Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi 110 029, INDIA.

Abstract

OBJECTIVE:

In vitro and animal studies suggest that antitumor effect of chemotherapeutic agents may be enhanced by antioxidants. Therefore, we initiated a clinical study to test the efficacy of high-dose multiple antioxidants (vitamins C, E and beta carotene) as an adjunct to chemotherapy (paclitaxel and carboplatin) in non-small-cell lung cancer.

METHODS:

136 patients of stage IIIb and stage IV NSCLC were randomized to receive chemotherapy (paclitaxel and

carboplatin) alone (chemotherapy arm, n = 72) or chemotherapy in combination with ascorbic acid 6100 mg/day, dl-alpha-tocopherol (vitamin E) 1050 mg/day and beta-carotene 60 mg/day (combination arm, n = 64). Survival were calculated by the Kaplan-Meier method and compared using the log-rank test.

RESULTS:

An overall response rate (RR) of 33% was observed in chemotherapy arm with 24 patients showing a partial response (PR) and none showing a complete response (CR). In combination arm the overall RR was 37% with 24 patients showing PR and two showing CR. The median survival times in chemotherapy arm and combination arm were nine and 11 months respectively. The overall survival (OS) rates in chemotherapy arm and combination arm at one year were 32.9% and 39.1%, and at two years, 11.1% and 15.6% respectively. None of these differences were statistically significant (p = 0.20). Toxicity profiles were similar in both arms.

CONCLUSIONS:

These results do not support the concern that antioxidants might protect cancer cells from the free radical damage induced by chemotherapy. Larger trials are needed to demonstrate whether high-dose multiple antioxidants in conjunction with chemotherapy increase the response rates and/or survival time in advanced lung cancer.

PMID: 15670980 [Indexed for MEDLINE]

[Similar articles](#)

80. Clin Gastroenterol Hepatol. 2004 Dec;2(12):1107-15.

[A pilot study of vitamin E versus vitamin E and pioglitazone for the treatment of nonalcoholic steatohepatitis.](#)

[Sanyal AJ](#)¹, [Mofrad PS](#), [Contos MJ](#), [Sargeant C](#), [Luketic VA](#), [Sterling RK](#), [Stravitz RT](#), [Shiffman ML](#), [Clore J](#), [Mills AS](#).

Author information:

1. Division of Gastroenterology, Hepatology and Nutrition, Department of Internal Medicine, Virginia Commonwealth University Medical Center, Richmond, VA 23298-0711, USA. ajsanyal@hsc.vcu.edu

Comment in

- [Treatment of nonalcoholic steatohepatitis: antioxidants or insulin sensitizers?](#) [Clin Gastroenterol Hepatol. 2004]

Abstract

BACKGROUND & AIMS:

Insulin resistance and oxidative stress contribute to the pathogenesis of nonalcoholic steatohepatitis (NASH). We conducted a pilot study for the following reasons: (1) to test the hypothesis that a combination of an antioxidant (vitamin E) and an insulin sensitizer (pioglitazone) would be superior to vitamin E alone

for the treatment of NASH, and (2) to define the effects of these interventions on insulin-sensitive metabolic functions and correlate the effects with changes in liver histology.

METHODS:

A randomized prospective trial was performed to compare the efficacy and safety of vitamin E alone (400 IU/day) vs. vitamin E (400 IU/day) and pioglitazone (30 mg/day) in nondiabetic, noncirrhotic subjects with NASH. Metabolic functions were assessed by a 2-step, hyperinsulinemic (10 and 40 mU/m²/min) euglycemic clamp.

RESULTS:

A total of 10 patients were randomized to each arm. Two patients on combination therapy discontinued treatment; one because of pregnancy and the other because of hepatotoxicity. Treatment with vitamin E only produced a significant decrease in steatosis (mean grade, 2.2 vs. 1.4; $P < .02$). Compared with baseline, combination therapy produced a significant decrease in steatosis (mean, 2.3 vs. 1; $P < .002$), cytologic ballooning (1.3 vs. 0.2; $P < .01$), Mallory's hyaline (0.7 vs. 0.2; $P < .04$), and pericellular fibrosis (1.2 vs. 0.6; $P < .03$). Although vitamin E had no significant effects, combination therapy produced a significant increase in metabolic clearance of glucose and a decrease in fasting free fatty acid (FFA) and insulin. The decrease in fasting FFA and insulin independently predicted improvement in hepatic steatosis and cytologic ballooning.

CONCLUSIONS:

A combination of vitamin E and pioglitazone produces a greater improvement in NASH histology. The improvement in steatosis and cytologic ballooning are related to treatment-associated decreases in fasting FFA and insulin levels.

PMID: 15625656 [Indexed for MEDLINE]

[Similar articles](#)



81. J Neural Transm (Vienna). 2005 May;112(5):649-60. Epub 2004 Oct 27.

High dose vitamin E therapy in amyotrophic lateral sclerosis as add-on therapy to riluzole: results of a placebo-controlled double-blind study.

[Graf M¹](#), [Ecker D](#), [Horowski R](#), [Kramer B](#), [Riederer P](#), [Gerlach M](#), [Hager C](#), [Ludolph AC](#), [Becker G](#), [Osterhage J](#), [Jost WH](#), [Schrank B](#), [Stein C](#), [Kostopoulos P](#), [Lubik S](#), [Wekwerth K](#), [Dengler R](#), [Troeger M](#), [Wuerz A](#), [Hoge A](#), [Schrader C](#), [Schimke N](#), [Krampfl K](#), [Petri S](#), [Zierz S](#), [Eger K](#), [Neudecker S](#), [Traufeller K](#), [Sievert M](#), [Neundörfer B](#), [Hecht M](#); [German vitamin E/ALS Study Group](#).

Author information:

1. michael.graf@psl.ap-hop-paris.fr

Abstract

Increasing evidence has suggested that oxidative stress may be involved in the pathogenesis of amyotrophic lateral sclerosis (ALS). The antioxidant vitamin E (alpha-tocopherol) has been shown to slow down the onset and progression of the paralysis in transgenic mice expressing a mutation in the superoxide dismutase gene found in certain forms of familial ALS. The current study, a double blind, placebo-controlled, randomised, stratified, parallel-group clinical trial, was designed to determine whether vitamin E (5000 mg per day) may be efficacious in slowing down disease progression when added to riluzole.

METHODS:

160 patients in 6 German centres with either probable or definite ALS (according to the El Escorial Criteria) and a disease duration of less than 5 years, treated with riluzole, were included in this study and were randomly assigned to receive either alpha-tocopherol (5000 mg per day) or placebo for 18 months. The Primary outcome measure was survival, calculating time to death, tracheostomy or permanent assisted ventilation, according to the WFN-Criteria of clinical trials. Secondary outcome measures were the rate of deterioration of function assessed by the modified Norris limb and bulbar scales, manual muscle testing (BMRC), spasticity scale, ventilatory function and the Sickness Impact Profile (SIP ALS/19). Patients were assessed at entry and every 4 months thereafter during the study period until month 16 and at a final visit at month 18. Vitamin E samples were taken for compliance check and Quality Control of the trial. For Safety, a physical examination was performed at baseline and then every visit until the treatment discontinuation at month 18. Height and weight were recorded at baseline and weight alone at the follow-up visits. A neurological examination as well as vital signs (heart rate and blood pressure), an ECG and VEP's were recorded at each visit. Furthermore, spontaneously reported adverse experiences and serious adverse events were documented and standard laboratory tests including liver function tests performed. For Statistical Analysis, the population to be considered for the primary outcome measure was an "intent-to-treat" (ITT) population which included all randomised patients who had received at least one treatment dose (n = 160 patients). For the secondary outcome measures, a two way analysis of variance was performed on a patient population that included all randomised patients who had at least one assessment after inclusion.

RESULTS:

Concerning the primary endpoint, no significant difference between placebo and treatment group could be detected either with the stratified Logrank or the Wilcoxon test. The functional assessments showed a marginal trend in favour of vitamin E, without reaching significance.

CONCLUSION:

Neither the primary nor the secondary outcome measures could determine whether a megadose of vitamin E is efficacious in slowing disease progression in ALS as an add-on therapy to riluzol. Larger or longer studies might be needed. However, administration of this megadose does not seem to have any significant side effects in this patient population.

PMID: 15517433 [Indexed for MEDLINE]

[Similar articles](#)



Antioxidant supplementation and nasal inflammatory responses among young asthmatics exposed to high levels of ozone.

[Sienra-Monge JJ¹](#), [Ramirez-Aguilar M](#), [Moreno-Macias H](#), [Reyes-Ruiz NI](#), [Del Río-Navarro BE](#), [Ruiz-Navarro MX](#), [Hatch G](#), [Crissman K](#), [Slade R](#), [Devlin RB](#), [Romieu I](#).

Author information:

1. Hospital Infantil de México, Federico Gómez, México.

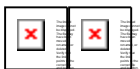
Abstract

The inflammatory response to ozone in atopic asthma suggests that soluble mediators of inflammation are released in response to oxidant stress. Antioxidants may alleviate additional oxidative stress associated with photochemical oxidant pollution. This study investigates the impact of antioxidant supplementation on the nasal inflammatory response to ozone exposure in atopic asthmatic children. We conducted a randomized trial using a double-blinded design. Children with asthma (n = 117), residents of Mexico City, were given randomly a daily supplement of vitamins (50 mg/day of vitamin E and 250 mg/day of vitamin C) or placebo. Nasal lavages were performed three times during the 4-month follow-up and analysed for content of interleukin-6 (IL-6), IL-8, uric acid and glutathione (GSx). IL-6 levels in the nasal lavage were increased significantly in the placebo group after ozone exposure while no increase was observed in the supplement group. The difference in response to ozone exposure between the two groups was significant (P = 0.02). Results were similar for IL-8, but with no significant difference between the groups (P = 0.12). GSx decreased significantly in both groups. Uric acid decreased slightly in the placebo group. Our data suggest that vitamin C and E supplementation above the minimum dietary requirement in asthmatic children with a low intake of vitamin E might provide some protection against the nasal acute inflammatory response to ozone.

PMCID: PMC1809210 **Free PMC Article**

PMID: 15498043 [Indexed for MEDLINE]

[Similar articles](#)



83. Nephrology (Carlton). 2004 Aug;9(4):217-22.

Oxidative stress from rapid versus slow intravenous iron replacement in haemodialysis patients.

[Tiranathanagul K¹](#), [Eiam-Ong S](#), [Tosukhowong P](#), [Praditpornsilpa K](#), [Tungsanga K](#).

Author information:

1. Division of Nephrology, Department of Medicine, Faculty of Medicine, Chulalongkorn University Hospital, Bangkok, Thailand.

Abstract

METHODS AND RESULTS:

Oxidative stress was examined in 19 erythropoietin-treated haemodialysis patients who were receiving 100 mg of iron sucrose every 2 weeks by two intravenous methods, rapid injection and slow infusion. There were no significant differences in incidence of iron oversaturation state between the two methods. Regarding oxidative stress markers, the values of plasma and red blood cell thiobarbituric acid reactive substances (TBARS) expressed in terms of malonyldialdehyde (MDA) equivalents following the two methods did not increase, and the values of area under the curve (AUC) of both markers were not different between both regimens. Also, there were no significant differences in the values of plasma and AUC of anti-oxidant markers including total anti-oxidant status, reduced thiols, and vitamin E among both periods treated with two intravenous iron methods.

CONCLUSION:

As such, both intravenous iron methods could be safely used without enhancing oxidative stress in haemodialysis patients. The rapid injection method would be the preferred method of intravenous iron administration because it is more convenient while still retaining the safety profile.

PMID: 15363053 [Indexed for MEDLINE]

[Similar articles](#)



84. Biol Blood Marrow Transplant. 2004 Sep;10(9):635-44.

[A multiagent strategy to decrease regimen-related toxicity in children undergoing allogeneic hematopoietic stem cell transplantation.](#)

[Thornley I¹](#), [Lehmann LE](#), [Sung L](#), [Holmes C](#), [Spear JM](#), [Brennan L](#), [Vangel M](#), [Bechard LJ](#), [Richardson P](#), [Duggan C](#), [Guinan EC](#).

Author information:

1. Department of Pediatric Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts, USA.

Abstract

Regimen-related toxicity (RRT) is a frequent cause of morbidity and mortality after allogeneic hematopoietic stem cell transplantation (HSCT). In this pilot study, we examined the feasibility and potential efficacy of administering a fixed combination of agents as a novel approach to reducing RRT in children undergoing HSCT. Thirty-seven patients were treated with ursodeoxycholic acid, folic acid, vitamin E, and parenteral nutrition titrated to measured energy expenditure in the peritransplantation period. Outcomes were compared with those in historical controls (n = 131). Compliance with oral ursodeoxycholic

acid and vitamin E of at least 90% was achieved in a mean of 86% (95% confidence interval, 75%-97%) of patients. In the study group, we observed (1) reduced prevalence and severity of mucositis ($P = .008$ and $.004$, respectively); (2) less severe hepatic toxicity ($P = .007$); and (3) shorter time to engraftment ($P = .02$) compared with the control group. These benefits appeared most pronounced among high-risk patients. The administration of this regimen, including oral medications, is feasible during the peritransplantation period, and it is well tolerated. The decreased RRT observed in comparison to historical controls suggests that combination approaches deserve exploration as a means of reducing the morbidity of HSCT.

Free Article

PMID: 15319775 [Indexed for MEDLINE]

[Similar articles](#)



85. Eur J Cancer. 2004 Jul;40(11):1713-23.

[Supplementation with antioxidant micronutrients and chemotherapy-induced toxicity in cancer patients treated with cisplatin-based chemotherapy: a randomised, double-blind, placebo-controlled study.](#)

[Weijl NI](#)¹, [Elsendoorn TJ](#), [Lentjes EG](#), [Hopman GD](#), [Wipkink-Bakker A](#), [Zwinderman AH](#), [Cleton FJ](#), [Osanto S](#).

Author information:

1. Department of Clinical Oncology, Leiden University Medical Center, Leiden, The Netherlands.

Abstract

Cisplatin-induced toxicities are mainly caused by the formation of free radicals, leading to oxidative organ damage. Plasma concentrations of antioxidants decrease significantly during cisplatin chemotherapy for cancer. Forty-eight cancer patients treated with cisplatin-based chemotherapy were randomised in a double-blind manner to receive either supplementation with vitamin C, vitamin E and selenium dissolved in a beverage or to receive a placebo beverage. Primary outcome measures were the amount of nephrotoxicity and ototoxicity induced by cisplatin. No significant differences were found between the two study groups with respect to these primary outcome measures. However, patients who achieved the highest plasma concentrations of the three antioxidant micronutrients had significantly less loss of high-tone hearing. In addition, significant correlations were found between the reduced/oxidised vitamin C ratio and malondialdehyde (MDA), markers of oxidative stress, and cisplatin-induced ototoxicity and nephrotoxicity. The lack of protection against cisplatin-induced toxicities in patients in the intervention arm may be related to poor compliance and/or inadequate supplementation. Supplementation with a higher dose (intensity) and in combination with other antioxidants should be investigated further.

PMID: 15251161 [Indexed for MEDLINE]

[Similar articles](#)



86. Exp Neurol. 2004 Aug;188(2):491-4.

[Pilot trial of high dosages of coenzyme Q10 in patients with Parkinson's disease.](#)

[Shults CW](#)¹, [Flint Beal M](#), [Song D](#), [Fontaine D](#).

Author information:

1. Department of Neurosciences, University of California, San Diego, La Jolla 92093-0662, USA.
cshults@ucsd.edu

Abstract

The safety and tolerability of high dosages of coenzyme Q10 were studied in 17 patients with Parkinson's disease (PD) in an open label study. The subjects received an escalating dosage of coenzyme Q10--1200, 1800, 2400, and 3000 mg/day with a stable dosage of vitamin E (alpha-tocopherol) 1200 IU/day. The plasma level of coenzyme Q10 was measured at each dosage. Thirteen of the subjects achieved the maximal dosage, and adverse events were typically considered to be unrelated to coenzyme Q10. The plasma level reached a plateau at the 2400 mg/day dosage and did not increase further at the 3000 mg/day dosage. Our data suggest that in future studies of coenzyme Q10 in PD, a dosage of 2400 mg/day (with vitamin E/alpha-tocopherol 1200 IU/day) is an appropriate highest dosage to be studied.

PMID: 15246848 [Indexed for MEDLINE]

[Similar articles](#)



87. Anticancer Res. 2004 Mar-Apr;24(2C):1255-60.

[Treatment with all-trans retinoic acid plus tamoxifen and vitamin E in advanced hepatocellular carcinoma.](#)

[Clerici C](#)¹, [Castellani D](#), [Russo G](#), [Fiorucci S](#), [Sabatino G](#), [Giuliano V](#), [Gentili G](#), [Morelli O](#), [Raffo P](#), [Baldoni M](#), [Morelli A](#), [Toma S](#).

Author information:

1. Clinic of Gastroenterology and Hepatology, University of Perugia, Italy. clerici@unipg.it

Abstract

BACKGROUND:

Low serum retinol and hepatic tocopherol levels correlate with hepatocellular carcinoma (HCC) risk. Antiestrogen tamoxifen seems useful in HCC patients. A pilot study was performed to evaluate the effect of all-trans retinoic acid associated with tamoxifen and vitamin E on patients with advanced HCC.

PATIENTS AND METHODS:

Fifteen consecutive patients with advanced HCC were included in the study. Patients were evaluated for survival, quality of life, liver function, tumor mass, toxicity related to the treatment and retinoid receptors in liver biopsies.

RESULTS:

The median survival of our patients was 22 months. Pain and asthenia were improved in the majority of patients. Every patient with baseline elevated liver enzymes showed an improvement in liver function. RAR-alpha, RXR-alpha, RAR-beta and RAR-gamma receptors were demonstrated in 100%, 73%, 47% and 40%, respectively.

CONCLUSION:

A combination therapy of all-trans retinoic acid, tamoxifen and vitamin E increases the survival rate and ameliorates the clinical outcome in patients with inoperable HCC.

Free Article

PMID: 15154656 [Indexed for MEDLINE]

[Similar articles](#)



88. Eur J Endocrinol. 2004 May;150(5):719-24.

A randomized trial of nicotinamide and vitamin E in children with recent onset type 1 diabetes (IMDIAB IX).

[Crinò A¹](#), [Schiaffini R](#), [Manfrini S](#), [Mesturino C](#), [Visalli N](#), [Beretta Anguissola G](#), [Suraci C](#), [Pitocco D](#), [Spera S](#), [Corbi S](#), [Matteoli MC](#), [Patera IP](#), [Manca Bitti ML](#), [Bizzarri C](#), [Pozzilli P](#); [IMDIAB group](#).

Author information:

1. Ospedale Bambino Gesù, Piazza S. Onofrio 4, 00163 Rome, Italy.

Abstract

OBJECTIVE:

Various adjuvant therapies have been introduced along with intensive insulin therapy in patients with recent onset type 1 diabetes. Nicotinamide (NA), administered at diagnosis of the disease, can have beneficial effects on the clinical remission rate, improve metabolic control and preserve or slightly increase beta-cell

function, probably by reducing toxicity due to free oxygen radicals. Vitamin E, a known antioxidant, inhibits lipid peroxidation; this can lead to protection of islet beta cells from the combined effects of interleukin 1, tumor necrosis factor and gamma interferon. The aim of the present study was to investigate whether the addition of vitamin E to NA could improve metabolic control and the residual beta-cell function, as measured by C-peptide secretion, in children and adolescents with recent onset type 1 diabetes; patients were followed-up for 2 years after diagnosis.

PATIENTS AND STUDY DESIGN:

Recent onset type 1 diabetes patients (n=64, mean age 8.8 years) were recruited by participating centres of the IMDIAB group. Thirty-two patients were randomized to NA (25 mg/kg body weight) plus vitamin E (15 mg/kg body weight); 32 patients acted as controls and received NA only at the same dose as above. Intensive insulin therapy was applied to both treatment groups.

RESULTS:

There were three drop outs during the 2-year follow-up period. Overall, patients assigned to the NA+vitamin E group or the NA group did not significantly differ in terms of glycated hemoglobin (HbA1c) levels, insulin requirement or baseline C-peptide secretion. Patients diagnosed at an age of less than 9 years showed significantly reduced C-peptide levels compared with those aged over 9 years at diagnosis and at the 2-year follow-up but there were no differences between the NA and NA+vitamin E treated groups. However at 6 months, patients over 9 years of age treated with NA+vitamin E showed significantly higher C-peptide compared with the NA group ($P<0.003$). In both age groups and in the different treatment groups, C-peptide levels found at diagnosis were preserved 2 years later.

CONCLUSIONS:

The use of NA alone, or in combination with vitamin E, along with intensive insulin therapy is able to preserve baseline C-peptide secretion for up to 2 years after diagnosis. This finding is of particular interest for pre-pubertal children with type 1 diabetes and has never been reported before.

Free Article

PMID: 15132730 [Indexed for MEDLINE]

[Similar articles](#)



89. Diabetes Care. 2003 Dec;26(12):3264-72.

Primary prevention of cardiovascular events with low-dose aspirin and vitamin E in type 2 diabetic patients: results of the Primary Prevention Project (PPP) trial.

[Sacco M¹](#), [Pellegrini F](#), [Roncaglioni MC](#), [Avanzini F](#), [Tognoni G](#), [Nicolucci A](#); [PPP Collaborative Group](#).

Author information:

1. Department of Clinical Pharmacology and Epidemiology, Istituto di Ricerche Farmacologiche Mario Negri, Consorzio Mario Negri Sud, S. Maria Imbaro (CH), Italy.

Comment in

- [Is aspirin resistance a real problem in people with type 2 diabetes?](#) [Diabetes Care. 2004]
- [Aspirin resistance in diabetic patients.](#) [Diabetes Care. 2004]

Abstract

OBJECTIVE:

We investigated in general practice the efficacy of antiplatelets and antioxidants in primary prevention of cardiovascular events in people with type 2 diabetes.

RESEARCH DESIGN AND METHODS:

The Primary Prevention Project (PPP) is a randomized, open trial with a two-by-two factorial design aimed to investigate low-dose aspirin (100 mg/day) and vitamin E (300 mg/day) in the prevention of cardiovascular events in patients with one or more cardiovascular risk factors. The primary end point was a composite end point of cardiovascular death, stroke, or myocardial infarction. A total of 1,031 people with diabetes in the PPP, aged ≥ 50 years, without a previous cardiovascular event were enrolled by 316 general practitioners and 14 diabetes outpatient clinics.

RESULTS:

The PPP trial was prematurely stopped (after a median of 3.7 years) by the independent data safety and monitoring board because of a consistent benefit of aspirin compared with the control group in a population of 4,495 patients with one or more major cardiovascular risk factors. In diabetic patients, aspirin treatment was associated with a nonsignificant reduction in the main end point (relative risk [RR] = 0.90, 95% CI 0.50-1.62) and in total cardiovascular events (0.89, 0.62-1.26) and with a nonsignificant increase in cardiovascular deaths (1.23, 0.69-2.19). In nondiabetic subjects, RRs for the main end point, total cardiovascular events, and cardiovascular deaths were 0.59 (0.37-0.94), 0.69 (0.53-0.90), and 0.32 (0.14-0.72), respectively. No significant reduction in any of the end points considered could be found with vitamin E in either diabetic or nondiabetic subjects.

CONCLUSIONS:

Our data suggest a lower effect of primary prevention of cardiovascular disease (CVD) with low-dose aspirin in diabetic patients as opposed to subjects with other cardiovascular risk factors. If confirmed, these findings might indicate that the antiplatelet effects of aspirin in diabetic patients are overwhelmed by aspirin-insensitive mechanisms of platelet activation and thrombus formation, thus making the balance between benefits and harms of aspirin treatment unfavorable. Further large-scale trials investigating the role of aspirin in the primary prevention of CVD in diabetic patients are urgently needed.

PMID: 14633812 [Indexed for MEDLINE]

[Similar articles](#)



90. Arch Ophthalmol. 2003 Sep;121(9):1269-78.

Biological safety assessment of docosahexaenoic acid supplementation in a randomized clinical trial for X-linked retinitis pigmentosa.

[Wheaton DH](#)¹, [Hoffman DR](#), [Locke KG](#), [Watkins RB](#), [Birch DG](#).

Author information:

1. Retina Foundation of the Southwest, Dallas, TX 75231, USA. dwheaton@retinafoundation.org

Abstract

BACKGROUND:

In a 4-year placebo-controlled trial to elevate blood docosahexaenoic acid levels in patients with X-linked retinitis pigmentosa (XLRP), the goal was to assess the potential benefit of docosahexaenoic acid supplementation in altering disease progression. However, docosahexaenoic acid (22:6omega3) is a highly unsaturated fatty acid and considered a target molecule for free-radical oxidative damage. Thus, nutritional provision of docosahexaenoic acid might lead to an increase in antioxidant stress. Additional concerns, such as decreased platelet aggregation, increased bleeding time, and alterations in lipoprotein cholesterol levels, have been reported in supplementation studies with long-chain polyunsaturates.

OBJECTIVE:

To assess the biological safety of long-term docosahexaenoic acid supplementation.

DESIGN:

Forty-four male patients (mean age, 16 years) enrolled in a randomized, double-masked, clinical trial and received docosahexaenoic acid, 400 mg/d, or placebo. Blood samples were collected every 6 months. Biological safety analysis included fatty acids, vitamin A and E concentrations, antioxidant capacity, platelet aggregation, alanine aminotransferase activity, and lipoprotein cholesterol and triglyceride profiles.

RESULTS:

Mean plasma docosahexaenoic acid levels were elevated 2.5-fold by supplementation compared with baseline. Patients receiving placebo capsules exhibited no change ($P = .35$) in plasma docosahexaenoic acid content. All adverse events reported were minor and equivalently distributed between groups. Plasma vitamin A concentrations remained unchanged during the trial. Mean plasma vitamin E concentrations were correlated with age ($P = .005$), such that as patients with XLRP matured, plasma vitamin E concentrations increased to approach normal values. There was a trend ($P = .10$) toward lower mean vitamin E concentrations in the docosahexaenoic acid-supplemented group after 4 years. Docosahexaenoic acid supplementation did not compromise plasma antioxidant capacity, platelet aggregation, liver function

enzyme activity, or plasma lipoprotein lipid content in patients with XLRP.

CONCLUSION:

Long-term docosahexaenoic acid supplementation to patients with XLRP was associated with no identifiable safety risks in this 4-year clinical trial.

PMID: 12963609 [Indexed for MEDLINE]

[Similar articles](#)



91. J Med Food. 2003 Spring;6(1):51-6.

Safety of an astaxanthin-rich Haematococcus pluvialis algal extract: a randomized clinical trial.

[Spiller GA](#)¹, [Dewell A](#).

Author information:

1. Health Research and Studies Center, Los Altos, CA 94023, USA. spiller@sphere.org

Abstract

A growing body of scientific literature indicates that astaxanthin is a more powerful antioxidant than other carotenoids and vitamin E and may confer numerous health benefits. The purpose of this investigation was to conduct a human safety study with a Haematococcus pluvialis algal extract with high levels of astaxanthin. Thirty-five healthy adults age 35-69 years were enrolled in a randomized, double-blind, placebo-controlled trial of 8 weeks' duration. All participants took three gelscaps per day, one at each meal. Nineteen participants received gelscaps with an algal extract in safflower oil, containing 2 mg of astaxanthin each (treatment); 16 participants received gelscaps containing safflower oil only (placebo). Blood pressure and blood chemistry tests, including a comprehensive metabolic panel and cell blood count, were conducted at the beginning of the trial and after 4 and 8 weeks of supplementation. No significant differences were detected between the treatment and the placebo groups after 8 weeks of supplementation with the algal extract in the parameters analyzed, except for serum calcium, total protein, and eosinophils ($P < .01$). Although the differences in these three parameters were statistically significant, they were very small and are of no clinical importance. These results reveal that 6 mg of astaxanthin per day from a H. pluvialis algal extract can be safely consumed by healthy adults.

PMID: 12804020 [Indexed for MEDLINE]

[Similar articles](#)

92. Neuropsychobiology. 2002;46 Suppl 1:28-30.

Severe tardive dyskinesia in affective disorders: treatment with vitamin E and C.

[Michael N](#)¹, [Sourgens H](#), [Arolt V](#), [Erfurth A](#).

Author information:

1. Department of Psychiatry, Münster University Hospital, Münster, Germany.

Abstract

Tardive dyskinesia caused by antipsychotic treatment is a severe problem not only in the management of schizophrenia, but also of affective disorders. Vitamin E monotherapy has been used in schizophrenic patients with tardive dyskinesia. Pharmacologists warn against high dosage of vitamin E because of its pro-oxidative effects on low-density lipoprotein with consecutive cardiac risks. Addition of vitamin C probably reduces this risk because of its interactions with vitamin E, i.e. vitamin C reduces vitamin E radicals formed when vitamin E scavenges the oxygen radicals. We have therefore tested the safety and efficacy of combining vitamin C and E in a sample of patients with affective disorders and tardive dyskinesia who had previously been treated with antipsychotics due to psychotic symptoms. In all 6 patients, a reduction of tardive symptomatology was seen. In our sample, no side effects were observed. Further studies on this combination therapy are suggested.

PMID: 12571430 [Indexed for MEDLINE]

[Similar articles](#)



93. Drugs Aging. 2002;19(10):793-805.

Health-related quality of life and long-term therapy with pravastatin and tocopherol (vitamin E) in older adults.

[Carlsson CM](#)¹, [Papcke-Benson K](#), [Carnes M](#), [McBride PE](#), [Stein JH](#).

Author information:

1. University of Wisconsin Medical School, Madison, Wisconsin 53792, USA.

Abstract

INTRODUCTION:

Concerns about the effects of HMG-CoA reductase inhibitors ('statins') on health-related quality of life may contribute to their underuse in older adults with and at risk for cardiovascular disease. These concerns also may prevent clinicians from enrolling older patients in clinical trials assessing the efficacy of statins as a preventive therapy for Alzheimer's disease.

OBJECTIVE:

To determine the effects of pravastatin and tocopherol (vitamin E), alone and in combination, on health-related quality of life in older adults.

STUDY DESIGN:

Double-blind, randomised, placebo-controlled, crossover study.

PARTICIPANTS:

Forty-one community-dwelling men and women aged ≥ 70 years with low-density lipoprotein-cholesterol (LDL-C) ≥ 3.62 mmol/L (140 mg/dl) participated.

METHODS:

Subjects received pravastatin for 6 months then pravastatin plus tocopherol for an additional 6 months (group 1), or tocopherol for 6 months then pravastatin plus tocopherol for an additional 6 months (group 2). Dosages were pravastatin 20 mg daily and tocopherol 400 IU daily.

MAIN OUTCOME MEASURES:

The following health-related quality-of-life measures were assessed at baseline, after 6 months and after 1 year: health perception, depression, physical function, cognitive function and sleep behaviour. In addition, data on adverse effects and laboratory abnormalities were obtained.

RESULTS:

Pravastatin reduced levels of total cholesterol (-21%, $p < 0.001$) and LDL-C (-29%, $p < 0.001$). Health-related quality-of-life scores, physical adverse effects, muscle enzyme levels and liver function tests did not change after 12 months of therapy with pravastatin, tocopherol or their combination.

CONCLUSION:

Both pravastatin and tocopherol have a good safety profile, are well tolerated and do not adversely affect health-related quality of life in older patients with hypercholesterolaemia. Given the significant beneficial cardiovascular effects of statin therapy in older adults and the potential role of statins in prevention of Alzheimer's disease, concerns about adverse effects on quality of life should not deter use of these medications in this population.

PMID: 12390056 [Indexed for MEDLINE]

[Similar articles](#)

94. Ophthalmic Epidemiol. 2002 Feb;9(1):49-80.

The Roche European American Cataract Trial (REACT): a randomized clinical trial to investigate the efficacy of an oral antioxidant micronutrient mixture to slow progression of age-related cataract.

[Chylack LT Jr¹](#), [Brown NP](#), [Bron A](#), [Hurst M](#), [Köpcke W](#), [Thien U](#), [Schalch W](#).

Author information:

1. Center for Ophthalmic Research, Department of Surgery, Brigham and Women's Hospital, Boston, MA, USA. Itchylack@rics.bwh.harvard.edu

Abstract

CONTEXT:

Funding surgery worldwide for age-related cataract (ARC), a leading cause of blindness, is a huge economic burden. Non-surgical means of slowing ARC progression could benefit patients and reduce this burden.

OBJECTIVE:

To determine if a mixture of oral antioxidant micronutrients [mg/day] (beta-carotene [18], vitamin C [750], and vitamin E [600]) would modify progression of ARC.

DESIGN:

REACT was a multi-centered, prospective, double-masked, randomized, placebo-controlled, 3-year trial.

SETTING:

Consecutive adult American and English outpatients with early ARC were recruited.

PATIENTS:

Four-hundred-and-forty-five patients were eligible; 297 were randomized; 231 (78%) were followed for two years; 158 (53%) were followed for three years; 36 (12%) were followed for four years. Twelve patients died during the trial (9 on vitamins; 3 on placebo ($p = 0.07$)). There were no serious safety issues.

INTERVENTION:

After a three-month placebo run-in, patients were randomized by clinical center to the vitamin or placebo groups and followed every four months.

MAIN OUTCOME MEASURE:

Cataract severity was documented with serial digital retroillumination imagery of the lens; progression was quantified by image analysis assessing increased area of opacity. This measure of area, 'increase % pixels opaque' (IPO), was the main outcome measure.

RESULTS:

There were no statistically significant differences between the treatment groups at baseline. The characteristics of dropouts and the mean follow-up times by treatment group were the same. After two years of treatment, there was a small positive treatment effect in U.S. patients ($p = 0.0001$); after three years a positive effect was apparent ($p = 0.048$) in both the U.S. and the U.K. groups. The positive effect in the U.S. group was even greater after three years: (IPO = 0.389 (vitamin) vs. IPO = 2.517 (placebo); $p = 0.0001$). There was no statistically significant benefit of treatment in the U.K. group. In spite of nearly perfect

randomization into treatment groups, the U.S. and U.K. cohorts differed significantly.

CONCLUSION:

Daily use of the afore-mentioned micronutrients for three years produced a small deceleration in progression of ARC.

PMID: 11815895 [Indexed for MEDLINE]

[Similar articles](#)

95. Arch Ophthalmol. 2001 Oct;119(10):1439-52.

A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E and beta carotene for age-related cataract and vision loss: AREDS report no. 9.

[Age-Related Eye Disease Study Research Group.](#)

Erratum in

- Arch Ophthalmol. 2008 Sep;126(9):1251.

Abstract

BACKGROUND:

Experimental and observational data suggest that micronutrients with antioxidant capabilities may retard the development of age-related cataract.

OBJECTIVE:

To evaluate the effect of a high-dose antioxidant formulation on the development and progression of age-related lens opacities and visual acuity loss.

DESIGN:

The 11-center Age-Related Eye Disease Study (AREDS) was a double-masked clinical trial. Participants were randomly assigned to receive daily oral tablets containing either antioxidants (vitamin C, 500 mg; vitamin E, 400 IU; and beta carotene, 15 mg) or no antioxidants. Participants with more than a few small drusen were also randomly assigned to receive tablets with or without zinc (80 mg of zinc as zinc oxide) and copper (2 mg of copper as cupric oxide) as part of the age-related macular degeneration trial. Baseline and annual (starting at year 2) lens photographs were graded at a reading center for the severity of lens opacities using the AREDS cataract grading scale.

MAIN OUTCOME MEASURES:

Primary outcomes were (1) an increase from baseline in nuclear, cortical, or posterior subcapsular opacity

grades or cataract surgery, and (2) at least moderate visual acuity loss from baseline (≥ 15 letters). Primary analyses used repeated-measures logistic regression with a statistical significance level of $P = .01$. Serum level measurements, medical histories, and mortality rates were used for safety monitoring.

RESULTS:

Of 4757 participants enrolled, 4629 who were aged from 55 to 80 years had at least 1 natural lens present and were followed up for an average of 6.3 years. No statistically significant effect of the antioxidant formulation was seen on the development or progression of age-related lens opacities (odds ratio = 0.97, $P = .55$). There was also no statistically significant effect of treatment in reducing the risk of progression for any of the 3 lens opacity types or for cataract surgery. For the 1117 participants with no age-related macular degeneration at baseline, no statistically significant difference was noted between treatment groups for at least moderate visual acuity loss. No statistically significant serious adverse effect was associated with treatment.

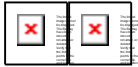
CONCLUSION:

Use of a high-dose formulation of vitamin C, vitamin E, and beta carotene in a relatively well-nourished older adult cohort had no apparent effect on the 7-year risk of development or progression of age-related lens opacities or visual acuity loss.

PMCID: PMC1472812 [Free PMC Article](#)

PMID: 11594943 [Indexed for MEDLINE]

[Similar articles](#)



96. Arch Ophthalmol. 2001 Oct;119(10):1417-36.

[A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8.](#)

[Age-Related Eye Disease Study Research Group.](#)

Erratum in

- Arch Ophthalmol. 2008 Sep;126(9):1251.

Comment in

-
-
-
-

-
-
-
- [Participants and Methods in AREDS Report No. 8.](#) [Arch Ophthalmol. 2008]

Abstract

BACKGROUND:

Observational and experimental data suggest that antioxidant and/or zinc supplements may delay progression of age-related macular degeneration (AMD) and vision loss.

OBJECTIVE:

To evaluate the effect of high-dose vitamins C and E, beta carotene, and zinc supplements on AMD progression and visual acuity.

DESIGN:

The Age-Related Eye Disease Study, an 11-center double-masked clinical trial, enrolled participants in an AMD trial if they had extensive small drusen, intermediate drusen, large drusen, noncentral geographic atrophy, or pigment abnormalities in 1 or both eyes, or advanced AMD or vision loss due to AMD in 1 eye. At least 1 eye had best-corrected visual acuity of 20/32 or better. Participants were randomly assigned to receive daily oral tablets containing: (1) antioxidants (vitamin C, 500 mg; vitamin E, 400 IU; and beta carotene, 15 mg); (2) zinc, 80 mg, as zinc oxide and copper, 2 mg, as cupric oxide; (3) antioxidants plus zinc; or (4) placebo.

MAIN OUTCOME MEASURES:

(1) Photographic assessment of progression to or treatment for advanced AMD and (2) at least moderate visual acuity loss from baseline ($>$ or $=$ 15 letters). Primary analyses used repeated-measures logistic regression with a significance level of .01, unadjusted for covariates. Serum level measurements, medical histories, and mortality rates were used for safety monitoring.

RESULTS:

Average follow-up of the 3640 enrolled study participants, aged 55-80 years, was 6.3 years, with 2.4% lost to follow-up. Comparison with placebo demonstrated a statistically significant odds reduction for the development of advanced AMD with antioxidants plus zinc (odds ratio [OR], 0.72; 99% confidence interval [CI], 0.52-0.98). The ORs for zinc alone and antioxidants alone are 0.75 (99% CI, 0.55-1.03) and 0.80 (99% CI, 0.59-1.09), respectively. Participants with extensive small drusen, nonextensive intermediate size drusen, or pigment abnormalities had only a 1.3% 5-year probability of progression to advanced AMD. Odds reduction estimates increased when these 1063 participants were excluded (antioxidants plus zinc: OR, 0.66; 99% CI, 0.47-0.91; zinc: OR, 0.71; 99% CI, 0.52-0.99; antioxidants: OR, 0.76; 99% CI, 0.55-1.05). Both zinc and antioxidants plus zinc significantly reduced the odds of developing advanced AMD in this higher-risk group. The only statistically significant reduction in rates of at least moderate visual acuity loss occurred in persons assigned to receive antioxidants plus zinc (OR, 0.73; 99% CI, 0.54-0.99). No statistically significant serious adverse effect was associated with any of the formulations.

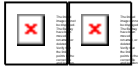
CONCLUSIONS:

Persons older than 55 years should have dilated eye examinations to determine their risk of developing advanced AMD. Those with extensive intermediate size drusen, at least 1 large druse, noncentral geographic atrophy in 1 or both eyes, or advanced AMD or vision loss due to AMD in 1 eye, and without contraindications such as smoking, should consider taking a supplement of antioxidants plus zinc such as that used in this study.

PMCID: PMC1462955 [Free PMC Article](#)

PMID: 11594942 [Indexed for MEDLINE]

[Similar articles](#)



97. J La State Med Soc. 2001 Jul;153(7):358-63.

[Combined intralesional interferon alpha 2B and oral vitamin E in the treatment of Peyronie's disease.](#)

[Novak TE](#)¹, [Bryan W](#), [Templeton L](#), [Sikka S](#), [Hellstrom WJ](#).

Author information:

1. Urological Residency Program, Walter Reed Medical Center, Washington, DC, USA.

Abstract

It has been recently reported that intralesional therapy with alpha interferon 2B resulted in significant improvement of both objective and subjective complaints (penile curvature, pain, plaque size, sexual function) associated with Peyronie's disease. Vitamin E, with its antioxidant properties, may play a role in reducing the inflammatory response. This study was designed to determine the safety and effectiveness of a high dose of alpha INF-2B injected weekly into the Peyronie's plaque combined with oral Vitamin E therapy. Twenty-nine patients with Peyronie's disease were evaluated with penile duplex Doppler for degree of penile curvature, deformity, and plaque size both prior to and after treatment. Each patient then received 4.0×10^6 units of alpha INF-2B in 10 cc of normal saline after appropriate local anesthesia. Injections were given once per week directly into the Peyronie's plaque for a period of 10 weeks. Patients also received 400 units of Vitamin E by mouth twice a day. Subjective data was obtained via a questionnaire prior to and at the conclusion of the study. Preliminary results demonstrated improvement of penile curvature in 39% of patients, with one patient experiencing complete resolution. Significant decreases in plaque sizes were noted in 11 of these patients, with softening of the plaques noted in all patients completing the study. Seven patients dropped out of the study prior to completing the 10 weeks: three with severe disease proceeded to surgery, two were lost to follow-up, one had exacerbation of his arthritis symptoms, and one quit secondary to flu-like symptoms. Subjective data from questionnaires revealed improvement in sexual function in those men with decreased curvature and plaque size. Weekly intralesional injections with 4.0×10^6 units improved plaque consistency and decreased curvature and plaque size ($P < 0.5$). Overall subjective sexual performance was reportedly improved. Increased dosage of alpha INF-2B resulted in increased severity of flu-like symptoms when compared to the lower (1×10^6 units) biweekly dosage. No significant difference

was noted with the addition of oral Vitamin E therapy.

PMID: 11519219 [Indexed for MEDLINE]

[Similar articles](#)

98. Eur J Cancer Prev. 2001 Jun;10(3):257-63.

An intervention trial to inhibit the progression of precancerous gastric lesions: compliance, serum micronutrients and S-allyl cysteine levels, and toxicity.

[You WC](#)¹, [Chang YS](#), [Heinrich J](#), [Ma JL](#), [Liu WD](#), [Zhang L](#), [Brown LM](#), [Yang CS](#), [Gail MH](#), [Fraumeni JF Jr](#), [Xu GW](#).

Author information:

1. National Cancer Institute, Division of Cancer Epidemiology and Genetics, Bethesda, MD 20892, USA.
youw@exchange.nih.gov

Abstract

Gastric cancer is the second most frequent cause of death from cancer in the world and the leading cause of death from cancer in China. In September 1995, we launched a randomized multi-intervention trial to inhibit the progression of precancerous gastric lesions in Linqu County, Shandong Province, an area of China with one of the world's highest rates of gastric cancer. Treatment compliance was measured by pill counts and quarterly serum concentrations of vitamin C, vitamin E and S-allyl cysteine. In 1999, toxicity information was collected from each trial participant to evaluate treatment-related side-effects during the trial. Compliance rates were 93% and 92.9% for 39 months of treatment with the vitamins/mineral and garlic preparation, respectively. The means for serum concentrations of vitamins C and E were 7.2 microg/ml and 1695 microg/dl among subjects in the active treatment groups compared with 3.1 microg/ml and 752 microg/dl among subjects in the placebo treatment group, respectively. No significant differences in side-effects were observed between the placebo treatment group and the vitamins/mineral and garlic preparation treatment groups during the 39-month trial period.

PMID: 11432713 [Indexed for MEDLINE]

[Similar articles](#)



99. Nephrol Dial Transplant. 2001 Jul;16(7):1448-51.

A randomized, double-blind, placebo-controlled trial of supplementary vitamins E, C and their combination for treatment of haemodialysis

cramps.

[Khajehdehi P¹](#), [Mojerlou M](#), [Behzadi S](#), [Rais-Jalali GA](#).

Author information:

1. Division of Nephrology, Department of Internal Medicine, Namazee Hospital, Shiraz University of Medical Sciences, Shiraz, Iran.

Abstract

BACKGROUND:

Muscle cramps that improve after carnitine or vitamin E therapies are common in haemodialysis (HD) patients. Because vitamin C participates in carnitine biosynthesis, and its levels are reduced in uraemia, subclinical vitamin C depletion may contribute to HD cramps. Our aim was to determine the effects of vitamins C, E and their combination on the frequency and intensity of HD cramps.

METHODS:

In this placebo-controlled, double-blind study, 60 HD-patients were randomized into four therapeutic groups. Each group (n=15) received six identical capsules daily for 8 weeks, containing one of the following: vitamin E (400 mg), vitamin C (250 mg), their combination, or placebo.

RESULTS:

The frequency and intensity of HD cramps decreased significantly in all three vitamin groups compared with the placebo group at the end of the trial, and compared with the pre-treatment values. At the end of the trial, vitamins E, C, their combination, and placebo produced cramp reductions of 54, 61, 97 and 7%, respectively. The percentage cramp reduction had no significant correlation with age, sex, aetiology of end-stage renal disease, serum electrolytes or HD duration, but showed a positive correlation ($r=0.33$, $P=0.01$) with the type of therapy. No vitamin-related adverse effects were encountered during the trial.

CONCLUSION:

Short-term treatment with the combination of vitamins E and C is safe and effective in reducing HD cramps; however, its safety for prolonged therapy has yet to be evaluated in HD patients.

PMID: 11427639 [Indexed for MEDLINE]

[Similar articles](#)

100. Invest New Drugs. 2001;19(1):21-7.

A phase I study of vitamin E, 5-fluorouracil and leucovorin for advanced malignancies.

[Blanke CD¹](#), [Stipanov M](#), [Morrow J](#), [Rothenberg M](#), [Chinery R](#), [Shyr Y](#), [Coffey R](#), [Johnson DH](#), [Leach SD](#), [Beauchamp RD](#).

Author information:

1. Department of Medicine, Oregon Health Sciences University, Portland 97232, USA.

Abstract

Six patients with incurable malignancies were originally treated with vitamin E, 3200 IU/day for fourteen days, followed by the same dose of vitamin E daily plus LCV (20 mg/m² i.v. bolus daily x 5) with 5FU (425 mg/m² i.v. bolus immediately following LCV). The same schedule of LCV and 5FU was repeated 4 weeks later, then every 5 weeks indefinitely. When 3 of the first 6 had grade 3/4 toxicity, six more patients were treated on the identical drugs and schedule. Seven of twelve total patients had one or more grade 3/4 toxicities. Neutropenia, abdominal pain, and diarrhea were most common. No patient had a documented response, though seven patients did have stable disease. Though the combination of vitamin E and chemotherapy was toxic, this trial demonstrated maximal therapeutic doses of vitamin E can be combined with standard 5FU and LCV, without significantly increasing the side effects of the chemotherapy itself.

PMID: 11291830 [Indexed for MEDLINE]

[Similar articles](#)

101. Lancet. 2001 Jan 13;357(9250):89-95.

Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomised trial in general practice. Collaborative Group of the Primary Prevention Project.

[de Gaetano G; Collaborative Group of the Primary Prevention Project.](#)

Erratum in

- Lancet 2001 Apr 7;357(9262):1134.

Comment in

-
- ACP J Club. 2001 Jul-Aug;135(1):8.
-
-
-
-

Comment on

-

Abstract

BACKGROUND:

In addition to the treatment of specific cardiovascular risk factors, intervention which interferes with the general mechanisms of atherosclerosis could further reduce the incidence of cardiovascular events. We aimed to investigate in general practice the efficacy of antiplatelets and antioxidants in primary prevention of cardiovascular events in people with one or more major cardiovascular risk factors.

METHODS:

We did a randomised controlled open 2x2 factorial trial to investigate low-dose aspirin (100 mg/day) and vitamin E (300 mg/day) in the prevention of cardiovascular events, in people with one or more of the following: hypertension, hypercholesterolaemia, diabetes, obesity, family history of premature myocardial infarction, or individuals who were elderly.

FINDINGS:

4495 people (2583 female, mean age 64.4 years) were included in the trial. After a mean follow-up of 3.6 years the trial was prematurely stopped on ethical grounds when newly available evidence from other trials on the benefit of aspirin in primary prevention was strictly consistent with the results of the second planned interim analysis. Aspirin lowered the frequency of all the endpoints, being significant for cardiovascular death (from 1.4 to 0.8%; relative risk 0.56 [95% CI 0.31-0.99]) and total cardiovascular events (from 8.2 to 6.3%; 0.77 [0.62-0.95]). Severe bleedings were more frequent in the aspirin group than the no-aspirin group (1.1% vs 0.3%; $p < 0.0008$). Vitamin E showed no effect on any prespecified endpoint. Analyses were by intention-to-treat.

INTERPRETATION:

In women and men at risk of having a cardiovascular event because of the presence of at least one major risk factor, low-dose aspirin given in addition to treatment of specific risk factors contributes an additional preventive effect, with an acceptable safety profile. The results on vitamin E's cardiovascular primary preventive efficacy are not conclusive per se, although our results are consistent with the negative results of other large published trials on secondary prevention.

PMID: 11197445 [Indexed for MEDLINE]

[Similar articles](#)



102. Am Heart J. 2000 Nov;140(5):792-803.

Effective and safe modification of multiple atherosclerotic risk factors in patients with peripheral arterial disease.

[Garg R¹](#), [Elam MB](#), [Crouse JR 3rd](#), [Davis KB](#), [Kennedy JW](#), [Egan D](#), [Herd JA](#), [Hunninghake DB](#), [Johnson WC](#), [Kostis JB](#), [Sheps DS](#), [Applegate WB](#).

Author information:

1. Division of Epidemiology and Clinical Applications, National Heart Lung and Blood Institute, Bethesda,

Abstract

BACKGROUND:

Patients with peripheral arterial disease (PAD) are at an increased risk of cardiovascular mortality and morbidity and thus are an excellent group in whom to evaluate the feasibility and the effect of an aggressive multifactorial intervention on atherosclerotic vascular disease risk factors. The Arterial Disease Multiple Intervention Trial (ADMIT) was designed to determine the efficacy, safety, and compliance of an multifactorial therapy on selected atherosclerotic disease risk factors in patients with PAD.

METHODS:

By a 2 x 2 x 2 factorial design, eligible participants (N = 468) were randomly assigned to low-dose warfarin, antioxidant vitamins, and niacin or its corresponding placebo, and followed up for 1 year. All participants were encouraged to use aspirin. Pravastatin was added to the drug regimen for those who needed to reduce LDL cholesterol to recommended levels.

RESULTS:

Niacin increased HDL cholesterol levels by 30%, with the majority of effect achieved at a dosage of 500 mg twice daily. Warfarin had an anticoagulant effect. The antioxidant vitamins resulted in a significant increase in vitamin E, C, and beta-carotene plasma levels. Overall, compliance was high and few adverse effects were reported.

CONCLUSIONS:

ADMIT demonstrates that it is both feasible and safe to modify multiple atherosclerotic disease risk factors effectively with intensive combination therapy in patients with PAD.

PMID: 11054628 [Indexed for MEDLINE]

[Similar articles](#)



103. Scand J Urol Nephrol. 2000 Feb;34(1):62-6.

Effect of vitamins on the lipid profile of patients on regular hemodialysis.

[Khajehdehi P¹](#).

Author information:

1. Division of Nephrology, Nemazee Hospital, Iran.

Abstract

OBJECTIVE:

The aim of this study was to investigate the lipid-lowering effect of vitamins compared to placebo and their short-term supplementation safety in patients on hemodialysis.

MATERIAL AND METHODS:

Eighty-four hemodialysis patients were randomly allocated to four therapeutic groups. Each group (n = 21) received one of the following treatments: vitamin C (200 mg), E (200 mg), D3 (50,000 IU) or placebo daily. Serum triglyceride, total cholesterol, low-density lipoprotein cholesterol (LDL-c), and high-density lipoprotein cholesterol (HDL-c) were measured before and following 3 months of vitamin therapy.

RESULTS:

LDL-c and total cholesterol levels as well as the ratios of LDL-c to HDL-c and cholesterol to HDL-c significantly decreased after vitamin C therapy. Triglyceride and the ratio of triglyceride to HDL-c significantly decreased following vitamin D3 therapy. HDL-c increased and the ratio of LDL-c to HDL-c decreased significantly after vitamin E therapy. No major side-effects were encountered during the 3 months' trial.

CONCLUSIONS:

Short-term supplementary vitamins are safe and beneficial for treatment of lipid abnormalities in hemodialysis patients.

PMID: 10757273 [Indexed for MEDLINE]

[Similar articles](#)

104. Lancet. 2000 Jan 22;355(9200):253-9.

Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Heart Outcomes Prevention Evaluation Study Investigators.

[No authors listed]

Erratum in

- Lancet 2000 Sep 2;356(9232):860.

Comment in

-
-
-

-
-
-
-
-

Abstract

BACKGROUND:

Diabetes mellitus is a strong risk factor for cardiovascular and renal disease. We investigated whether the angiotensin-converting-enzyme (ACE) inhibitor ramipril can lower these risks in patients with diabetes.

METHODS:

3577 people with diabetes included in the Heart Outcomes Prevention Evaluation study, aged 55 years or older, who had a previous cardiovascular event or at least one other cardiovascular risk factor, no clinical proteinuria, heart failure, or low ejection fraction, and who were not taking ACE inhibitors, were randomly assigned ramipril (10 mg/day) or placebo, and vitamin E or placebo, according to a two-by-two factorial design. The combined primary outcome was myocardial infarction, stroke, or cardiovascular death. Overt nephropathy was a main outcome in a substudy.

FINDINGS:

The study was stopped 6 months early (after 4.5 years) by the independent data safety and monitoring board because of a consistent benefit of ramipril compared with placebo. Ramipril lowered the risk of the combined primary outcome by 25% (95% CI 12-36, $p=0.0004$), myocardial infarction by 22% (6-36), stroke by 33% (10-50), cardiovascular death by 37% (21-51), total mortality by 24% (8-37), revascularisation by 17% (2-30), and overt nephropathy by 24% (3-40, $p=0.027$). After adjustment for the changes in systolic (2.4 mm Hg) and diastolic (1.0 mm Hg) blood pressures, ramipril still lowered the risk of the combined primary outcome by 25% (12-36, $p=0.0004$).

INTERPRETATION:

Ramipril was beneficial for cardiovascular events and overt nephropathy in people with diabetes. The cardiovascular benefit was greater than that attributable to the decrease in blood pressure. This treatment represents a vasculoprotective and renoprotective effect for people with diabetes.

PMID: 10675071 [Indexed for MEDLINE]

[Similar articles](#)





Hogan Lovells US LLP
Columbia Square
555 Thirteenth Street, NW
Washington, DC 20004
T +1 202 637 5600
F +1 202 637 5910
www.hoganlovells.com

August 19, 2018

Via Electronic Mail

Judy Kidwell, PhD
General Health Scientist
Office of Food Additive Safety
Center for Food Safety and Applied Nutrition
240.402.1071
Judith.kidwell@fda.hhs.gov

RE: Response to FDA's Questions regarding GRN 781

Dear Dr. Kidwell,

On behalf of NutriFusion LLC (NutriFusion), we are responding to the agency's questions regarding GRN 000781, which covers the intended use of vitamin E extracted from edible portions of commonly consumed fruits and vegetables. Pursuant to the agency's request, we are responding within 10 business days of your August 3rd correspondence.

For your ease of reference, we repeat the agency's questions first, followed by our response.

- 1) There are inconsistencies in your description of the notified substance. In section 5.0 (use prior to 1958) and the beginning of section 2.4 (p.4, Manufacturing Process), you refer to the NutriFusion blend and the nutrient blend, respectively. You should refer only to blends for the final use of the substance. Please update the notice to be consistent in referring to the substance and not a nutrient blend.*

NutriFusion Response: We have updated the GRAS notice by using the term "vitamin E extract" to refer to the notified substance consistently. See **Attachment 1** for the updated GRAS notice.

- 2) In section 2.2, you state that the substance is a "free-flowing powder" with no other descriptors. α -tocopherol is typically a yellow to red color (see Food Chemical Codex for α -tocopherol concentrate, CASRN 59-02-9). Please comment on the color of the α -tocopherol and whether it will impart color to food.*

NutriFusion Response: We would like to clarify the notified vitamin E extract should be characterized as the acetate ester of " α -tocopherol." The α -tocopherol acetate is the naturally-occurring vitamin E ester extracted from fruits and vegetables. We apologize for failing to specify in the original notification that it covers the acetate ester form. We have updated the notification to clarify it covers α -tocopherol acetate.

As for the color, the vitamin E extract actually has a white to off-white color. The vitamin E extract is usually blended with other vitamin extracts before added to foods. When added to foods, the α -tocopherol acetate is not added for purposes of imparting color to the food.

- 3) *Attachment 1 of your notice contains results of analyses for four lots of the product for d- α -tocopherol acetate, total starch, moisture and silica (as SiO₂). d- α -tocopherol acetate is not the same substance as α -tocopherol. Additionally, d- α -tocopherol acetate is not found in edible fruits and vegetables. The reported assay method, AOAC.2012.09M is for both d- α -tocopherol acetate (referred to as vitamin E acetate) and d- α -tocopherol. Please provide certificates of analysis demonstrating that the product was analyzed for the notified substance, α -tocopherol.*

NutriFusion Response: As discussed above, we hereby clarify the notified substance is alpha-tocopherol acetate, an ester of the naturally-occurring alpha-tocopherol extracted from edible fruits and vegetables. During the manufacturing process (updated in the revised GRAS Notice in **Attachment 1**, acetic acid is used as a common food-grade solvent to elute the nutrients. During the washing step, acetic acid solvent converts alpha-tocopherol to alpha-tocopherol acetate.

- 4) *You state that you use a solvent extract and/or solid phase extraction using “solvents commonly used in food processing (e.g. water, alcohol, or critical CO₂)”. Please clarify whether water, ethanol, or critical CO₂ are the only solvents used, and, if not, identify other solvents used. Please update the manufacturing process to specify the identities of the solvents and provide residual solvent batch analyses for solvents used. Provide specifications for residual solvent in the final product, if necessary. Please provide a statement that all processing agents used in the manufacturing process are food grade.*

NutriFusion Response: We hereby clarify that for the vitamin E extract, the GRAS notification is limited to the use of water, acetic acid, ethanol, and critical CO₂ as the solvents. With regard to your request for information on the testing for residual solvents, NutriFusion has not asked the laboratory to test the vitamin E extract for residual solvents because the company did not consider such testing necessary as part of its safety assessment given the fact that water, and ethanol are naturally found in fruits and critical CO₂ would not be expected to be present given its volatility. Moreover, an analysis of the product reveals essentially all of the extract has been characterized.

The vitamin E extract contains 4-6% water. Because water is an inherent constituent of fruits and vegetables, even if a residual solvent analysis was conducted, it is not possible to determine whether the water content is from the residual solvent or naturally-occurring. The same is also true for ethanol. Public literature reports the presence of low levels of naturally-occurring ethanol in fruit juices at levels up to 0.77 g/L. ^{1/} As such, testing for residual ethanol would be incapable of distinguishing from the naturally-occurring ethanol inherent in the raw materials and that from the solvent. The acetic acid is affirmed as generally recognized as safe (GRAS) by FDA in 21 CFR § 184.1005 (“Acetic acid”) thus obviating the need to set specifications for acetic acid in the final product.

Regarding critical CO₂, the solvent is extremely volatile under room temperature and storage conditions of the finished product. It is reported that unlike other solvents, the use of solvents such as critical CO₂ will produce a solvent-free product with no residue left behind. ^{2/} The fact that

^{1/} Gorgus, Eva, Maike Hittinger, and Dieter Schrenk. "Estimates of ethanol exposure in children from food not labeled as alcohol-containing." *Journal of analytical toxicology* 40.7 (2016): 537-542.

^{2/} Sapkale, G. N., et al. "Supercritical fluid extraction." *Int. J. Chem. Sci* 8.2 (2010): 729-743.

CO₂ also is found naturally in the atmosphere further complicates the ability to distinguish the CO₂ that may be present due to the use of the solvent and that present due to the air dispersed within the ascorbic acid powder.

Unlike industrial solvents such as hexane that can present a health or safety issue if present at high levels in the food product, water, ethanol, acetic acid, and CO₂, even if present at low residual levels in the vitamin E extract, would not pose any human safety concern. We would not expect to find any residual CO₂ given its volatility and there would be no way to determine whether detected ethanol, or water is from the use of the solvent or from the water and ethanol that is found naturally in the fruit or vegetable.

We also did not consider testing for residual solvents necessary given the characterization of approximately 100 percent of the vitamin E extract. Table 2 of the GRN 000781 provides the quantitative composition analysis of four batches of the vitamin E extract as follows. In the Table below, we combine the weight percentages of the vitamin E, starch, silica, and moisture content for the four different lots.

Constituent	Lot#- 100701A2	Lot#- 100701A3	Lot#- 100701A4	Lot#- 100701A5
Vitamin E	53.7%	52.8%	53.1%	53.5%
Total Starch	40.2%	41.8%	40.7%	41.0%
Moisture	5.5%	4.6%	5.1%	5.2%
Silica (as SiO ₂)	0.044%	0.06%	0.052%	0.052%
Total Weight%	99.44	99.26	98.95	99.75

As the above table indicates, close to 100% of the vitamin E extract content has been characterized. Even without residual solvent analysis, it is reasonable to assume that the finished vitamin E extract will contain only insignificant levels of any residual solvents (if there is any present).

Given these factors, we trust the agency will agree residual solvent analysis is unnecessary as part of the safety assessment of vitamin E that is extracted from edible fruits and vegetables.

Further, we hereby confirm that all processing agents and chemicals used in the manufacturing process are food grade.

- 5) *In Attachment 3 of the notice, you provide results of analyses for various nutrients in a dietary supplement manufactured using your product. For vitamin E, the reported results cite AOAC 974.29M, the method for the analysis of vitamin A in food. Please provide a link or the reference for the analytical method used for determining vitamin E in dietary supplements.*

NutriFusion Response: We thank you for bringing this to our attention. We reached out to the analytical lab for clarification. The correct reference used by the lab for determining vitamin E is AOAC Official Method 2012.09. A copy of the method is attached. See **Attachment 2**.

- 6) *In Attachment 4 of the notice, you provide results of analyses for vitamin E in cooked pasta. You provide the method for preparing the pasta but not the method of analysis. Please provide the method for determining vitamin E in the cooked pasta.*

NutriFusion Response: The lab used the AOAC Official Method 2012.09 (**Attachment 2**).

- 7) *The intended use of the substance should be more clearly defined in the notice.*

- a. *α-tocopherols may be added to food for use as both a nutrient or as an antioxidant. You do not provide the intended use for adding α-tocopherols from fruits and vegetables to foods. Therefore, you should be more explicit whether the intended use is as a nutrient or as an antioxidant or both;*
- b. *Also, in section 1.4, 2.7 and 3.0 you stated that the use of α-tocopherols from fruits and vegetables is substitutional for authorized commercially available vitamin E. However, in the notice, only α-tocopherol is defined as vitamin E. α-tocopherol acetates, another form of vitamin E, also may be added to foods for use as a nutrient. Therefore, please update the language in sections 1.4, 2.7 and 3.0 to better reflect the intended use by defining “authorized commercially available vitamin E” and explain if the substance is substitutional for use of α-tocopherols only or also for α-tocopherols acetates.*

NutriFusion Response: We thank you for bringing to our attention that vitamin E extract can both be a nutrient and an antioxidant. We also apologize for failing to be more precise in the original notification and disclosing the notification covers α-tocopherol acetate. FDA lists α-tocopherol acetate as an ingredient that is GRAS with no limits other than GMPs. 21 CFR §182.8892 (“[alpha]-Tocopherol acetate”). We hereby clarify that because the intended use will be as a substitute for other commercially available forms of vitamin E, and currently vitamin E may be added to food for use as both a nutrient or as an antioxidant, the GRAS notice would cover both nutrient and antioxidant uses. We have revised the GRAS notice accordingly in **Attachment 1**. We also made changes to the corresponding sections of the GRAS notice to clarify that the term “other commercially available forms of vitamin E” for this notification is limited to α-tocopherol acetate.

- 8) *In sections 1.2 and 2.7 of the notice, you list the maximum recommended use levels of vitamin E in food. Please provide a reference for these use levels.*

NutriFusion Response: In the GRAS notice, NutriFusion provides that the maximum use levels of vitamin E extract in foods for children four and over and adults is 15 mg/serving (i.e., 100% of the Reference Daily Intake (RDI or DV) of vitamin E)). The maximum use levels in foods for infants six month and older is 2.5 mg/serving (i.e., 50% of the RDI or DV) for children one through three years old is 3 mg/serving (i.e., 50% of the RDI or DV). The RDI or DV values of vitamin E are from FDA’s Guidance titled “Frequently Asked Questions for Industry on Nutrition Facts Labeling Requirements” (**Attachment 3**).

- 9) *In Section 6.1, the you state “the intended use of the NutriFusion vitamin E extract is roughly equivalent in all instances with the consumption of five or more servings of fruits and vegetables per day - the existing dietary recommendation.” Please provide support for this statement (e.g., reference(s)).*

NutriFusion Response: Five or more servings of fruits and vegetables per day is from the USDA’s Food Guide Pyramid, in which it is recommended that daily intake of 3-5 servings of the vegetable group and 2-4 servings of the fruit group. See: <https://health.gov/dietaryguidelines/dga2000/document/build.htm>. The more recent dietary recommendations place the fruit and vegetable recommendations in terms of cups of fruits and vegetables. The current dietary guidelines recommend men consume two cups of fruit per day (see, <https://www.choosemyplate.gov/fruit>) and three cups of vegetables (see, <https://www.choosemyplate.gov/vegetables>). Generally, the dietary guidelines treat ½ cup as equating to a fruit or vegetable serving. See, <https://health.gov/dietaryguidelines/dga2000/usingdietguide.pdf>.

- 10) *In Sections 1.4, 2.7 and 3.0, you refer to food intake by different subpopulations (6-12 months, 1-4 years, and 4 plus years) but are not consistent in referring to all the*

subpopulations (e.g., 4 years plus is not mentioned in section 1.4 and 6-12 months is not listed in section 3.0). Please refer to the same subpopulations with consistent terminology throughout the notice. Also, please report current exposure for each of those subpopulations.

NutriFusion Response: Thank you for bringing this to our attention. We have made changes and refer to the subpopulations using three age groups – 6-12 months, 1-3 years, and 4 years and over. The intended use levels and the current exposure for each of these three subpopulations can also be summarized using the table below.

Age Group	Intended Maximum Use Levels	Current Exposure (90 th percentile)
6-12 months	2.5 mg/serving (50% of the DV)	12.79 mg/day*
1-3 years	3 mg/serving (50% of the DV)	6.2 mg/day
4 years and over	15 mg/serving (100% of the DV)	13.7 mg/day

*Calculated based on the level of vitamin E contained in one leading brand of infant formula product. See details in the revised GRAS notice in **Attachment 1**.

11) In Section 6.3, you state that “The current cumulative intake of vitamin E in children one to three years old, children above four, and adults are well below the ULs set by IOM.” On the same page, you state that “The IOM established a UL for adult at 1,000 mg/day and a UL for children 1-3 years at 200 mg/day.”; however, you did not provide a UL for children between the ages of 4-18 years old. Please identify the UL IOM established for children between 4-18 years of age to allow comparison with the cumulative intake for this age group.

NutriFusion Response: The UL levels for children between 4-18 years of age are provided in Table 9 of the GRAS notice, which is also copied below:

Age Groups	90th Percentile Intake (Male) ³	90th Percentile Intake (Female)	UL ⁴
1-3	6.2 mg/day	5.5 mg/d	200 mg/d
4-8	7.5 mg/day	7.7 mg/d	300 mg/d
9-13	9.4 mg/day	8.5 mg/d	600 mg/d
14-18	9.9 mg/day	8.6 mg/d	800 mg/d
19-30	12.8 mg/day	9.5 mg/d	1,000 mg/d
31-50	13.7 mg/day	11 mg/d	1,000 mg/d
50 and over	12.5 mg/day	11.1 mg/d	1,000 mg/d

12) In Section 6.2, you state the EC SCF established a UL of 270 mg/day for adults and a UL of 100 mg/day for children 1-3 years of age. Please identify the UL EC SCF established for children between 4-18 years of age. (Note that, according to the report: Tolerable Upper Intake Levels for Vitamins and Minerals by the Scientific Committee on Food, February 2006, page 249, the EC SCF rounded the UL to 300 mg/day in adults. (See http://www.efsa.europa.eu/sites/default/files/efsa_rep/blobserver_assets/ndatolerableuil.pdf))

NutriFusion Response: The ULs established by the EC SCF for children between 4-18 years of age can be summarized with the table below:

³ Millen, B. E., A. H. Lichtenstein, and S. Abrams. "Scientific Report of the 2015 Dietary Guidelines Advisory Committee." Washington (DC): Department of Health and Human Services (2015).

⁴ See *supra* note 9.

Age Group	UL (mg/day)
4-6	120
7-10	160
11-14	220
15-17	260

13) In Section 6.1, page 13, you state that "As reported in Table 2, the GRAS substance is not expected to contain protein." The unidentified constituents listed in Table 2 vary between 1.05% to 0.25%. Also, you did not provide a specification for protein content nor indicate whether the protein level was determined in the product. Please clarify.

NutriFusion Response: On the basis of the extraction processes that are used we would not expect the products to contain protein. We, nonetheless, recognize that it is possible one of the proteins found in the source plant could be present in the extracted vitamin E. We have revised the notification and eliminated the sentence that we would not expect the substance to contain protein. As the agency pointed out, there are unidentified constituents at levels ranging from 0.25% to 1.25%. To the extent a consumer has an allergy or sensitivity to one of the fruits or vegetables used as the source materials, the vitamin E product could contain that particular substance. However, any concerns with allergies and sensitivities are handled through labeling. The labels of the foods bearing the NutriFusion vitamin E extract will identify each fruit or vegetable used in the extraction process. Individuals with a food allergy or sensitivity to one of the fruits or vegetables used in the extraction process, therefore, will be able to identify the possible presence of the plant material and can avoid the product.

14) Please discuss the absorption, distribution, metabolism, and excretion (ADME) of vitamin E and provide reference(s) for this discussion. Examples of the kind of discussion required are 1) the ADME section from the report: *Tolerable Upper Intake Levels for Vitamins and Minerals by the Scientific Committee on Food, February 2006, page 244.* (http://www.efsa.europa.eu/sites/default/files/efsa_rep/blobserver_assets/ndatolerableuil.pdf) or 2) a summary of the ADME section from the publication: *EFSA Panel on Dietetic Products, Nutrition, and Allergies (NDA). (2015). Scientific Opinion on Dietary Reference Values for vitamin E as α -tocopherol. EFSA Journal, 13(7), 4149.*

NutriFusion Response: The route of vitamin E after oral intake follows in general the pathway of other lipids. Pancreatic and intestinal enzymatic digestion followed by the circulation and distribution to the liver and non-hepatic tissues is the same for all vitamin E forms. ^{5/} Vitamin E absorption from the intestinal lumen is dependent upon biliary and pancreatic secretions, micelle formation, uptake into enterocytes, and chylomicron secretion. ^{6/} In the gastro-intestinal system the absorption rate of vitamin E varies inter-individually between 20%-80%. ^{7/} The transport of vitamin E in blood circulation follows largely that of cholesterol within lipoprotein metabolism. ^{8/} Under normal physiological conditions, vitamin E is mostly transported *via* chylomicrons, very low density

^{5/} Schmölz, Lisa, et al. "Complexity of vitamin E metabolism." *World journal of biological chemistry* 7.1 (2016): 14.

^{6/} Gallo-Torres, Hugo E. "Obligatory role of bile for the intestinal absorption of vitamin E." *Lipids* 5.4 (1970): 379-384.

^{7/} Bjørneboe, Anders, Gunn-Elin Aa Bjørneboe, and Christian A. Drevon. "Absorption, transport and distribution of vitamin E." *the Journal of Nutrition* 120.3 (1990): 233-242.

^{8/} Kolleck, Ingrid, et al. "HDL is the major source of vitamin E for type II pneumocytes." *Free Radical Biology and Medicine* 27.7-8 (1999): 882-890.

lipoproteins (VLDL) and high density lipoproteins (HDL), whereas under fasting conditions low density lipoproteins (LDL) take on this task. 9/

The metabolism of vitamin E starts with one cycle of ω -hydroxylation followed by five cycles of β -oxidation. The principal catabolic pathway is independent of the saturation of the side-chain or the substitution of the chromanol ring system. 10/ The major route of excretion of ingested vitamin E is fecal elimination. Excess α -tocopherol, as well as forms of vitamin E not preferentially used, is probably excreted unchanged in bile. 11/

15) You state that your safety conclusion is based on IOM's safety evaluation from 2001 and EC SCF's safety evaluation from 2003. Please state whether you performed an updated literature search for the period between 2003 and the present. If not, please perform an updated literature search and discuss your findings. Please include the following article in your discussion along with your other findings: EFSA Panel on Dietetic Products, Nutrition, and Allergies (NDA). (2015). *Scientific Opinion on Dietary Reference Values for vitamin E as α -tocopherol*. *EFSA Journal*, 13(7), 4149.

NutriFusion Response: NutriFusion completed an independent review of the recent literature on the adverse effects of vitamin E in humans. We conducted searches in the medical literature database, PubMed, to identify studies indexed since Jan, 2000 to identify reports of human clinical trials related to adverse effects of vitamin E. We conducted the searches using keywords including "vitamin E," "alpha-tocopherol," "tolerable," "safety," or "toxicity." We completed the search on July 10, 2018 and identified a total of 104 human studies (abstracts attached, see **Attachment 4**). We carefully reviewed the abstracts of these studies and conclude that human safety data published subsequent to 2000 do not demonstrate any new toxicological concerns for vitamin E other than those already reported.

We also reviewed the 2015 EFSA Report *Scientific Opinion on Dietary Reference Values for vitamin E as α -tocopherol*. *EFSA Journal*, 13(7), 4149. This report discusses the risk of excess vitamin E intake on Page 10 by referencing the Maydani et al. (1998), through which a UL of 300 mg for adults was adopted. There is no discussion on any new toxicological concerns that have been identified since 2003.

16) You provide only a brief description of the conclusions of IOM's and EC SCF's safety evaluations of vitamin E and do not mention or discuss any of the studies IOM and EC SCF considered in their safety determination except for two brief sentences for one study. Please discuss safety studies pertaining to vitamin E and provide a brief discussion on their overall conclusions. At a minimum, discuss species, duration, dose levels, findings, and provide your conclusions on the levels you consider safe based on the results. With clinical trials,

9/ Bjørneboe, Anders, et al. "Transport and distribution of α -tocopherol in lymph, serum and liver cells in rats." *Biochimica et Biophysica Acta (BBA)-Molecular Cell Research* 889.3 (1986): 310-315.

10/ Zhao, Yang, et al. "Analysis of multiple metabolites of tocopherols and tocotrienols in mice and humans." *Journal of agricultural and food chemistry* 58.8 (2010): 4844-4852.

11/ Traber, Maret G., and Herbert J. Kayden. "Preferential incorporation of alpha-tocopherol vs gamma-tocopherol in human lipoproteins." *The American journal of clinical nutrition* 49.3 (1989): 517-526.

please concentrate only on reported side effects (safety data) or the lack of it. FDA does not consider beneficial effects in its GRAS evaluation; as such, they should not be included. Below is a list of studies we identified in the literature. Your literature review and safety narrative should include these as well as any other relevant studies you identify.

Acute toxicity - Krasavage WJ and Terhaar CJ (1977). d-alpha-Tocopheryl poly(ethylene glycol) 1000 succinate. Acute toxicity, subchronic feeding, reproduction, and teratologic studies in the rat. *J Agric Food Chem* 25: 273-278.

Subchronic toxicity

- Abdo KM, Rao G, Montgomery CA (1986). Thirteen week toxic study of d-tocopheryl acetate (vitamin E) in Fischer 344 rats. *Fd Chem Toxic* 24: 10431050.
- Dymysza, H. A., & Park, J. (1975, January). EXCESS DIETARY VITAMIN-E IN RATS. In *FEDERATION PROCEEDINGS* (Vol. 34, No. 3, pp. 912-912). 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3998: FEDERATION AMER SOC EXP BIOL.

Chronic toxicity

- Yang NY and Desai ID (1977). Effect of high levels of dietary vitamin E on hematological indices and biochemical parameters in rats. *J Nutr* 107: 14101417.
- Wheldon GH, Bhatt A, Keller P, Hummler H (1983). d,1-alpha-Tocopheryl acetate (vitamin E): a long term toxicity and carcinogenicity study in rats. *Int J Vitam Nutr Res* 53: 287-296.

Reproductive toxicity/teratogenicity

- Krasavage WJ and Terhaar CJ (1977). d-alpha-Tocopheryl poly(ethylene glycol) 1000 succinate. Acute toxicity, subchronic feeding, reproduction, and teratologic studies in the rat. *J Agric Food Chem* 25: 273-278.
- Hook EB, Healy KM, Niles AM, Skalko RG (1974). Letter: Vitamin E: teratogen or anti-teratogen? *Lancet* 1: 809.

Genotoxicity

- Gebhart E, Wagner H, Grziwok K, Behnsen M (1985). The actions of anticlastogens in human lymphocyte cultures and their modification by rat-liver S9 mix. Chapter II. Studies with vitamins C and E. *Mut Res* 149: 83-94.
- Shamberger RJ, Corlett CL, Beaman KD, Kasten BL (1979). Antioxidants reduce the mutagenic effects of malonaldehyde and β -propiolactone. Part IX. Antioxidants and cancer. *Mut Res* 66: 349-355.
- Beckmann C, Roy RM, Sproule A (1982) Modification of radiation-induced sex-linked recessive lethal mutation frequency by tocopherol. *Mut Res* 105: 73-77.

Human studies (For this section please make sure that you discuss if the cumulative intake level from the proposed uses of vitamin E may result in decreased blood coagulation. If not, provide scientific data supporting your conclusion.)

- Farrell PM and Bieri JG (1975). Megavitamin E supplementation in man. *Am J Clin Nutr* 18: 1381-1386.
- Tsai AC, Kelly JJ, Peng B, Cook N (1978). Study on the effect of megavitamin supplementation in man. *Am J Clin Nutr* 31: 831-838.

- Steiner M (1991). Influence of vitamin E on platelet function in humans. *J Am Coll Nutr* 10: 466-473.
- Steiner M (1993). Vitamin E: more than an antioxidant. *Clin Cardiol* 16: 16-18.
- Kitagawa M and Mino M (1989). Effects of elevated d-alpha (RRR)-tocopherol dosage in man. *J Nutr Sci Vitaminol* 35: 133-142.
- Meydani SN, Meydani M, Bluymberg JB, Leka LS, Pedrosa M, Diamond R, Schaefer EJ (1998). Assessment of the safety of supplementation with different amounts of vitamin E in healthy older adults. *Am J Clin Nutr* 68: 311-318.

NutriFusion Response: NutriFusion has reviewed the literature, including the studies identified above, on vitamin E and prepared the summary, below, that we incorporate into our GRAS notice.

Acute toxicity: Mature rats (Charles River COBS, CD) of both sexes were fasted for 16 h prior to administration by gavage of 7000 mg/kg body weight of either alpha-tocopherol poly(ethylene glycol) 1000 succinate (TPGS), polyethylene glycol, or d-alpha-tocopherol acid succinate NF. This was the highest dose practicable. ^{12/} Six of 60 mature rats involved in the test died, 5 within 24 h and 1 within 48 h after treatment. All deaths, however, were attributed to mechanical injury at the time of intubation. The LD50 for the TPGS is >7000 mg/kg body weight for young adult rats of both sexes.

Subchronic toxicity: A 13-week study was conducted by administering d-alpha-tocopherol acetate (vitamin E) in corn oil by gavage to groups of ten male and ten female Fischer 344 rats at doses of 0, 125, 500 or 2000 mg/kg body weight daily for 13 weeks. ^{13/} The dose of corn oil given was 3.5 ml/kg. Additional groups of ten males and ten females were included and served as untreated controls. Deaths occurred only in males at 2000 mg/kg. Vitamin E dosing had no effect on body weight or food consumption. The liver-to-body weight ratio of females at 2000 mg/kg was significantly increased. In males, high levels of vitamin E (2000 mg/kg) caused prolongation of both prothrombin and activated partial thromboplastin (APTT) times, reticulocytosis and a decrease in haematocrit values and haemoglobin concentrations. APTT was also lengthened in females at this dose level. High levels (2000 mg/kg) caused haemorrhagic diathesis in both males and females and increased medullary erythropoiesis in the spleen of one male. The above findings indicate that vitamin E administration in excessive amounts is potentially toxic. The no observed adverse effect level (NOAEL) for these observed effects can be determined to be 125 mg/kg.

In another subchronic study, five groups of weanling rats were fed a normal level of alpha-tocopherol acetate (35 mg/kg diet) and 25, 50, 100 and 1000 times the control amount. ^{14/} After an 8-week feeding, rats fed the 1000x diet had significantly lower feed and protein efficiencies. Mating the animals showed that fertility and survival of pups to weanling were not affected by the diets, but that the number of pups born alive was reduced in the 1000x group. The overall results of this study indicate that dietary levels of 25 and 50 times the normal allowance of vitamin E produced no

^{12/} Krasavage, Walter J., and Clarence J. Terhaar. "d-. alpha.-Tocopheryl poly (ethylene glycol) 1000 succinate: acute toxicity, subchronic feeding, reproduction, and teratologic studies in the rat." *Journal of Agricultural and Food Chemistry* 25.2 (1977): 273-278.

^{13/} Abdo, K. M., et al. "Thirteen-week toxicity study of d-α-tocopheryl acetate (vitamin E) in Fischer 344 rats." *Food and Chemical Toxicology* 24.10-11 (1986): 1043-1050.

^{14/} Dymsha, H. A., and J. Park. "EXCESS DIETARY VITAMIN-E IN RATS." *FEDERATION PROCEEDINGS*. Vol. 34. No. 3. 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3998: FEDERATION AMER SOC EXP BIOL, 1975.

detectable adverse effects. However, the 1000x level (i.e., 35,000 mg/kg diet) was apparently detrimental to rats.

Chronic study: Groups of weanling female Wistar rats were fed diets containing 0, 25, 250, 2500, 10,000, or 25,000 IU vitamin E/kg diet for 8 and 16 months. ^{15/} Vitamin E depressed body-weight gain at concentrations of 10,000 and 25,000 IU/kg diet, and increased relative heart and spleen weights were seen at 8 months and 16 months, respectively. There was an increase in plasma alkaline phosphatase and a decrease in the ash content of bone after 16 months at these two dose levels. Prothrombin time was reduced at 12 months, but not at 9 or 16 months. Urinary excretion of creatine and creatinine was normal at 11 months. No histological examinations were reported.

Groups of 60 male and 60 female Charles River CD rats, initial body weight 134 g (males) or 130 g (females), were fed a diet supplemented with dl-alpha-tocopherol acetate at levels calculated to give a dose of 500, 1000, or 2000 mg/kg body weight per day. ^{16/} A control group received un-supplemented basal diet stated to contain 39 mg vitamin E/kg body weight and 10 mg vitamin K₃/kg body weight. Mortality due to hemorrhage in males during the first 26 weeks, maximally 10% in the high-dose group, was balanced by a similar number of deaths in control males between weeks 26 and 52, and thereafter alpha-tocopherol did not adversely affect survival. Pro-thrombin times were prolonged in males of all treatment groups at week 4 until week 13, but these returned to normal by week 26 (after initiation of vitamin K supplementation in week 24); females were unaffected. After 52 weeks of treatment, 10 rats/sex/dose were killed, necropsied, and examined histologically. The remaining animals remained on the respective diets until termination at 104 weeks. At necropsy, no macroscopic changes related to treatment were observed.

Reproductive toxicity/teratogenicity: At the end of a 90-day study on d-alpha-tocopherol (polyethylene glycol) 1000 succinate (TPGS), half the rats from each dose group were maintained on their respective diets and used for a reproduction study. ^{17/} The dietary concentrations of TPGS were 0, 0.002, 0.2, & 2%. The animals were mated on day 112 of treatment to produce the F_{1a} generation and on day 175 to produce the F_{1b} generation. The F₀ animals were maintained on their respective diets to 265-265 days of treatment, then sacrificed and examined histopathologically. Reproductive indices (mean gestation period, litter size, sex ratio, and mortality of pups or parents) were unaffected by treatment. Clinical chemical and haematological parameters were normal in the F₀ generation 10 days before terminal sacrifice. In another investigation on reproductive toxicity of vitamin E showed 1/91 affected mice fetuses at a daily dosage level of 0.4 ml vitamin E. The study, in the form of a letter to the journal, does not contain detailed discussion of the results. In all, the reproduction/teratology studies we reviewed did not indicate that vitamin E had adverse effects on reproductive function.

Genotoxicity: Studies reviewed show the vitamin E is not genotoxic. In investigations of the potential anticlastogenic activity in human lymphocytes *in vitro*, vitamin E did not induce chromosomal

^{15/} Yang NY and Desai ID (1977). Effect of high levels of dietary vitamin E on hematological indices and biochemical parameters in rats. *J Nutr* 107: 1410-1417.

^{16/} Wheldon GH, Bhatt A, Keller P, Hummler H (1983). d,1-alpha-Tocopheryl acetate (vitamin E): a long term toxicity and carcinogenicity study in rats. *Int J Vitam Nutr Res* 53: 287-296.

^{17/} See *supra* note 12.

damage or sister chromatid exchange. 18/ In the *Salmonella typhimurium* assay, dl-alpha-tocopherol caused a significant decrease in point mutations induced by malonaldehyde or beta-propiolactone. 19/ In a sex-linked recessive lethal mutation assay in *Drosophila*, alpha-tocopheryl acetate in the nutrient medium at 500 IU/kg did not affect the mutation rate in irradiated males but caused a significant reduction in lethal mutations in subsequent generations bred from unirradiated females. 20/

Human studies:

Farrell, P. M., & Bieri, J. G. (1975): To assess possible toxic effects of vitamin E supplementation, a group of 28 adults voluntarily ingesting 100 to 800 IU/day of tocopherol for an average of 3 years were evaluated in this study. 21/ No gross evidence of toxicity was apparent on reviewing past medical histories with the subjects. Laboratory screening for toxic side effects of vitamin E supplementation by performance of 20 standard clinical blood tests failed to reveal any disturbance in liver, kidney, muscle, thyroid gland, erythrocytes, leukocytes, coagulation parameters, or blood glucose. It is concluded that megavitamin E supplements in this group produced no apparent toxic side effects and that subjective claims for beneficial effects were highly variable.

Tsai, A. C., et al. (1978): A study was conducted to examine the effect of megavitamin E supplementation in healthy college student volunteers. 22/ Two hundred two subjects were randomly assigned to either of two treatment groups, one control and the other experimental. Each subject in the experimental group orally received 600 IU *dl*- α -tocopheryl acetate daily, while each subject in the control group received identical placebo tablets. The experiment was "double blind" and proceeded for a period of 4 weeks. The study indicated that under our experimental conditions, megavitamin E supplementation does not have a significant effect, beneficial or undesirable, on general health conditions, but it can cause a significant reduction of serum thyroid hormone levels and also an elevation of serum triglyceride levels in female.

Steiner, Manfred (1991): Aggregation of platelets derived from individuals on a dietary supplementation of alpha-tocopherol ranging from 400 to 1200 IU/day showed no significant reduction. 23/ Steiner, Manfred (1993): while the *in vivo* human study showed up to 1200 IU/day of vitamin E did not inhibit platelet aggregation, doses of 400 IU/day provide greater than 75% inhibition of platelet adhesion to a variety of adhesive proteins when tested at low shear rate in a laminar flow

18/ Gebhart, E., M. Schinzel, and K. W. Ruprecht. "Cytogenetic studies using various clastogens in two patients with Werner syndrome and control individuals." *Human genetics* 70.4 (1985): 324-327.

19/ Shamberger, Raymond J., et al. "Antioxidants reduce the mutagenic effect of malonaldehyde and β -propiolactone: Part IX, antioxidants and cancer." *Mutation Research/Genetic Toxicology* 66.4 (1979): 349-355.

20/ Beckman, C., R. M. Roy, and A. Sproule. "Modification of radiation-induced sex-linked recessive lethal mutation frequency by tocopherol." *Mutation research* 105.1/2 (1982): 73-77.

21/ Farrell, Philip M., and John G. Bieri. "Megavitamin E supplementation in man." *The American journal of clinical nutrition* 28.12 (1975): 1381-1386.

22/ Tsai, A. C., et al. "Study on the effect of megavitamin E supplementation in man." *The American journal of clinical nutrition* 31.5 (1978): 831-837.

23/ Steiner M (1991). Influence of vitamin E on platelet function in humans. *J Am Coll Nutr* 10: 466-473.

chamber (*in vitro*). 24/ The antiadhesive effect of vitamin E appears to be related to a reduction in the number and size of pseudopodia upon platelet activation.

KITAGAWA, Makoto. (1989): A study was conducted to investigate the effects of a high level of alpha-tocopherol in healthy college student volunteers. 25/ Of 19 volunteers, 14 were given daily doses of 600 mg (900 IU) of alpha-tocopherol for 12 weeks, and the remaining 5 were given identical placebo capsules. During the study, there were no changes in laboratory values for thyroid, liver, or kidney functions, and coagulation activity or immunoglobulin levels. Healthy status continued without any abnormal symptoms, and without any subjective complaints on the questionnaire. In the control group also, no changes occurred during the investigation.

Meydani et al. (1998): The authors assessed the effects of 4 month of supplementation with 60, 200, or 800 IU (55, 182, or 727 mg) alpha-tocopherol/d on general health, nutrient status, liver enzyme function, thyroid hormone concentrations, creatinine concentrations, serum autoantibodies, killing of *Candida albicans* by neutrophils, and bleeding time in 88 healthy subjects aged >65 years participating in a double-blind, placebo-controlled trial. 26/ No side effects were reported by the subjects. Vitamin E supplementation had no effect on body weight, plasma total proteins, albumin, glucose, plasma lipids or the lipoprotein profile, total bilirubin, alkaline phosphatase, serum aspartate aminotransferase, serum alanine aminotransferase, lactate dehydrogenase, serum urea nitrogen, total red blood cells, white blood cells or white blood cell differential counts, platelet number, bleeding time, hemoglobin, hematocrit, thyroid hormones, or urinary or serum creatinine concentrations. Values from all supplemented groups were within normal ranges for older adults and were not significantly different from values in the placebo group. Vitamin E supplementation had no significant effects on plasma concentrations of other antioxidant vitamins and minerals, glutathione peroxidase, superoxide dismutase, or total homocysteine. There was no significant effect of vitamin E on serum nonspecific immunoglobulin concentrations or anti-DNA and anti-thyroglobulin antibodies. The authors concluded that 4 month of supplementation with 60-800 IU vitamin E/d had no adverse effects.

In summary, the critical effect is on blood clotting and that the study by Meydani et al. (1998) provided the best basis for an evaluation of the tolerable upper intake level. The most recent systematic review conducted by EFSA on vitamin E in 2015 adopted the ULs set by SCF back in 2003. 27/ When compared, the highest 90th percentile intake levels among different subpopulation (i.e., 13.7 mg/day) is way below the lowest UL established based on blood clotting for different subpopulation (i.e., 100 mg/day), therefore, the intended use of vitamin E will not result in decreased blood coagulation.

We trust you will agree after reviewing the information in this submission that we have addressed each of the questions and have provided sufficient data and information supporting our view that the vitamin E extracted from fruits and vegetables is GRAS.

24/ Steiner M (1993). Vitamin E: more than an antioxidant. *Clin Cardiol* 16: 16-18.

25/ KITAGAWA, Makoto. "Effects of elevated d-alpha (RRR)-tocopherol dosage in man." *Journal of nutritional science and vitaminology* 35.2 (1989): 133-142.

26/ Meydani, Simin Nikbin, et al. "Assessment of the safety of supplementation with different amounts of vitamin E in healthy older adults." *The American journal of clinical nutrition* 68.2 (1998): 311-318.

27/ 2015 EFSA Report *Scientific Opinion on Dietary Reference Values for vitamin E as α -tocopherol*. *EFSA Journal*, 13(7), 4149.

If you have any questions with our response or any further questions regarding GRN 000781, please feel free to contact me.

Sincerely,

(b) (4)



Martin J. Hahn
Partner
martin.hahn@hoganlovells.com
202 637 5926

Enclosures:

Attachment 1 Revised GRAS Notice for Vitamin E (Alpha-Tocopherol Acetate)

Attachment 2 AOAC Official Method 2012.09

Attachment 3 FDA's Guidance titled "Frequently Asked Questions for Industry on Nutrition Facts Labeling Requirements"

Attachment 4 Abstracts of Recent Safety Literature on Vitamin E

Kidwell, Judith L.

From: Tao, Xin <xin.tao@hoganlovells.com>
Sent: Monday, August 20, 2018 4:25 PM
To: Kidwell, Judith L.
Cc: Hahn, Martin J.
Subject: RE: GRN 781
Attachments: Dymsza Excess dietary Vitamin E in Rats.pdf; Hook Letter Vitamin E.PDF

Judy,

Please see our [response](#) to the toxicology questions below. For your ease of reference, we first copy the FDA questions below, followed by our response. Please let us know if your toxicology team has further questions. We are also happy to answer any additional chemistry questions the agency may have.

- 1) For the subchronic toxicity study by Dymsza and Park (1975), please state a) what the diets containing “25, 50, 100, and 1000 times the control amount” are when expressed as mg/kg bw/day and 2) what the no observed adverse effect level (NOAEL) or no observed effect level (NOEL) is.

NutriFusion Response: The study, which was published as a summary, did not provide the details on the type of diets used. We are providing a copy of the original 1977 study for the agency’s reference. The overall results of this study indicate that dietary levels of 25 and 50 times the normal allowance of vitamin E produced no detectable adverse effects. Using the normal control amount of 35 mg/kg, we can estimate the NOAEL as $50 \times 35 \text{ mg/kg bw/day} = 1750 \text{ mg/kg bw/day}$.

- 2) For the chronic toxicity study by Yang and Desai (1977), please state a) what the diets containing 0, 25, 250, 2500, 10000, or 25000 IU vitamin E/kg diet are when expressed as mg/kg bw/day and 2) what the NOAEL or NOEL is.

NutriFusion Response: The detailed composition of the diets are dextrose (64.9%), casein (20%), corn oil (10%), salt mix (4%), vitamin mix (0.6%), and choline chloride (0.5%). 0, 25, 250, 2500, 10000 or 25000 IU vitamin E (as dl- α -tocopheryl acetate)/kg diet can be converted to approximately 0, 1.25, 12.5, 125, 1250, 500 and 1250 mg/kg bw/day. No adverse effects were associated with vitamin E at levels of 2500 IU/kg diet. The NOAEL can be estimated to be approximately 125 mg/kg bw/day.

- 3) For the chronic toxicity study by Wheldon *et al.* (1983), please state what the NOAEL or NOEL is, if any.

NutriFusion Response: A NOAEL for general systemic toxicity could not be established in this study due to the effects on blood clotting and liver tissue.

- 4) For the combined subchronic/reproductive toxicity/teratogenicity study by Krasavage *et al.* (1977), please state a) what the diets containing 0, 0.002, 0.2, and 2% TPGS are when expressed as mg Vitamin E/kg bw/day and 2) what the reproductive and parental NOAELs or NOELs are.

NutriFusion Response: TPGS was fed at concentrations of 0.002, 0.2, and 2.0% in a basal diet of ground Purina Laboratory Chow supplemented with 5.0% corn oil. The 0.002% dose level of TPGS fed in this study provided a 200-g rat, which ingested 20 g of diet per day, with a daily intake of 0.5 mg/kg bw/day of vitamin E. Similarly, the other dosages correspond to 50 mg/kg and 500 mg/kg of vitamin E intake. NOAEL for reproductive toxicity in this study can be determined to be $\geq 500 \text{ mg/kg bw/day}$ vitamin E.

5) On page 10 of your response you state that “In another investigation on reproductive toxicity of vitamin E showed 1/91 affected mice fetuses at a daily dosage level of 0.4 ml vitamin E.” Please a) provide a reference for this statement, b) state what 0.4 mL of vitamin E is in mg/kg bw/day, and c) discuss what effects were seen.

NutriFusion Response: The reference of the study is *Hook EB, Healy KM, Niles AM, Skalko RG (1974). Letter: Vitamin E: teratogen or anti-teratogen? Lancet 1: 809.* We have attached a copy of the original study.

The authors observed one incidence of malformation in fetuses (teratogenic effect) when 0.4 ml. vitamin E was fed to rice. This one malformed offspring has open eye and micrognathia – a syndrome noted before in this strain in offspring of mice treated with known teratogens. However, the rate of all malformations in previous control series has been about 1%, implying the 1% malformation findings may be spontaneous, rather than due to the intake of vitamin E. This 1974 study (attached) is summarized in a letter to the journal, and the findings apparently have not been peer-reviewed. We do not view this single study summarizing vitamin E is a teratogen. The dosed use is 0.4 ml or 591 IU of vitamin E, which can be converted to about 19.7 IU/g bw/day (based on a body weight of 30 g of mice) or 13199 mg/kg bw/day vitamin E.

Best regards,
Martin & Xin

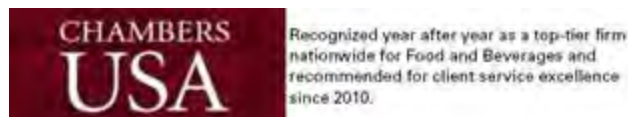
Xin Tao

Senior Associate

Hogan Lovells US LLP
Columbia Square
555 Thirteenth Street, NW
Washington, DC 20004

Tel: +1 202 637 5600
Direct: +1 202 637 6986
Mobile: +1 979-422-7860
Fax: +1 202 637 5910
Email: xin.tao@hoganlovells.com
www.hoganlovells.com

Please consider the environment before printing this e-mail.



From: Kidwell, Judith L. [mailto:Judith.Kidwell@fda.hhs.gov]
Sent: Monday, August 20, 2018 12:44 PM
To: Tao, Xin
Cc: Hahn, Martin J.
Subject: RE: GRN 781

Hi Xin – We have some additional toxicology questions based on the information you sent. (Our chemistry reviewer is on travel, so it may take a day or so for her to get back to me.)

Toxicology questions:

- 1) For the subchronic toxicity study by Dymsha and Park (1975), please state a) what the diets containing “25, 50, 100, and 1000 times the control amount” are when expressed as mg/kg bw/day and 2) what the no observed adverse effect level (NOAEL) or no observed effect level (NOEL) is.
- 2) For the chronic toxicity study by Yang and Desai (1977), please state a) what the diets containing 0, 25, 250, 2500, 10000, or 25000 IU vitamin E/kg diet are when expressed as mg/kg bw/day and 2) what the NOAEL or NOEL is.

- 3) For the chronic toxicity study by Wheldon *et al.* (1983), please state what the NOAEL or NOEL is, if any.
- 4) For the combined subchronic/reproductive toxicity/teratogenicity study by Krasavage *et al.* (1977), please state a) what the diets containing 0, 0.002, 0.2, and 2% TPGS are when expressed as mg Vitamin E/kg bw/day and 2) what the reproductive and parental NOAELs or NOELs are.
- 5) On page 10 of your response you state that “In another investigation on reproductive toxicity of vitamin E showed 1/91 affected mice fetuses at a daily dosage level of 0.4 ml vitamin E.” Please a) provide a reference for this statement, b) state what 0.4 mL of vitamin E is in mg/kg bw/day, and c) discuss what effects were seen.

Let me know if you have questions or need clarification. We think this information should be easily available.

Regards,
Judy

Judy Kidwell
General Health Scientist
Office of Food Additive Safety
Center for Food Safety and Applied Nutrition
240.402.1071
Judith.kidwell@fda.hhs.gov



This e-mail message is intended for the exclusive use of the recipient(s) named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at judith.kidwell@fda.hhs.gov.

From: Tao, Xin [mailto:xin.tao@hoganlovells.com]
Sent: Sunday, August 19, 2018 11:12 PM
To: Kidwell, Judith L. <Judith.Kidwell@fda.hhs.gov>
Cc: Hahn, Martin J. <martin.hahn@hoganlovells.com>
Subject: RE: GRN 781

Dear Dr. Kidwell,

On behalf of NutriFusion LLC (NutriFusion), we are responding to the agency’s questions regarding GRN 000781, which covers the intended use of vitamin E extracted from edible portions of commonly consumed fruits and vegetables. Pursuant to the agency’s request, we are responding within 10 business days of your August 3rd correspondence. The detail response is attached.

As discussed in the attachments, we would like to clarify the notified vitamin E extract should be characterized as the acetate ester of “ α -tocopherol.” The α -tocopherol acetate is the naturally-occurring vitamin E ester extracted from fruits and vegetables. We apologize for failing to specify in the original notification that it covers the acetate ester form. We have updated the notification to clarify it covers α -tocopherol acetate. We trust you will agree after

reviewing the information in this submission that we have addressed each of the questions and have provided sufficient data and information supporting our view that the vitamin E extracted from fruits and vegetables is GRAS.

Please let us know if the agency has any further questions after review.

Best regards,
Martin & Xin

Xin Tao
Associate

Hogan Lovells US LLP
Columbia Square
555 Thirteenth Street, NW
Washington, DC 20004

Tel: +1 202 637 5600
Direct: +1 202 637 6986
Mobile: +1 979-422-7860
Fax: +1 202 637 5910
Email: xin.tao@hoganlovells.com
www.hoganlovells.com

Please consider the environment before printing this e-mail.



From: "Kidwell, Judith L." <Judith.Kidwell@fda.hhs.gov>
Date: August 3, 2018 at 9:36:01 AM EDT
To: "Hahn, Martin J. (martin.hahn@hoganlovells.com)" <martin.hahn@hoganlovells.com>
Subject: GRN 781

Hi Martin – We have a request for additional information/clarification regarding NutriFusion’s GRAS notice for the use of α -tocopherol. I have attached our request as a PDF file.

Once you’ve had a chance to review the request and consult with the notifier, I would appreciate your suggesting a time-frame for responding. We believe that the information can be provided in a relatively short time period (e.g., 2 weeks), and want to be sure that’s reasonable.

Please contact me if any of the questions are unclear or require further explanation. Thank you.

Regards,
Judy

Judy Kidwell
General Health Scientist
Office of Food Additive Safety
Center for Food Safety and Applied Nutrition
240.402.1071
Judith.kidwell@fda.hhs.gov

About Hogan Lovells

Hogan Lovells is an international legal practice that includes Hogan Lovells US LLP and Hogan Lovells International LLP. For more information, see www.hoganlovells.com.

CONFIDENTIALITY. This email and any attachments are confidential, except where the email states it can be disclosed; it may also be privileged. If received in error, please do not disclose the contents to anyone, but notify the sender by return email and delete this email (and any attachments) from your system.