Item A

This petition seeks inclusion of **ASCORBYL PALMITATE** on the National List at §205.605(b) as a synthetic non-agricultural substance allowed in or on processed infant formula products labeled as "organic" or "made with organic (specified ingredients)."

Item B

1. The substance's chemical or common name.

Ascorbyl palmitate is an ester of ascorbic acid (a substance providing Vitamin C) and palmitic acid, a saturated fatty acid which comprises 25% of the fatty acids in breast milk lipid. Ascorbyl palmitate is known as "vitamin C ester," which should not be confused with "Ester-C®," a branded Vitamin C supplement comprised of calcium ascorbate.

Other chemical names for ascorbyl palmitate are Vitamin C palmitate; L-ascorbyl palmitate; 2,3-didehydro-L-threo-hexono-1,4-lactone-6-palmitate; 6-palmitoyl-3-keto-L-gulofuranolactone; and L-ascorbic acid 6-hexadecanoate.

2a. The petitioner's name, address and telephone number and other contact information.

International Formula Council
1100 Johnson Ferry Road NE, Suite 300
Atlanta, GA 30342
Contact: Mardi Mountford, Executive Vice President
Phone: (678) 303-3027
Email: mmountford@kellencompany.com

2b. Sources of the petitioned substance.

The number of manufacturers of ascorbyl palmitate is very large. The information available for ascorbyl palmitate on the Hazardous Substances Data Bank (see Appendix A) lists the names of 20 suppliers from around the world (pages 30-32).

The supplier of the ascorbyl palmitate used in infant formulas is DSM Nutritional Products. Contact information for DSM Nutritional Products:

Postal address
DSM Nutritional Products GmbH
Postfach 1145
D-79629 Grenzach-Wyhlen, Germany
http://www.dsm-grenzach.de

Street address
DSM Nutritional Products GmbH
Emil-Barell-Str. 3
D-79639 Grenzach-Wyhlen, Germany
Tel.: +49 7624 9090

3. The intended or current use of the substance.

Ascorbic acid, which is water-soluble, has antioxidant activity, both in the body and in foods. Ascorbyl palmitate is fat-soluble, so it provides a means for providing the antioxidant activity of ascorbic acid in edible oils blends such as those used in infant formulas.

Note that ingestion of ascorbyl palmitate does not result in any significant incorporation into the body because ascorbyl palmitate is hydrolyzed to palmitate and ascorbic acid in the human digestive tract before it is absorbed. The ascorbic acid released by the hydrolysis of ascorbyl palmitate appears to be as bioavailable as ascorbic acid itself.

This petition requests the addition of ascorbyl palmitate solely for use in infant formula labeled as "organic." Ascorbyl palmitate is used in many conventional food products as an antioxidant. The standard of identity for margarine (21 CFR 166.110) permits use of ascorbyl palmitate. FDA regulations allow use of ascorbyl palmitate in foods for human consumption (21 CFR 182.3149) and in animal drugs, feeds, and related products (21 CFR 582.3149) in accordance with good manufacturing (or feeding) practice. Ascorbyl palmitate in foods prevents rancidity and the browning of cut apples.

4. A list of the handling activities for which the substance will be used.

This petition seeks allowance of ascorbyl palmitate as an antioxidant ingredient in infant formula products. Infant formulas commonly contain a variety of polyunsaturated chain fatty acids (PUFA) as part of the lipid component of the overall nutrient system. Examples of PUFA include linoleic acid, alpha-linolenic acid, arachidonic acid (ARA), docosahexaenoic acid (DHA), and others. The Infant Formula Act and FDA regulations require a minimum amount of linoleic acid in order to provide essential fatty acid. ARA and DHA have been shown to provide beneficial effects in preterm infants such as enhanced brain and vision development.

PUFA tend to be more sensitive to oxidation than many other ingredients commonly found in nutritional formulas. Due to their chemical structure, exposure of PUFA to heat and atmospheric levels of oxygen can cause a series of chemical reactions resulting in free radical formation. These free radicals can continue to break down PUFA in an auto-oxidative process. The result is the development of undesirable off-flavors and odors and the eventual degradation of the beneficial polyunsaturated fatty acids. PUFA are especially susceptible to oxidation during high-heat processing, spray drying processing, or even during relatively short storage periods after the formula has been sealed and packaged. Oxidative stability has become especially challenging with infant formulas that contain ARA and DHA, two fatty acids found in human milk that are important for visual and cognitive development.

One method of controlling the undesirable oxidation of PUFA in powdered infant formulas is the addition of safe antioxidants soluble in edible oils, such as ascorbyl palmitate, beta-carotene, mixed tocopherols, and others.

5. Detailed description of the manufacturing process.

Ascorbyl palmitate is prepared by condensing palmitoyl chloride and ascorbic acid in the presence of a dehydrochlorinating agent such as pyridine. It is also formed by the reaction of L-ascorbic acid and palmitic acid, which can be catalyzed by lipase enzyme.

6. Summary of any available previous reviews of the petitioned substance.

The **Hazardous Substances Data Bank** information on ascorbyl palmitate available at the National Library of Medicine website (http://toxnet.nlm.nih.gov) is attached as Appendix A.

The Select Committee on GRAS Substances (SCOGS) was established by the Life Sciences Research Office (LSRO) under contract with the Food and Drug Administration to evaluate over 370 substances used as food additives. The Select Committee of GRAS Substances (SCOGS) was a group of qualified scientists assigned to provide an independent evaluation of the safety of food additives, including ascorbyl palmitate. In their report[1] published in 1979, their judgment was: "There is no evidence in the available information on ascorbyl palmitate that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public when they are used at levels that are now current or might reasonably be expected in the future."

7. Information regarding the regulatory status of ascorbyl palmitate.

FDA regulations allow use of ascorbyl palmitate as an antioxidant in foods for human consumption (21 CFR 182.3149) and in animal drugs, feeds, and related products (21 CFR 582.3149) in accordance with good manufacturing (or feeding) practice. The standard of identity for margarine (21 CFR 166.110) permits use of ascorbyl palmitate limited to 0.02% percent by weight of the finished food. FSIS also permits ascorbyl palmitate in margarine at up to 0.02% to retard rancidity (9 CFR 424.21).

The FDA is the official U.S. government representative to the Codex Alimentarius Commission of the Joint FAO/WHO Food Standards Programme. The Codex Alimentarius Commission Standard for Infant Formula (CODEX STAN 72-1981) has listed L-ascorbyl palmitate (and mixed tocopherols concentrate) as permissible antioxidants in infant formula for over thirty years, at a maximum level of 1 mg/100 mL of prepared ready-to-feed infant formula, singly or in combination with mixed tocopherol concentrate.

[1] Evaluation of the Health Aspects of Ascorbic Acid, Sodium Ascorbate, Calcium Ascorbate, Erythorbic Acid, Sodium Erythorbate, and Ascorbyl Palmitate as Food Ingredients. - Final report. Federation of American Societies for Experimental Biology, Bethesda, MD. Life Sciences Research Office. 1979. Report Number: SCOGS-59; 60 pages. NTIS Order Number: PB80-128796.

Moreover, the Codex Alimentarius Commission created Advisory Lists of Mineral Salts and Vitamin Compounds for Use in Foods for Infants and Children, CAC/GL 10-1979. For Vitamin C, CAC/GL 10-1979 lists four (4) vitamin forms: ascorbic acid, sodium ascorbate, calcium ascorbate, and ascorbyl-6-palmitate. It is no accident that the list of vitamins prepared for the Processing, Handling, and Labeling Committee of the National Organic Standards Board in 1994 or 1995, that was included in the Nutrient Vitamins TAP Report (at page 7), listed these same four vitamin forms for Vitamin C. One of the "vitamins" approved by the NOSB in October/November 1995 was "Vitamin C." "Vitamin C" is not a substance, but a vitamin activity provided by a substance, such as the four vitamin forms enumerated in CAC/GL 10-1979 and in the listing included in the "Nutrient Vitamins" TAP Report.

According to the EPA's FIFRA Requirements, residues of ascorbyl palmitate are exempted from the requirement of a tolerance when used in accordance with good agricultural practice as inert (or occasionally active) ingredients in pesticide formulations applied to growing crops or to raw agricultural commodities after harvest (40 CFR 180.910) and in pesticide formulations applied to animals (40 CFR 180.930).

8a. The Chemical Abstract Service (CAS) No. of ascorbyl palmitate is 137-66-6. The INS number ("E number") of ascorbyl palmitate is 304.

8b. Labels of products that contains the petitioned substance

See Appendix B

9. The substance's physical properties and chemical mode of action

Ascorbyl palmitate is a white or yellowish-white solid with a soapy taste and a citrus-like odor. It is very slightly soluble in water but freely soluble in alcohol, animal oil, and vegetable oil. It melts at 107° to 117°C (around 234°F).

Ascorbyl palmitate prevents oxidative rancidity development by quenching singlet oxygen. The ascorbic acid part of the molecule donates hydrogen (a reducing agent). This phenomenon is also called "oxygen scavenging."

(a) Chemical interactions with other substances, especially substances used in organic production

As a fat-soluble source of ascorbic acid, ascorbyl palmitate acts synergistically with tocopherols to protect fats and oils from rancidity.

Ascorbyl palmitate may protect against certain drugs. Male MEl mice in which hepatotoxicity had been induced by the feeding of 600 mg/kg acetaminophen had covalent binding of acetaminophen metabolites to hepatic proteins, a depletion of hepatic nonprotein sulfhydryl

groups after 2 hours, and a dramatic increase in plasma alanine aminotransferase activity after 24 hours. The coadministration of acetaminophen and ascorbyl palmitate reduced this binding within 2 and 4 hours (to 31% and 22%, respectively), reduced the depletion in nonprotein sulfhydryl groups and aminotransferase activity, and completely prevented the 35% mortality observed at 24 hours after acetaminophen treatment alone. Ascorbyl palmitate appeared to prevent hepatic damage by removing the reactive acetaminophen metabolites and by having a sparing action on reduced hepatic glutathione.

(b) toxicity and environmental persistence

For at least thirty years, the Codex Alimentarius Commission Standard for Infant Formula (CODEX STAN 72-1981) has listed L-ascorbyl palmitate (and mixed tocopherols concentrate) as permissible antioxidants in infant formula, at a level of up to 1 mg/100 mL in prepared ready-to-feed product.

Rats (10 per group) were given 2% and 5% ascorbyl palmitate (AP) in feed for 9 months. Significant growth retardation occurred in rats given 5% AP**,** and 2 of 10 had bladder stones and hyperplasia of the bladder epithelium. One rat of the high dose group had lesions of nephritis. Slight growth retardation occurred in rats fed the 2% AP diet, but no other signs of toxicity were observed. Female mice fed AP for 63 days had no signs of toxicity during a tumor inhibition study at doses up to 3000 mg/kg/day.

High doses of ascorbic acid increase oxalic acid production and excretion. Rats fed 125 mg AP per kg per day for 728 days (0.25% of diet) had no harmful effects. This intake was the equivalent of 53 mg/kg of ascorbic acid per day. In the same study, however, a different group of rats had body weight decreases at dietary doses of 2500 mg/kg/day and above. The highest dose that did not cause a toxicological effect was 1000 mg/kg/day. Additionally, oxalate stones were observed in the urinary bladders of two of the eight rats in the second group when a dose of 2500 mg/kg/day was administered.

Ascorbyl palmitate has antitumor activity. AP was topically applied at small doses inhibited 12-O-tetradecanoylphorbol-13-acetate-induced (TPA-induced) ornithine decarboxylase activity, tumor production, and DNA synthesis in mouse epithelial cells. A dose of 4 µmol of AP inhibited by 60-70% after one topical application of 2 nmol TPA. When 5 nmol TPA was administered with 5 pmol AP twice weekly to previously initiated mice, 91% of tumors were inhibited per mouse.

Ascorbyl palmitate is nonmutagenic and actually behaves as a membrane-active antimutagen.

(c) environmental impacts from its use and/or manufacture

Ascorbyl palmitate's production and use as an antioxidant and as a chemical preservative food additive may result in its release to the environment through various waste streams. If released to air, an estimated vapor pressure of $2.09X10^{-15}$ mm Hg at 25 deg C indicates ascorbyl palmitate

will exist solely in the particulate phase in the atmosphere. Particulate-phase ascorbyl palmitate will be removed from the atmosphere by wet or dry deposition. Ascorbyl palmitate does not contain chromophores that absorb at wavelengths >290 nm, and therefore is not expected to be susceptible to direct photolysis by sunlight. If released to soil, ascorbyl palmitate is expected to have moderate mobility based upon an estimated Koc of 450. Volatilization from moist soil surfaces is not expected to be an important fate process based upon an estimated Henry's Law constant of $1.4X10^{-7}$ atm-cu m/mole. Biodegradation data were not available.

If released into water, ascorbyl palmitate is expected to adsorb to suspended solids and sediment based upon the estimated K_{oc}. Volatilization from water surfaces is not expected to be an important fate process based upon this compound's estimated Henry's Law constant. An estimated bioconcentration factor (BCF) of 180 suggests the potential for bioconcentration in aquatic organisms is high, provided the compound is not metabolized by the organism. An estimated base-catalyzed second-order hydrolysis rate constant of 2.85X10-2 L/mole-sec corresponds to half-lives of 7.7 years and 280 days at pH values of 7 and 8, respectively.

Occupational exposure to ascorbyl palmitate may occur through inhalation and dermal contact with this compound at workplaces where ascorbyl palmitate is produced or used. Use data indicate that the general population may be exposed to ascorbyl palmitate via ingestion of food and via use of pharmaceutical products and antioxidants containing ascorbyl palmitate.

(d) effects on human health

The 1979 opinion on ascorbyl palmitate of the Select Committee on GRAS Substances (SCOGS) of the Life Sciences Research Office (LSRO)[2], which reviewed the safety of over 370 food additives under contract with the Food and Drug Administration and affirmed the GRAS status of ascorbyl palmitate, was that there is no evidence in the available information on ascorbyl palmitate that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public when used at levels that are now current or might reasonably be expected in the future.

Ascorbyl palmitate is used widely in cosmetics. Ascorbyl palmitate at concentrations of 1%, 3%, and 5% in petrolatum (0.025 g) was applied under occlusive conditions to the scapular back of human subjects three times per week for 3 consecutive weeks, and once in the 4th week (10 applications). Ascorbyl palmitate at 1-5% was not sensitizing.

(e) effects on soil organisms, crops, or livestock

Oral supplementation of ascorbyl palmitate equivalent to 20 mg ascorbic acid per kg body weight on pulmonary and systemic antioxidant status was studied in six healthy ponies. Two

[2] Evaluation of the Health Aspects of Ascorbic Acid, Sodium Ascorbate, Calcium Ascorbate, Erythorbic Acid, Sodium Erythorbate, and Ascorbyl Palmitate as Food Ingredients. - Final rept. *Federation of American Societies for Experimental Biology, Bethesda, MD. Life Sciences Research Office.* 1979, 60 pages. Report No.: SCOGS-59. **NTIS Order Number:** PB80-128796.

weeks supplementation with ascorbyl palmitate significantly increased mean plasma ascorbic acid concentrations compared to control (29 ±5 and 18 ± 7 µmol/L; $p < 0.05$). The concentration of ascorbic acid in bronchoalveolar lavage fluid increased in five out of six ponies following supplementation with ascorbyl palmitate compared with control (30 ± 10 and 18 ±8 µmol/L; $p < 0.01$). AP did not alter the concentration of glutathione, uric acid or alpha-tocopherol in plasma or bronchoalveolar lavage fluid. In conclusion, the concentration of lung lining fluid ascorbic acid is increased following ascorbyl palmitate supplementation (20 mg/kg body weight) in an ascorbate-synthesizing species.

10a. Safety information about the substance including a Material Safety Data Sheet (MSDS).

An MSDS for ascorbyl palmitate is attached as Appendix C.

10b. National Institute of Environmental Health Studies Substance Report.

An NIEHS substance report may not exist. Appendix A provides the Hazardous Substance Data Bank information on ascorbyl palmitate.

11. Research information about ascorbyl palmitate.

The opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies of the European Food Safety Authority on a request from the European Commission related to the Tolerable Upper Intake Level of Vitamin C in the form of L-ascorbic acid, its calcium, potassium and sodium salts, and L-ascorbyl-6-palmitate is attached as Appendix D. This opinion indicates that safe ascorbic acid intakes can far exceed the amount of ascorbic acid added as ascorbyl palmitate in infant formulas.

Reviews and bibliographies presenting contrasting positions to those presented herein have not been located.

12. A Petition Justification Statement.

Infant formulas are, by FDA regulation, high-fat products providing up to 50% of food energy from lipid. It is important to protect the fats and oils used in infant formulas from oxidation. Fat oxidation is a real danger in powdered infant formula especially, since these products are dried by high temperature spray-drying in an oxygen-containing atmosphere.

The National List at §205.605(b) currently permits addition to foods labeled as "organic" of the antioxidant tocopherols "derived from vegetable oil when rosemary extracts are not a suitable alternative." For infant formula, rosemary extracts are not a suitable option. Rosemary and

rosemary extracts and oils may be GRAS (21 CFR 182.10 and 21 CFR 182.20) for use as spices and flavorings in foods for the general population, but have not been tested and accepted for use in infant formula, the food that constitutes the sole item of diet of infants for an extended period of time. Rosemary oil and extracts contains a range of compounds with various pharmacological activities. An antioxidant found in rosemary (*Rosmarinus officinalis)* and common sage (*Salvia officinalis*) is carnosic acid**,** a benzenediol diterpene. Although carnosic acid is used as a preservative or antioxidant in food and nonfood products (e.g. toothpaste, mouthwash, chewing gum, and skin care products), carnosic acid has medicinal properties, as well as being a potent antioxidant. Because of possible side effects (abortifacient, other toxic side effects; unknown effects in infants) of the components of rosemary oil and rosemary extracts, it is not prudent to use these substances in foods for young infants.

Tocopherols derived from vegetable oil are in fact currently used in infant formulas as antioxidants to protect the edible oils from oxidation and rancidity, but their functionality is limited. One reason that ascorbyl palmitate is added to infant formulas is that it works synergistically with tocopherols. A number of different and complementary antioxidant systems are required to enable the sensitive lipid component of infant formulas to survive the several processing steps of infant formula manufacture and packaging.

Ascorbyl palmitate combines the vitamin form ascorbic acid (providing Vitamin C activity) and the fatty acid palmitic acid, one of the most common fatty acids in human milk. Ascorbyl palmitate is a safe and effective antioxidant in infant formula. It is GRAS.

Lastly, one of the nutrient vitamins approved by the NOSB in October/November 1995 was "Vitamin C." "Vitamin C" is not a substance, but a vitamin activity provided by a substance. The Codex Alimentarius Commission created Advisory Lists of Mineral Salts and Vitamin Compounds for Use in Foods for Infants and Children, CAC/GL 10-1979. For Vitamin C, CAC/GL 10-1979 lists four (4) vitamin forms: ascorbic acid, sodium ascorbate, calcium ascorbate, and ascorbyl-6-palmitate. It is no accident that the list of vitamins prepared for the Processing, Handling, and Labeling Committee of the National Organic Standards Board in 1994 or 1995 and that was included in the Nutrient Vitamins TAP Report (at page 7) listed these same four vitamin forms for Vitamin C. Consequently, sixteen years ago, the NOSB actually approved ascorbyl palmitate, at least as a source of Vitamin C activity, for use in foods labeled as "organic."

13. Confidential Business Information Statement

This petition contains no confidential business information.

Appendices

Petition for addition to the National List of ASCORBYL PALMITATE on the National List of Substances Allowed as Ingredients in or on Processed Products Labeled as "organic" or "made with organic (specified ingredients or food group(s))."

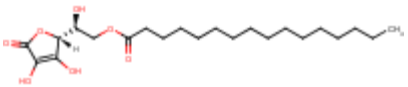
Appendix A – Hazardous Substance Data Bank information

Appendix B – Labels of infant formulas containing this substance

Appendix C - MSDS

Appendix D - Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies of the European Food Safety Authority (EFSA)

Ascorbyl palmitate



CASRN: 137-66-6

Human Health Effects:

Human Toxicity Excerpts:

/HUMAN EXPOSURE STUDIES/ One hundred nineteen subjects were enrolled in a modified Draize assay for skin sensitization potential. Of those, 106 completed the study. **Ascorbyl palmitate** at concentrations of 1%, 3%, and 5% in petrolatum (0.025 g) was applied under occlusive conditions to the scapular back using a Finn Chamber. The test materials were applied three times per week for 3 consecutive weeks, and once in the 4th week (10 applications). The patch sites were evaluated 48 or 72 hours after application. Twelve days after the last patch was removed, a challenge patch was applied to an untreated skin site on the scapular back. The patch was removed at 48 hours, and the site was scored at patch removal and at 96 hours. One subject had a rash on his torso during the 3rd week of the study, but this was attributed to exclusionary medication that was not reported on the subject's personal and medical history, and was not related to the test substances. During induction, the 1 % preparation caused seven 1 + reactions in a single subject. No reactions were noted for the 3% preparation, and one subject had five 1 + reactions after being treated with the 5% preparation. Under the conditions of this study, the investigators concluded that 1-5% **ascorbyl palmitate** was not sensitizing.
[Cosmetic Ingredient Review; Final Report of the Cosmetic Ingredient Review Expert Panel; Final Report on the Safety Assessment of Ascorbyl Palmitate, Ascorbyl Dipalmitate, Ascorbyl Stearate, Erythorbic Acid, and Sodium Erythorbate; Scientific Regulatory Reference CD-ROM (2006). Cosmetic, Toiletry, and Fragrance Association, Washington D.C.] **PEER REVIEWED**

/HUMAN EXPOSURE STUDIES/ A maximization test using 15 female and 13 male subjects was performed to determine the contact sensitization potential of an eye cream containing 0.2% **ascorbyl palmitate.** Skin sites on the upper outer arm, volar forearm, or back of each subject were pretreated with 0.1 mL of sodium lauryl sulfate (SLS) at a concentration of 0.25% and covered with occlusive patches for 24 hours. At patch removal, 0.1 mL of the test eye cream was applied to the same site and covered with occlusive tape. This induction patch remained in place for 48 hours, after which it was removed and the test site was examined for signs of irritation. If no irritation was observed, the pretreatment-treatment procedure was repeated at the same skin site for a total of five induction exposures. If irritation was observed, the treatment patch only was applied for the duration of the study. Ten days after the last induction patch application, 0.1 mL of SLS (5.0%) was applied to an untreated skin site under an occlusive patch for 1 hour. The SLS patch was removed and replaced with a challenge patch containing the eye cream. At 48 h

and 72 hours, the skin sites were examined for sensitization. Twenty-six subjects completed the study; the remaining 2 subjects withdrew for reasons unrelated to the study. No adverse reactions or signs of dermal sensitization were observed during this study.
[Cosmetic Ingredient Review; Final Report of the Cosmetic Ingredient Review Expert Panel; Final Report on the Safety Assessment of Ascorbyl Palmitate, Ascorbyl Dipalmitate, Ascorbyl Stearate, Erythorbic Acid, and Sodium Erythorbate; Scientific Regulatory Reference CD-ROM (2006). Cosmetic, Toiletry, and Fragrance Association, Washington D.C.] **PEER REVIEWED**

/ALTERNATIVE and IN VITRO TESTS/ Rapidly growing tumor cells in rodents and humans have high glutathione S-transferase (GST) activity, and GST can be involved in tumor cell drug resistance. **Ascorbyl palmitate** significantly inhibited human term placental and fetal liver GST activity towards its second substrate, 1-chloro-2, 4-dinitrobenzene (K=10.0 uM). The I50 (uM) for **ascorbyl palmitate** was 45 +/- 0.3 when tested using cultures of human fetal liver, and 6 +/- 1.5 using cultures of rat liver.
[Cosmetic Ingredient Review; Final Report of the Cosmetic Ingredient Review Expert Panel; Final Report on the Safety Assessment of Ascorbyl Palmitate, Ascorbyl Dipalmitate, Ascorbyl Stearate, Erythorbic Acid, and Sodium Erythorbate; Scientific Regulatory Reference CD-ROM (2006). Cosmetic, Toiletry, and Fragrance Association, Washington D.C.] **PEER REVIEWED**

/OTHER TOXICITY INFORMATION/ Glutathione-S-transferase (GST) activity from human term placenta and human fetal liver towards 1-chloro-2,4-dinitrobenzene as the second substrate was significantly inhibited by the saturated fatty acids, stearic (SA) and palmitic (PA) acids and fatty acid esters, ascorbyl stearate (Asc-S) and **ascorbyl palmitate (**Asc-P). The nature of inhibition of human placental GST was competitive towards CDNB with Ki values of 3.1, 10.0, 13.5 and 18.5 uM for Asc-S, Asc-P, PA and SA, respectively. The inhibitory effect of Asc-S on human term placental GST was reversible. I50 values for Asc-S, Asc-P, SA and PA were 15, 45, 83 and 78 uM, respectively, for partially purified human fetal liver GSTs and 21, 6, 88 and 117 uM, respectively, for partially pure rat liver GSTs...
[Mitra A et al; Toxicol Lett 60 (3): 281-8 (1992)] **PEER REVIEWED** PubMed Abstract

Probable Routes of Human Exposure:
NIOSH (NOES Survey 1981-1983) has statistically estimated that 3,051 workers (1,122 of these were female) were potentially exposed to **ascorbyl palmitate** in the US(1). Occupational exposure to **ascorbyl palmitate** may occur through inhalation and dermal contact with this compound at workplaces where **ascorbyl palmitate** is produced or used. Use data indicate that the general population may be exposed to **ascorbyl palmitate** via ingestion of food and via use of pharmaceutical products and antioxidants containing **ascorbyl palmitate. (**SRC)
[(1) NIOSH; NOES. National Occupational Exposure Survey conducted from 1981-1983. Estimated numbers of employees potentially exposed to specific agents by 2-digit standard industrial classification (SIC). Available from, as of May 24, 2010: http://www.cdc.gov/noes/ **PEER REVIEWED**

Emergency Medical Treatment:

Emergency Medical Treatment:

EMT Copyright Disclaimer:

The following Overview, *** VITAMINS-MULTIPLE ***, is relevant for this HSDB record chemical.

Life Support:

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o   This overview assumes that basic life support measures
       have been instituted.
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Clinical Effects:

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0.2.1 SUMMARY OF EXPOSURE
   0.2.1.1 ACUTE EXPOSURE
     A)  Toxicity following acute overdoses with multiple
         vitamin preparations is unlikely unless a massive
         amount has been ingested.
     B)  The expected signs and symptoms of toxicity would be
         that of the individual vitamin preparations, especially
         A and D and iron (see appropriate individual
         Managements). Gastrointestinal irritation and diarrhea
         are the most frequently reported findings after
         ingestion.
     C)  Most of the water soluble vitamins (folic acid,
         thiamine (B1), riboflavin (B2), cyanocobalamin (B12),
         biotin, pantothenic acid) produce no acute toxic
         symptoms. Chronic ingestion of megadoses may be a more
         serious problem. An acute intravenous overdose of
         vitamin C has resulted in renal failure.
  0.2.4 HEENT
   0.2.4.1 ACUTE EXPOSURE
     A)  Chronic administration of large doses of niacin has
         been associated with cystoid maculopathy.
  0.2.7 NEUROLOGIC
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0.2.7.1 ACUTE EXPOSURE
A) Pure sensory axonal neuropathy, with symptoms of paresthesias, numbness, pain, and weakness may occur after chronic ingestion of pyridoxine.

0.2.8 GASTROINTESTINAL
0.2.8.1 ACUTE EXPOSURE
A) Nausea, vomiting, abdominal pain, and diarrhea are common, especially following ingestion of multiple vitamins with iron (see iron management).
B) Vitamin C tablets may become lodged in the esophagus when swallowed with minimal fluids.

0.2.9 HEPATIC
0.2.9.1 ACUTE EXPOSURE
A) Chronic high-dose niacin use has been associated with both cholestatic and hepatocellular liver injury, particularly with sustained-release preparations.

0.2.10 GENITOURINARY
0.2.10.1 ACUTE EXPOSURE
A) Large intravenous doses of vitamin C may precipitate acute renal failure. Riboflavin may cause a bright yellow discoloration of urine.

0.2.13 HEMATOLOGIC
0.2.13.1 ACUTE EXPOSURE
A) Vitamin C supplementation may cause hemolytic anemia in premature neonates.

0.2.14 DERMATOLOGIC
0.2.14.1 ACUTE EXPOSURE
A) Niacin (vitamin B3) may cause intense cutaneous flushing lasting up to 2 to 3 hours with no other apparent toxicity. Nicotinamide lacks these effects. Topical vitamin E has rarely caused contact dermatitis and erythema multiforme.

0.2.19 IMMUNOLOGIC
0.2.19.1 ACUTE EXPOSURE
A) Anaphylactoid reactions occur rarely after intravenous thiamine.

0.2.20 REPRODUCTIVE HAZARDS
A) There is a well-established association between some vitamin A congeners and a teratogenic outcome in infants whose mothers were exposed during pregnancy.

Laboratory:

A) Plasma levels of the individual vitamins are not clinically useful. However, if iron toxicity is suspected, a serum iron should be determined (see IRON Management).
B) No specific lab work (CBC, electrolytes, urinalysis) is needed unless otherwise indicated.

Treatment Overview:

0.4.2 ORAL EXPOSURE
A) Gastrointestinal decontamination is not necessary in most cases. It should be considered if a potentially toxic dose of vitamin A or D has been ingested. Acute ingestion of 300,000 units of vitamin A by children or 1 million units by adults has caused toxicity (see vitamin A management for details).

B) ACTIVATED CHARCOAL: Administer charcoal as a slurry (240 mL water/30 g charcoal). Usual dose: 25 to 100 g in adults/adolescents, 25 to 50 g in children (1 to 12 years), and 1 g/kg in infants less than 1 year old.
C) Dilution with fluids may be indicated following accidental ingestion of vitamin C tablets.
D) Toxicity is unlikely following acute ingestion of multiple vitamin preparations without iron. Iron toxicity may occur following ingestion of those preparations which contain iron salts (see Multivitamins - Iron management).
E) Vitamin A toxicity may occur following massive overdose (see Vitamin A management).
F) Vitamin D toxicity may occur following massive overdose (see Vitamin D management).

Range of Toxicity:

A) Toxicity following acute overdoses of multiple vitamin preparations is unlikely unless the preparation contains significant amounts of iron, vitamin A, or vitamin D.

UNITED STATES
RECOMMENDED DAILY ALLOWANCES OF VITAMINS AND MINERALS

	Units	Adults & Children greater than 4 years age	Pregnant or Lactating women
Vitamin A	International Unit	5000	8000
Vitamin D	International Unit	400	400
Vitamin E	International Unit	30	30
Vitamin C	mg	60	60
Folic Acid	mg	0.4	0.8
Thiamine B1	mg	1.5	1.7
Riboflavin B2	mg	1.7	2
Niacin	mg	20	20
Vitamin B6	mg	2	2.5
Vitamin B12	mcg	6	8
Biotin	mg	0.3	0.3
Pantothenic Acid	mg	10	10
Calcium	g	1	1.3
Phosphorus	g	1	1.3
Iodine	mcg	150	150
Iron	mg	18	18
Magnesium	mg	400	450
Copper	mg	2	2
Zinc	mg	15	15

UNITED STATES
RECOMMENDED DAILY ALLOWANCES OF VITAMINS AND MINERALS

Units	Infants (0 to 12 mo)	Children less than 4 years	Adults and Children greater than 4 years

Vitamin A	International Unit	1500	2500	5000
Vitamin D	International Unit	400	400	400
Vitamin E	International Unit	5	10	30
Vitamin C	mg	35	40	60
Folic Acid	mg	0.1	0.2	0.4
Thiamine B1	mg	0.5	0.7	1.5
Riboflavin B2	mg	0.6	0.8	1.7
Niacin	mg	8	9	20
Vitamin B6	mg	0.4	0.7	2
Vitamin B12	mcg	2	3	6
Biotin	mg	0.05	0.15	0.3
Pantothenic Acid	mg	3	5	10
Calcium	g	0.6	0.8	1
Phosphorus	g	0.5	0.8	1
Iodine	mcg	45	70	150
Iron	mg	15	10	18
Magnesium	mg	70	200	400
Copper	mg	0.6	1	2
Zinc	mg	5	8	15

[Rumack BH POISINDEX(R) Information System Micromedex, Inc., Englewood, CO, 2011; CCIS Volume 149, edition expires Nov, 2011. Hall AH & Rumack BH (Eds): TOMES(R) Information System Micromedex, Inc., Englewood, CO, 2011; CCIS Volume 149, edition expires Nov, 2011.] **PEER REVIEWED**

Antidote and Emergency Treatment:

/SRP:/ Immediate first aid: Ensure that adequate decontamination has been carried out. If patient is not breathing, start artificial respiration, preferably with a demand valve resuscitator, bag-valve-mask device, or pocket mask, as trained. Perform CPR if necessary. Immediately flush contaminated eyes with gently flowing water. Do not induce vomiting. If vomiting occurs, lean patient forward or place on the left side (head-down position, if possible) to maintain an open airway and prevent aspiration. Keep patient quiet and maintain normal body temperature. Obtain medical attention. /Poisons A and B/

[Currance, P.L. Clements, B., Bronstein, A.C. (Eds).; Emergency Care For Hazardous Materials Exposure. 3Rd edition, Elsevier Mosby, St. Louis, MO 2005, p. 160] **PEER REVIEWED**

/SRP:/ Basic treatment: Establish a patent airway (oropharyngeal or nasopharyngeal airway, if needed). Suction if necessary. Watch for signs of respiratory insufficiency and assist ventilations if needed. Administer oxygen by nonrebreather mask at 10 to 15 L/min. Monitor for pulmonary edema and treat if necessary ... . Monitor for shock and treat if necessary ... . Anticipate seizures and treat if necessary ... . For eye contamination, flush eyes immediately with water. Irrigate each eye continuously with 0.9% saline (NS) during transport ... . Do not use emetics. For ingestion, rinse mouth and administer 5 mL/kg up to 200 mL of water for dilution if the patient

can swallow, has a strong gag reflex, and does not drool ... . Cover skin burns with dry sterile dressings after decontamination ... . /Poisons A and B/
[Currance, P.L. Clements, B., Bronstein, A.C. (Eds).; Emergency Care For Hazardous Materials Exposure. 3Rd edition, Elsevier Mosby, St. Louis, MO 2005, p. 160] **PEER REVIEWED**

/SRP:/ Advanced treatment: Consider orotracheal or nasotracheal intubation for airway control in the patient who is unconscious, has severe pulmonary edema, or is in severe respiratory distress. Positive-pressure ventilation techniques with a bag valve mask device may be beneficial. Consider drug therapy for pulmonary edema ... . Consider administering a beta agonist such as albuterol for severe bronchospasm ... . Monitor cardiac rhythm and treat arrhythmias as necessary ... . Start IV administration of D5W /SRP: "To keep open", minimal flow rate/. Use 0.9% saline (NS) or lactated Ringer's if signs of hypovolemia are present. For hypotension with signs of hypovolemia, administer fluid cautiously. Watch for signs of fluid overload ... . Treat seizures with diazepam or lorazepam ... . Use proparacaine hydrochloride to assist eye irrigation ... . /Poisons A and B/
[Currance, P.L. Clements, B., Bronstein, A.C. (Eds).; Emergency Care For Hazardous Materials Exposure. 3Rd edition, Elsevier Mosby, St. Louis, MO 2005, p. 160-1] **PEER REVIEWED**

Animal Toxicity Studies:

Non-Human Toxicity Excerpts:

/LABORATORY ANIMALS: Acute Exposure/ An aqueous (10%) solution of **ascorbyl palmitate** and undiluted ascorbyl dipalmitate were instilled into the conjunctival sac of albino rabbits in a modified Draize ocular irritancy test. The test volume was 0.1 mL. **ascorbyl palmitate** was not irritating to the eyes of rabbits, and ascorbyl dipalmitate was minimally irritating.
[Cosmetic Ingredient Review; Final Report of the Cosmetic Ingredient Review Expert Panel; Final Report on the Safety Assessment of Ascorbyl Palmitate, Ascorbyl Dipalmitate, Ascorbyl Stearate, Erythorbic Acid, and Sodium Erythorbate; Scientific Regulatory Reference CD-ROM (2006). Cosmetic, Toiletry, and Fragrance Association, Washington D.C.] **PEER REVIEWED**

/LABORATORY ANIMALS: Acute Exposure/ A 10% aqueous solution of **ascorbyl palmitate** and undiluted ascorbyl dipalmitate were nonirritating to the intact, shaved skin of albino rabbits in a modified Draize dermal irritancy test when the test materials were applied with occlusive patches for 24 hours.
[Cosmetic Ingredient Review; Final Report of the Cosmetic Ingredient Review Expert Panel; Final Report on the Safety Assessment of Ascorbyl Palmitate, Ascorbyl Dipalmitate, Ascorbyl Stearate, Erythorbic Acid, and Sodium Erythorbate; Scientific Regulatory Reference CD-ROM (2006). Cosmetic, Toiletry, and Fragrance Association, Washington D.C.] **PEER REVIEWED**

/LABORATORY ANIMALS: Subchronic or Prechronic Exposure/ Rats (10 per group) were given 2% and 5% **ascorbyl palmitate** in feed for 9 months. Significant growth retardation occurred in rats given 5% **ascorbyl palmitate,** and 2 of 10 had bladder stones and hyperplasia of

the bladder epithelium. One rat of the high dose group had lesions of nephritis. Slight growth retardation occurred in rats fed the 2% diet, but no other signs of toxicity were observed.
[Cosmetic Ingredient Review; Final Report of the Cosmetic Ingredient Review Expert Panel; Final Report on the Safety Assessment of Ascorbyl Palmitate, Ascorbyl Dipalmitate, Ascorbyl Stearate, Erythorbic Acid, and Sodium Erythorbate; Scientific Regulatory Reference CD-ROM (2006). Cosmetic, Toiletry, and Fragrance Association, Washington D.C.] **PEER REVIEWED**

/LABORATORY ANIMALS: Subchronic or Prechronic Exposure/ Female mice fed **ascorbyl palmitate** for 63 days had no signs of toxicity during a tumor inhibition study at doses up to 3000 mg/kg/day.
[Cosmetic Ingredient Review; Final Report of the Cosmetic Ingredient Review Expert Panel; Final Report on the Safety Assessment of Ascorbyl Palmitate, Ascorbyl Dipalmitate, Ascorbyl Stearate, Erythorbic Acid, and Sodium Erythorbate; Scientific Regulatory Reference CD-ROM (2006). Cosmetic, Toiletry, and Fragrance Association, Washington D.C.] **PEER REVIEWED**

/LABORATORY ANIMALS: Chronic Exposure or Carcinogenicity/ **Ascorbyl palmitate** when topically applied at small doses inhibited 12-O-tetradecanoylphorbol-13-acetate-induced (TPA-induced) ornithine decarboxylase activity, tumor production, and DNA synthesis in mouse epithelial cell. A dose of 4 umol of **ascorbyl palmitate** inhibited by 60-70% after one topical application of 2 nmol TPA. When 5 nmol TPA was administered with 5 pmol **ascorbyl palmitate** twice weekly to previously initiated mice, 91% of tumors were inhibited per mouse.
[Cosmetic Ingredient Review; Final Report of the Cosmetic Ingredient Review Expert Panel; Final Report on the Safety Assessment of Ascorbyl Palmitate, Ascorbyl Dipalmitate, Ascorbyl Stearate, Erythorbic Acid, and Sodium Erythorbate; Scientific Regulatory Reference CD-ROM (2006). Cosmetic, Toiletry, and Fragrance Association, Washington D.C.] **PEER REVIEWED**

/LABORATORY ANIMALS: Chronic Exposure or Carcinogenicity/ Female 5-week-old CF-1 mice were either fed a control diet or a diet containing 2% **ascorbyl palmitate** for 2 weeks. One half of each group (12 mice per group), was injected subcutaneously with 10 mg/kg azoxymethanol in saline, which induces formation of focal areas of dysplasia (FADs), and the other half with normal saline once weekly for 6 weeks, while fed their respective diets. One week after the last injection, the mice were given intraperitoneal injections of 25 uCi [3H] thymidine in water. An hour later, the animals were sacrificed and the colons removed and processed for microscopic examination. Multiple 500 uM sections of distal colon from each mouse were examined for the number of FADs, observed as cells with variable shape and size nuclei, lack of nuclear polarity, and a loss of mucin. Oral administration of **ascorbyl palmitate** did not produce signs of toxicity or affect body weight. Subcutaneously administered azoxymethanol induced proliferation of colonic epithelial cells and the expansion of the proliferative compartment as well as the formation of FADs. No FADs were observed in either the control mice or those fed **ascorbyl palmitate.** Also, **ascorbyl palmitate** did not inhibit proliferation of or reduce the number of induced FADs.
[Cosmetic Ingredient Review; Final Report of the Cosmetic Ingredient Review Expert Panel; Final Report on the Safety Assessment of Ascorbyl Palmitate, Ascorbyl Dipalmitate, Ascorbyl Stearate, Erythorbic Acid, and Sodium Erythorbate; Scientific Regulatory Reference CD-ROM (2006). Cosmetic, Toiletry, and Fragrance Association, Washington D.C.] **PEER REVIEWED**

/LABORATORY ANIMALS: Chronic Exposure or Carcinogenicity/ Rats (eight per group) were fed a diet of heat-treated lard containing 2% or 5% **ascorbyl palmitate (**equivalent to 424 mg/kg and 1060 mg/kg, or 0.05% and 0.25% of the total diet) during a 2-year study. Growth rate decreased at the higher dose, and two of eight rats had oxalate stones after 9 months of treatment.
[Cosmetic Ingredient Review; Final Report of the Cosmetic Ingredient Review Expert Panel; Final Report on the Safety Assessment of Ascorbyl Palmitate, Ascorbyl Dipalmitate, Ascorbyl Stearate, Erythorbic Acid, and Sodium Erythorbate; Scientific Regulatory Reference CD-ROM (2006). Cosmetic, Toiletry, and Fragrance Association, Washington D.C.] **PEER REVIEWED**

/LABORATORY ANIMALS: Chronic Exposure or Carcinogenicity/ Rats fed 125 mg **ascorbyl palmitate** per kg per day for 728 days (0.25% of diet) had no harmful effects. This intake was the equivalent of 53 mg/kg of ascorbic acid per day. In the same study, however, a different group of rats had body weight decreases at dietary doses of 2500 mg/kg/day and above. The highest dose that did not cause a toxicologic effect was 1000 mg/kg/day. Additionally, oxalate stones were observed in the urinary bladders of two of the eight rats in the second group when a dose of 2500 mg/kg/day was administered.
[Cosmetic Ingredient Review; Final Report of the Cosmetic Ingredient Review Expert Panel; Final Report on the Safety Assessment of Ascorbyl Palmitate, Ascorbyl Dipalmitate, Ascorbyl Stearate, Erythorbic Acid, and Sodium Erythorbate; Scientific Regulatory Reference CD-ROM (2006). Cosmetic, Toiletry, and Fragrance Association, Washington D.C.] **PEER REVIEWED**

/LABORATORY ANIMALS: Chronic Exposure or Carcinogenicity/ ... The modifying effect of hemicalcium ascorbate (Ca-Asc), and its lipophilic derivatives, 2-O-octadecylascorbic acid (CV-3611) and **ascorbyl palmitate (**AscP), on hepatocarcinogenesis by 3'-methyl-4-dimethylaminoazobenzene (3'-Me-DAB) /was examined/ in ODS rats (a mutant unable to synthesize ascorbic acid). Male 14-week-old ODS rats were given a modified AIN-A diet or the diet containing 0.06% 3'-Me-DAB, and drinking water containing 0.1% ascorbic acid. Rats were divided into the following eight groups: Group 1, no treatment (basal diet alone); Group 2, Ca-Asc; Group 3, CV-3611; Group 4, AscP; Group 5, 3'-Me-DAB; Group 6, 3'-Me-DAB + Ca-Asc; Group 7, 3'-Me-DAB + CV-3611; and Group 8, 3'-Me-DAB + AscP. Ca-Asc (2 g/kg), CV-3611 (0.2 g/kg), and AscP (0.6 g/kg) was administered once every day by gavage. 3'-Me-DAB was given in the basal diet. After 17 weeks, animals were killed by exsanguination, and the liver was weighed and processed for histological examination. Treatment by CV-3611 exerted a marked inhibitory effect on the development of 3'-Me-DAB-induced hepatocellular carcinomas (HCC) as measured by multiplicity. Although less effective than CV-3611, Ca-Asc and AscP also showed inhibitory effect...
[Shimpo K et al; Cancer Detect Prev 20 (2): 137-45 (1996)] **PEER REVIEWED**
PubMed Abstract

/LABORATORY ANIMALS: Chronic Exposure or Carcinogenicity/ Rats fed 5% of a 1-ascorbyl-D-isosorbyl palmitate mixture for 9 months developed bladder stones and showed retarded growth, but no effects were noted at the 2% level.
[Clayton, G. D. and F. E. Clayton (eds.). Patty's Industrial Hygiene and Toxicology: Volume 2A, 2B, 2C: Toxicology. 3rd ed. New York: John Wiley Sons, 1981-1982., p. 2290] **PEER REVIEWED**

/GENOTOXICITY/ /The authors/ performed both the Ames test, using Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, and TA 1538, and the tryptophan reversion assay using Escherichia coil strain WP2. Doses of **ascorbyl palmitate** (dissolved in 0.067 M potassium or sodium sulfate buffer at pH 7.0) from 0.01 to 3.3 mg per plate were tested, and doses greater than 3.3 mg per plate were toxic to bacteria. In both assays, **ascorbyl palmitate** was nonmutagenic. [Cosmetic Ingredient Review; Final Report of the Cosmetic Ingredient Review Expert Panel; Final Report on the Safety Assessment of Ascorbyl Palmitate, Ascorbyl Dipalmitate, Ascorbyl Stearate, Erythorbic Acid, and Sodium Erythorbate; Scientific Regulatory Reference CD-ROM (2006). Cosmetic, Toiletry, and Fragrance Association, Washington D.C.] **PEER REVIEWED**

/GENOTOXICITY/ The mechanism of antimutagenic activity of ascorbic acid (AA) and its derivatives was studied using the Salmonella typhimurium TA100 bacterial test system. All substances studied inhibited N-methyl-N'-nitro-N-nitrosoguanidine (MNNG)-induced mutagenesis. **Ascorbyl palmitate** (AP) markedly decreased the numbers of his+ revertants, behaving as a membrane-active antimutagen. A comparative study of the antioxidative activity of the investigated substances in the methyl oleate (MO) system has demonstrated that AA and its derivatives have pro-oxidant properties within the limits of the concentrations studied. The results obtained do not agree with the common view of the mode of action of these antimutagens, including both inhibition of free radical processes and MNNG reductive inactivation. [Tyrsina EG et al; Mutat Res 321 (1-2): 81-7 (1994)] **PEER REVIEWED** PubMed Abstract

/ALTERNATIVE and IN VITRO TESTS/ ... The in vitro effect of ascorbyl esters, viz., **ascorbyl-palmitate** (As-P), -stearate (As-S) and mouse interferon-alpha/beta (MulFN-alpha/beta) on /mouse glioma-26/ cell viability, proliferation and glutathione S-transferase (GST) activity was investigated. Cell viability and proliferation were examined by colorimetric MTT assay and [3H]-thymidine incorporation, respectively. Incubation (24 hr) of G-26 cells with As-S, As-P or MulFN-alpha/beta, resulted in a dose dependent decrease in cell viability (IC50 = 125 uM As-S; 175 uM As-P and 3.6 x 10+4 U/mL MulFN-alpha/beta) and proliferation (IC50 = 157 uM As-S; 185 uM As-P and 3.6 x 10+4 U/mL MulFN-alpha/beta). A combined exposure to 175 uM As-S and 800 U/mL of MulFN-alpha/beta resulted in a greater than an additive effect on cell viability and proliferation. The inhibition of cell proliferation/viability by interferon was species specific and was observed only with homologous MulFN-alpha/beta, but not with human interferon-alpha lymphoblastoid or human interferon-beta. Ascorbyl esters inhibited cytosolic GST activity (1-50 = 15.0 uM As-S and 28.5 uM As-P) towards 1-chloro-2,4-dinitrobenzene in a dose dependent manner. The apparent Ki values for affinity purified GST, deduced from Dixon plots were 0.95 uM and 2.0 uM for As-S and As-P, respectively. Significant inhibition of GST was also observed in the cytosol isolated from G-26 cells exposed to 300 uM As-S or 800 U/mL MulFN-alpha/beta.
[Naidu AK et al; J Neurooncol 16 (1): 1-10 (1993)] **PEER REVIEWED** PubMed Abstract

/ALTERNATIVE and IN VITRO TESTS/ Effects of 6-O-palmitoyl ascorbate (ascorbate) developed to increase the antitumor activity of ascorbic acid on DNA synthesis and proliferation of Ehrlich ascites tumor cells were investigated. Treatment of the cells with the acylated ascorbate at 25-50 uM for 1 hr resulted in no effect on DNA synthesis, assayed by pulse

incorporation of [3H]thymidine after a culture period of 20 hr, but led to 49%-87% enhanced DNA synthesis after 4 days, suggesting that long-term culture is required for promotion by ascorbate to occur. At a dose as high as 75 uM acylated ascorbate, however, cellular DNA synthesis was 64% inhibited after 20 hr and 99% after 4 days. The results suggest that acylated ascorbate exhibits a dual action on DNA synthesis: promotion at low doses and inhibition at high doses, both of which are potentiated in a time-dependent manner. In contrast to the above-mentioned results at 37 degrees C, acylated ascorbate at 25-75 uM inhibited but did not promote DNA synthesis at 42 degrees C whatever the culture period. Similar results were exhibited when proliferation of cells cultured for a long period was investigated. At 37 degrees C, 50 uM acylated ascorbate increased the number of the cells to 3.6 times the control values after 8 days and to 1.9 times after 11 days; in contrast, a 75-uM dose decreased the cell number considerably. Combination with hyperthermia (42 degrees C) suppressed the increase and cell growth was completely inhibited at 75 uM.
[Kageyama K et al; J Cancer Res Clin Oncol 122 (1): 41-4 (1996)] **PEER REVIEWED** PubMed Abstract

/ALTERNATIVE and IN VITRO TESTS/ Primary cultures of heart endothelial and muscle cells prepared from 2-5-day-old Wistar rats were exposed to heated corn oil. Thermally oxidized fats when ingested can result in toxicity signs such as altered fatty acid composition of tissue lipids, depressed growth, formation of pyknotic nuclei, and necrosis of other tissues. Those oxidized lipids also increased the severity of vitamin E deficiency. When 10 mg **ascorbyl palmitate** in 100 mL ethanol was emulsified and used to treat the monolayer heart cell cultures at 96 hours, the mitotic index increased, but the mean cell count values were not different. Treatment with **ascorbyl palmitate** also tended to prevent necrosis, but did not reduce intracellular lipidosis.
[Cosmetic Ingredient Review; Final Report of the Cosmetic Ingredient Review Expert Panel; Final Report on the Safety Assessment of Ascorbyl Palmitate, Ascorbyl Dipalmitate, Ascorbyl Stearate, Erythorbic Acid, and Sodium Erythorbate; Scientific Regulatory Reference CD-ROM (2006). Cosmetic, Toiletry, and Fragrance Association, Washington D.C.] **PEER REVIEWED**

/OTHER TOXICITY INFORMATION/ The effect of some additives, phenylalanine, **ascorbyl palmitate** and sodium ascorbyl phosphate on the oxidation of linoleic acid and porcine ear skin induced by UV irradiation was investigated, in the absence and in the presence of variously uncoated and coated titania powders. ... Sodium ascorbyl phosphate and **ascorbyl palmitate** displayed a stronger antioxidant effect than phenylalanine toward linoleic acid peroxidation. On porcine skin all the three molecules exhibited both antiradical and antioxidant activity. Their protective effect against peroxidation was higher with porcine skin lipids than with linoleic acid, referable to the chemical differences in the two lipid substrates.
[Carlotti ME et al; J Photochem Photobiol B 96 (2): 130-5 (2009)] **PEER REVIEWED** PubMed Abstract

Non-Human Toxicity Values:
LD50 Guinea pig dermal >3 g/kg
[Cosmetic Ingredient Review; Final Report of the Cosmetic Ingredient Review Expert Panel; Final Report on the Safety Assessment of Ascorbyl Palmitate, Ascorbyl Dipalmitate, Ascorbyl Stearate, Erythorbic Acid, and Sodium Erythorbate; Scientific Regulatory Reference CD-ROM (2006). Cosmetic, Toiletry, and Fragrance Association, Washington D.C.] **PEER REVIEWED**

LD50 Mouse oral >2 g/kg /33% suspension/
[Cosmetic Ingredient Review; Final Report of the Cosmetic Ingredient Review Expert Panel; Final Report on the Safety Assessment of Ascorbyl Palmitate, Ascorbyl Dipalmitate, Ascorbyl Stearate, Erythorbic Acid, and Sodium Erythorbate; Scientific Regulatory Reference CD-ROM (2006). Cosmetic, Toiletry, and Fragrance Association, Washington D.C.] **PEER REVIEWED**

LD50 Rat oral >5 g/kg /33% suspension/
[Cosmetic Ingredient Review; Final Report of the Cosmetic Ingredient Review Expert Panel; Final Report on the Safety Assessment of Ascorbyl Palmitate, Ascorbyl Dipalmitate, Ascorbyl Stearate, Erythorbic Acid, and Sodium Erythorbate; Scientific Regulatory Reference CD-ROM (2006). Cosmetic, Toiletry, and Fragrance Association, Washington D.C.] **PEER REVIEWED**

Metabolism/Pharmacokinetics:

Metabolism/Metabolites:
Vitamin C (ascorbic acid) is a non-enzymatic antioxidant important in protecting the lung against oxidative damage and is decreased in lung lining fluid of horses with airway inflammation. To examine possible therapeutic regimens in a species with ascorbate-synthesising capacity, ... Te effects of oral supplementation of two forms of ascorbic acid, (each equivalent to 20 mg ascorbic acid per kg body weight) on the pulmonary and systemic antioxidant status of six healthy ponies in a 3 x 3 Latin square design. Two weeks supplementation with **ascorbyl palmitate** significantly increased mean plasma ascorbic acid concentrations compared to control (29 +/-- 5 and 18 +/- 7 umol/L, respectively; $p < 0.05$). Calcium ascorbyl-2-monophosphate, a more stable form of ascorbic acid, also increased mean plasma ascorbic acid concentrations, but not significantly (23 +/- 1 umol/L; $p = 0.07$). The concentration of ascorbic acid in bronchoalveolar lavage fluid increased in five out of six ponies following supplementation with either **ascorbyl palmitate** or calcium ascorbyl-2-monophosphate compared with control (30 +/- 10, 25 +/- 4 and 18 +/- 8 umol/L, respectively; $p < 0.01$). Neither supplement altered the concentration of glutathione, uric acid or alpha-tocopherol in plasma or bronchoalveolar lavage fluid. In conclusion, the concentration of lung lining fluid ascorbic acid is increased following ascorbic acid supplementation (20 mg/kg body weight) in an ascorbate-synthesising species.
[Deaton CM et al; Free Radic Res 37 (4): 461-7 (2003)] **PEER REVIEWED** PubMed Abstract

It has been known that solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) have occlusive effects, but **ascorbyl palmitate** **(**AP) incorporation moisturized skin significantly better than placebo in short-term ($p < 0.001$) and long-term trials ($p < 0.01$) for both SLN and NLC. In the second part of the study, SLN and NLC were found to sustain the penetration of AP through excised human skin about 1/2 and 2/3 times compared to NE ($p < 0.001$ and $p < 0.01$), respectively...
[Uner M et al; Pharmazie 60 (10): 751-5 (2005)] **PEER REVIEWED** PubMed Abstract

6-O-Palmitoyl-L-ascorbic acid dissolved in a sodium taurocholate solution was hydrolyzed by homogenates of the pancreas, liver, and intestines of guinea pigs.
[INAGAKI C ET AL; VITAMINS 37(2) 147 (1968)] **PEER REVIEWED**

Absorption, Distribution & Excretion:
When incorporated into the cell membranes of human red blood cells, **ascorbyl palmitate** has been found to protect them from oxidative damage and to protect alpha-tocopherol (a fat-soluble antioxidant) from oxidation by free radicals. However, the protective effects of **ascorbyl palmitate** on cell membranes have only been demonstrated in the test tube. Taking **ascorbyl palmitate** orally probably doesn't result in any significant incorporation into cell membranes because most of it appears to be hydrolyzed (broken apart into palmitate and ascorbic acid) in the human digestive tract before it is absorbed. The ascorbic acid released by the hydrolysis of **ascorbyl palmitate** appears to be as bioavailable as ascorbic acid alone.
[Linus Pauling Institute at Oregon State University; Micronutrient Information Center; The Bioavailability of Different Forms of Vitamin C (Ascorbic Acid). Available from, as of August 8, 2010: http://lpi.oregonstate.edu/infocenter/vitamins/vitaminC/vitCform.html **PEER REVIEWED**

When applied topically to guinea pigs, **ascorbyl palmitate** penetrated the skin barrier so that ascorbic acid content in the skin, liver, and blood increased eight-, seven-, and four-fold, respectively, when compared to control animals that did not receive **ascorbyl palmitate.**
[Cosmetic Ingredient Review; Final Report of the Cosmetic Ingredient Review Expert Panel; Final Report on the Safety Assessment of Ascorbyl Palmitate, Ascorbyl Dipalmitate, Ascorbyl Stearate, Erythorbic Acid, and Sodium Erythorbate; Scientific Regulatory Reference CD-ROM (2006). Cosmetic, Toiletry, and Fragrance Association, Washington D.C.] **PEER REVIEWED**

(14)C-**Ascorbyl palmitate** was applied to the skin of scorbutic (affected by scurvy) guinea pigs. Following the topical application, ascorbic acid concentrations in the skin, liver, kidneys, and blood were four to eight times greater than in the control.
[Cosmetic Ingredient Review; Final Report of the Cosmetic Ingredient Review Expert Panel; Final Report on the Safety Assessment of Ascorbyl Palmitate, Ascorbyl Dipalmitate, Ascorbyl Stearate, Erythorbic Acid, and Sodium Erythorbate; Scientific Regulatory Reference CD-ROM (2006). Cosmetic, Toiletry, and Fragrance Association, Washington D.C.] **PEER REVIEWED**

Ascorbyl palmitate dissolved in a sodium taurocholate solution was hydrolyzed by homogenates of the liver, pancreas, and intestines of guinea pigs. Approximately 80% of **ascorbyl palmitate** was hydrolyzed to free ascorbic acid by homogenates of the small intestine and pancreas. ... **Ascorbyl palmitate** (the equivalent of 20 mg of ascorbic acid) was orally administered to guinea pigs, and the amount of free ascorbic acid excreted in the urine was measured. Greater amounts of acid were excreted at 0-24 hours than at 24-48 hours. A similar trend was found in these organs of free ascorbic acid content when L-ascorbic acid was administered instead, but a reverse tendency was observed with **ascorbyl palmitate.**
[Cosmetic Ingredient Review; Final Report of the Cosmetic Ingredient Review Expert Panel; Final Report on the Safety Assessment of Ascorbyl Palmitate, Ascorbyl Dipalmitate, Ascorbyl Stearate, Erythorbic Acid, and Sodium

Erythorbate; Scientific Regulatory Reference CD-ROM (2006). Cosmetic, Toiletry, and Fragrance Association, Washington D.C.] **PEER REVIEWED**

Mechanism of Action:
... Whether L-ascorbic acid 6-palmitate (AAP), an amphipathic derivative of AA, has chemopreventive effects /was examined/ using a gap-junctional intercellular communication (GJIC) model. AAP and ascorbic acid (AA) exhibited dose-dependent free radical-scavenging activities and inhibited hydrogen peroxide (H(2)O(2))-induced intracellular reactive oxygen species (ROS) production in normal rat liver epithelial cells. Unexpectedly, however, AAP did not protect against the inhibition of GJIC induced by H(2)O(2); instead, it inhibited GJIC synergistically with H(2)O(2). AAP inhibited GJIC in a dose-dependent and reversible manner. This inhibitory effect was not due to the conjugated lipid structure of AAP, as treatment with palmitic acid alone failed to inhibit GJIC under the same conditions. The inhibition of GJIC by AAP was restored in the presence of mitogen-activated protein kinase/extracellular signal-regulated kinase (ERK) kinase (MEK) inhibitor U0126, but not in the presence of other signal inhibitors and antioxidant (PKC inhibitors, EGFR inhibitor, NADPH oxidase inhibitor, catalase, vitamin E, or AA), indicating the critical involvement of MEK signaling in the GJIC inhibitory activity of AAP. Phosphorylation of ERK and connexin 43 (Cx43) was observed following AAP treatment, and this was reversed by U0126. These results suggest that the AAP-induced inhibition of GJIC is mediated by the phosphorylation of Cx43 via activation of the MEK-ERK pathway.
[Lee KM et al; Mutat Res 660 (1-2): 51-6 (2009)] **PEER REVIEWED** PubMed Abstract

Interactions:
Male MEl mice in which hepatotoxicity had been induced by the feeding of 600 mg/kg acetaminophen had covalent binding of acetaminophen metabolites to hepatic proteins, a depletion of hepatic nonprotein sulphydryl groups after 2 hours, and a dramatic increase in plasma alanine aminotransferase activity after 24 hours. The coadministration of acetaminophen and **ascorbyl palmitate** reduced this binding within 2 and 4 hours (to 31% and 22%, respectively), reduced the depletion in nonprotein sulfhdryl groups and aminotransferase activity, and completely prevented the 35% mortality observed at 24 hours after acetaminophen treatment alone. **Ascorbyl palmitate** appeared to prevent hepatic damage by removing the reactive acetaminophen metabolites and by having a sparing action on reduced hepatic glutathione.
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[Meves A et al; J Invest Dermatol 119 (5): 1103-8 (2002)] **PEER REVIEWED**
PubMed Abstract

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... The modifying effect of hemicalcium ascorbate (Ca-Asc), and its lipophilic derivatives, 2-O-octadecylascorbic acid (CV-3611) and **ascorbyl palmitate** (AscP), on hepatocarcinogenesis by 3'-methyl-4-dimethylaminoazobenzene (3'-Me-DAB) /was examined/ in ODS rats (a mutant unable to synthesize ascorbic acid). Male 14-week-old ODS rats were given a modified AIN-A diet or the diet containing 0.06% 3'-Me-DAB, and drinking water containing 0.1% ascorbic acid. Rats were divided into the following eight groups: Group 1, no treatment (basal diet alone); Group 2, Ca-Asc; Group 3, CV-3611; Group 4, AscP; Group 5, 3'-Me-DAB; Group 6, 3'-Me-DAB + Ca-Asc; Group 7, 3'-Me-DAB + CV-3611; and Group 8, 3'-Me-DAB + AscP. Ca-Asc (2 g/kg), CV-3611 (0.2 g/kg), and AscP (0.6 g/kg) was administered once every day by gavage. 3'-Me-DAB was given in the basal diet. After 17 weeks, animals were killed by exsanguination, and the liver was weighed and processed for histological examination. Treatment by CV-3611 exerted a marked inhibitory effect on the development of 3'-Me-DAB-induced hepatocellular carcinomas (HCC) as measured by multiplicity. Although less effective than CV-3611, Ca-Asc

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[Jonker D et al; Toxicology 52 (3): 287-95 (1988)] **PEER REVIEWED** PubMed Abstract

Groups of male Swiss-Webster mice were gavaged with acetaminophen (APAP), APAP + ascorbyl stearate (AS), or APAP + **ascorbyl palmitate** (AP) at a dose of 600 mg/kg for each chemical. APAP alone caused a significant increase in liver weight/body weight ratio and hepatic glutathione (GSH) depletion. Co-administration of the ascorbate esters AP or AS with APAP prevented an increase in liver weight/body weight ratios and hepatic glutathione depletion. APAP + AS treatments caused significantly greater reductions in rectal temperature at 15-30 min post-dosing periods when compared to APAP + AP or AS treatments. Blood levels of APAP had the same relationship. The study indicates a correlation between APAP blood levels and antipyretic effect of APAP + AS and APAP + AP coadministrations. While both ascorbate esters probably afford protection against APAP-induced hepatotoxicity in mice by reducing the reactive intermediate back to the parent compound, the APAP + AS combination provides better therapeutic efficacy as an antipyretic at the 15-30 min post-dosing periods.
[Mitra A et al; Toxicol Lett 44 (1-2): 39-46 (1988).] **PEER REVIEWED**
PubMed Abstract

Bromobenzene undergoes metabolic activation via 2,3- and 3,4-epoxidation catalyzed by the hepatic cytochrome P-450 mixed-function oxidase system. Its reactive metabolites, especially bromobenzene 3,4-oxide, presumably lead to severe centrolobular necrosis. A study of relative rate of binding of 14C-bromobenzene metabolites to hepatic microsomal protein indicated a significant difference in the rate of binding of the bromobenzene 3,4-oxide compared to its positional isomer, bromobenzene 2,3-oxide. However, the rate of bromobenzene metabolism indicated no significant difference in the formation of products o-bromophenol and p-bromophenol. A search for protective agents revealed that 6,7-dimethyl-5,6,7,8-tetrahydropterine and **ascorbyl palmitate** were very effective in protecting against macromolecular adduct formation at a concentration of 1 mM-in fact, at least a twofold increase in protection compared to the known protective agents such as glutathione or cysteine. Furthermore, 6,7-dimethyl-5,6,7,8-tetrahydropterine and **ascorbyl palmitate** inhibited the metabolism of bromobenzene over 90% at a concentration of 2.5 mM.
[Zannoni VG et al; Drug Nutr Interact 1 (3): 193-204 (1982).] **PEER REVIEWED** PubMed Abstract

The nitrosation of dipropylamine and pyrrolidine were examined in 2 phase systems comprising aqueous buffer and non-polar solvent. **Ascorbyl palmitate** generally reduced nitrosation.
[MOTTRAM DS; PATTERSON RLS; J SCI FOOD AGRIC 20(4) 352 (1977)] **PEER REVIEWED**

Pharmacology:

Therapeutic Uses:
Antimutagenic Agents; Antioxidants
[National Library of Medicine's Medical Subject Headings online file (MeSH, 1999)] **PEER REVIEWED**

Ascorbyl palmitate has a vitamin C activity approximately equal to that of L-ascorbic acid. ... Vitamin C is an essential cofactor for prolyl and lysyl hydroxylases, the enzymes involved in the

intracellular biosynthesis of collagen.
[Cosmetic Ingredient Review; Final Report of the Cosmetic Ingredient Review Expert Panel; Final Report on the Safety Assessment of Ascorbyl Palmitate, Ascorbyl Dipalmitate, Ascorbyl Stearate, Erythorbic Acid, and Sodium Erythorbate; Scientific Regulatory Reference CD-ROM (2006). Cosmetic, Toiletry, and Fragrance Association, Washington D.C.] **PEER REVIEWED**

/Experimental Therapy/ QR-333, a topical compound that contains quercetin, a flavonoid with aldose reductase inhibitor effects, **ascorbyl palmitate,** and vitamin D(3), was formulated to decrease the oxidative stress that contributes to peripheral diabetic neuropathy and thus alleviate its symptoms. ... This randomized, placebo-controlled, double-blind trial included 34 men and women (21-71 years of age) with Type 1 or 2 diabetes and diabetic neuropathy who applied QR-333 or placebo (2:1 ratio), three times daily for 4 weeks, to each foot where symptoms were experienced. ... QR-333 reduced the severity of numbness, jolting pain, and irritation from baseline values. Improvements were also seen in overall and specific quality-of-life measures. QR-333 was well tolerated. Eleven patients in the QR-333 group reported 23 adverse events (all mild or moderate); 4 in the placebo group reported 5 events (all moderate). One patient who applied QR-333 noted a pricking sensation twice, the only adverse event considered possibly related to study treatment...
[Valensi P et al; Diabetes Complications 19 (5): 247-53 (2005)] **PEER REVIEWED** PubMed Abstract

The presence of **ascorbyl palmitate** in oral supplements contributes to the ascorbic acid content of the supplement and probably helps protect fat-soluble antioxidants in the supplement.
[Linus Pauling Institute at Oregon State University; Micronutrient Information Center; The Bioavailability of Different Forms of Vitamin C (Ascorbic Acid). Available from, as of August 8, 2010: http://lpi.oregonstate.edu/infocenter/vitamins/vitaminC/vitCform.html **PEER REVIEWED**

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Groups of male Swiss-Webster mice were gavaged with acetaminophen (APAP), APAP + ascorbyl stearate (AS), or APAP + **ascorbyl palmitate** (AP) at a dose of 600 mg/kg for each chemical. APAP alone caused a significant increase in liver weight/body weight ratio and hepatic glutathione (GSH) depletion. Co-administration of the ascorbate esters AP or AS with APAP prevented an increase in liver weight/body weight ratios and hepatic glutathione depletion. APAP + AS treatments caused significantly greater reductions in rectal temperature at 15-30 min post-dosing periods when compared to APAP + AP or AS treatments. Blood levels of APAP had the same relationship. The study indicates a correlation between APAP blood levels and antipyretic effect of APAP + AS and APAP + AP coadministrations. While both ascorbate esters probably afford protection against APAP-induced hepatotoxicity in mice by reducing the reactive intermediate back to the parent compound, the APAP + AS combination provides better therapeutic efficacy as an antipyretic at the 15-30 min post-dosing periods.
[Mitra A et al; Toxicol Lett 44 (1-2): 39-46 (1988).] **PEER REVIEWED** PubMed Abstract

Bromobenzene undergoes metabolic activation via 2,3- and 3,4-epoxidation catalyzed by the hepatic cytochrome P-450 mixed-function oxidase system. Its reactive metabolites, especially bromobenzene 3,4-oxide, presumably lead to severe centrolobular necrosis. A study of relative rate of binding of 14C-bromobenzene metabolites to hepatic microsomal protein indicated a significant difference in the rate of binding of the bromobenzene 3,4-oxide compared to its positional isomer, bromobenzene 2,3-oxide. However, the rate of bromobenzene metabolism indicated no significant difference in the formation of products o-bromophenol and p-bromophenol. A search for protective agents revealed that 6,7-dimethyl-5,6,7,8-tetrahydropterine and **ascorbyl palmitate** were very effective in protecting against macromolecular adduct formation at a concentration of 1 mM-in fact, at least a twofold increase in protection compared to the known protective agents such as glutathione or cysteine. Furthermore, 6,7-dimethyl-5,6,7,8-tetrahydropterine and **ascorbyl palmitate** inhibited the metabolism of bromobenzene over 90% at a concentration of 2.5 mM.
[Zannoni VG et al; Drug Nutr Interact 1 (3): 193-204 (1982).] **PEER REVIEWED** PubMed Abstract

The nitrosation of dipropylamine and pyrrolidine were examined in 2 phase systems comprising aqueous buffer and non-polar solvent. **Ascorbyl palmitate** generally reduced nitrosation.
[MOTTRAM DS; PATTERSON RLS; J SCI FOOD AGRIC 20(4) 352 (1977)] **PEER REVIEWED**

Environmental Fate & Exposure:

Environmental Fate/Exposure Summary:

Ascorbyl palmitate's production and use as an antioxidant and as a chemical preservative food additive may result in its release to the environment through various waste streams. If released to

air, an estimated vapor pressure of 2.09X10-15 mm Hg at 25 deg C indicates **ascorbyl palmitate** will exist solely in the particulate phase in the atmosphere. Particulate-phase **ascorbyl palmitate** will be removed from the atmosphere by wet or dry deposition. **Ascorbyl palmitate** does not contain chromophores that absorb at wavelengths >290 nm, and therefore is not expected to be susceptible to direct photolysis by sunlight. If released to soil, **ascorbyl palmitate** is expected to have moderate mobility based upon an estimated Koc of 450. Volatilization from moist soil surfaces is not expected to be an important fate process based upon an estimated Henry's Law constant of 1.4X10-7 atm-cu m/mole. Biodegradation data were not available. If released into water, **ascorbyl palmitate** is expected to adsorb to suspended solids and sediment based upon the estimated Koc. Volatilization from water surfaces is not expected to be an important fate process based upon this compound's estimated Henry's Law constant. An estimated BCF of 180 suggests the potential for bioconcentration in aquatic organisms is high, provided the compound is not metabolized by the organism. An estimated base-catalyzed second-order hydrolysis rate constant of 2.85X10-2 L/mole-sec corresponds to half-lives of 7.7 years and 280 days at pH values of 7 and 8, respectively. Occupational exposure to **ascorbyl palmitate** may occur through inhalation and dermal contact with this compound at workplaces where **ascorbyl palmitate** is produced or used. Use data indicate that the general population may be exposed to **ascorbyl palmitate** via ingestion of food and via use of pharmaceutical products and antioxidants containing **ascorbyl palmitate. (**SRC)
PEER REVIEWED

Probable Routes of Human Exposure:
NIOSH (NOES Survey 1981-1983) has statistically estimated that 3,051 workers (1,122 of these were female) were potentially exposed to **ascorbyl palmitate** in the US(1). Occupational exposure to **ascorbyl palmitate** may occur through inhalation and dermal contact with this compound at workplaces where **ascorbyl palmitate** is produced or used. Use data indicate that the general population may be exposed to **ascorbyl palmitate** via ingestion of food and via use of pharmaceutical products and antioxidants containing **ascorbyl palmitate. (**SRC)
[(1) NIOSH; NOES. National Occupational Exposure Survey conducted from 1981-1983. Estimated numbers of employees potentially exposed to specific agents by 2-digit standard industrial classification (SIC). Available from, as of May 24, 2010: http://www.cdc.gov/noes/ **PEER REVIEWED**

Artificial Pollution Sources:
Ascorbyl palmitate's production and use as an antioxidant and as a chemical preservative food additive(1) may result in its release to the environment through various waste streams(SRC).
[(1) Cosmetic Ingredient Review; Final Report of the Cosmetic Ingredient Review Expert Panel; Final Report on the Safety Assessment of Ascorbyl Palmitate, Ascorbyl Dipalmitate, Ascorbyl Stearate, Erythorbic Acid, and Sodium Erythorbate; Scientific Regulatory Reference CD-ROM (2006). Cosmetic, Toiletry, and Fragrance Association, Washington D.C.] **PEER REVIEWED**

Environmental Fate:
TERRESTRIAL FATE: Based on a classification scheme(1), an estimated Koc value of 450(SRC), determined from a structure estimation method(2), indicates that **ascorbyl palmitate**

is expected to have moderate mobility in soil(SRC). Volatilization of **ascorbyl palmitate** from moist soil surfaces is not expected to be an important fate process(SRC) given an estimated Henry's Law constant of 1.4X10-7 atm-cu m/mole(SRC), using a fragment constant estimation method(3). **Ascorbyl palmitate** is not expected to volatilize from dry soil surfaces(SRC) based upon an estimated vapor pressure of 2.09X10-15 mm Hg at 25 deg C(SRC), determined from a fragment constant method(4). Biodegradation data in soil were not available(SRC, 2010).
[(1) Swann RL et al; Res Rev 85: 17-28 (1983) (2) US EPA; Estimation Program Interface (EPI) Suite. Ver. 4.0. Jan, 2009. Available from, as of May 21, 2010: http://www.epa.gov/oppt/exposure/pubs/episuitedl.htm (3) Meylan WM, Howard PH; Environ Toxicol Chem 10: 1283-93 (1991) (4) Lyman WJ; p. 31 in Environmental Exposure From Chemicals Vol I, Neely WB, Blau GE, eds, Boca Raton, FL: CRC Press (1985)] **PEER REVIEWED**

AQUATIC FATE: Based on a classification scheme(1), an estimated Koc value of 450(SRC), determined from a structure estimation method(2), indicates that **ascorbyl palmitate** is expected to adsorb to suspended solids and sediment(SRC). Volatilization from water surfaces is not expected(3) based upon an estimated Henry's Law constant of 1.4X10-7 atm-cu m/mole(SRC), developed using a fragment constant estimation method(4). According to a classification scheme(5), an estimated BCF of 180(SRC), from an estimated log Kow of 6.0(6) and a regression-derived equation(2), suggests the potential for bioconcentration in aquatic organisms is high, provided the compound is not metabolized by the organism(SRC). Biodegradation data in water were not available(SRC, 2010).
[(1) Swann RL et al; Res Rev 85: 17-28 (1983) (2) US EPA; Estimation Program Interface (EPI) Suite. Ver. 4.0. Jan, 2009. Available from, as of May 21, 2010: http://www.epa.gov/oppt/exposure/pubs/episuitedl.htm (3) Lyman WJ et al; Handbook of Chemical Property Estimation Methods. Washington, DC: Amer Chem Soc pp. 15-1 to 15-29 (1990) (4) Meylan WM, Howard PH; Environ Toxicol Chem 10: 1283-93 (1991) (5) Franke C et al; Chemosphere 29: 1501-14 (1994) (6) Meylan WM, Howard PH; J Pharm Sci 84: 83-92 (1995)] **PEER REVIEWED**

ATMOSPHERIC FATE: According to a model of gas/particle partitioning of semivolatile organic compounds in the atmosphere(1), **ascorbyl palmitate,** which has an estimated vapor pressure of 2.09X10-15 mm Hg at 25 deg C(SRC), determined from a fragment constant method(2), is expected to exist solely in the particulate phase in the ambient atmosphere. Particulate-phase **ascorbyl palmitate** may be removed from the air by wet or dry deposition(SRC). **Ascorbyl palmitate** does not contain chromophores that absorb at wavelengths >290 nm(3), and therefore is not expected to be susceptible to direct photolysis by sunlight(SRC).
[(1) Bidleman TF; Environ Sci Technol 22: 361-367 (1988) (2) Lyman WJ; p. 31 in Environmental Exposure From Chemicals Vol I, Neely WB, Blau GE, eds, Boca Raton, FL: CRC Press (1985) (3) Lyman WJ et al; Handbook of Chemical Property Estimation Methods. Washington, DC: Amer Chem Soc pp. 8-12 (1990)] **PEER REVIEWED**

Environmental Abiotic Degradation:
A base-catalyzed second-order hydrolysis rate constant of 2.85X10-2 L/mole-sec(SRC) was estimated using a structure estimation method(1); this corresponds to half-lives of 7.7 years and 280 days at pH values of 7 and 8, respectively(1). **Ascorbyl palmitate** does not contain chromophores that absorb at wavelengths >290 nm(2), and therefore is not expected to be

susceptible to direct photolysis by sunlight(SRC).
[(1) Mill T et al; Environmental Fate and Exposure Studies Development of a PC-SAR for Hydrolysis: Esters, Alkyl Halides and Epoxides. EPA Contract No. 68-02-4254. Menlo Park, CA: SRI International (1987) (2) Lyman WJ et al; Handbook of Chemical Property Estimation Methods. Washington, DC: Amer Chem Soc pp. 8-12 (1990)] **PEER REVIEWED**

Environmental Bioconcentration:
An estimated BCF of 180 was calculated in fish for **ascorbyl palmitate** (SRC), using an estimated log Kow of 6.0(1) and a regression-derived equation(2). According to a classification scheme(3), this BCF suggests the potential for bioconcentration in aquatic organisms is high(SRC), provided the compound is not metabolized by the organism(SRC).
[(1) Meylan WM, Howard PH; J Pharm Sci 84: 83-92 (1995) (2) US EPA; Estimation Program Interface (EPI) Suite. Ver. 4.0. Jan, 2009. Available from, as of May 21, 2010: http://www.epa.gov/oppt/exposure/pubs/episuitedl.htm (3) Franke C et al; Chemosphere 29: 1501-14 (1994)] **PEER REVIEWED**

Soil Adsorption/Mobility:
Using a structure estimation method based on molecular connectivity indices(1), the Koc of **ascorbyl palmitate** can be estimated to be 450(SRC). According to a classification scheme(2), this estimated Koc value suggests that **ascorbyl palmitate** is expected to have moderate mobility in soil.
[(1) US EPA; Estimation Program Interface (EPI) Suite. Ver. 4.0. Jan, 2009. Available from, as of May 21, 2010: http://www.epa.gov/oppt/exposure/pubs/episuitedl.htm (2) Swann RL et al; Res Rev 85: 17-28 (1983)] **PEER REVIEWED**

Volatilization from Water/Soil:
The Henry's Law constant for **ascorbyl palmitate** is estimated as 1.4X10-7 atm-cu m/mole(SRC) using a fragment constant estimation method(1). This Henry's Law constant indicates that **ascorbyl palmitate** is expected to be essentially nonvolatile from water surfaces(2). **Ascorbyl palmitate** is not expected to volatilize from dry soil surfaces(SRC) based upon an estimated vapor pressure of 2.09X10-15 mm Hg(SRC), determined from a fragment constant method(3).
[(1) Meylan WM, Howard PH; Environ Toxicol Chem 10: 1283-93 (1991) (2) Lyman WJ et al; Handbook of Chemical Property Estimation Methods. Washington, DC: Amer Chem Soc pp. 15-1 to 15-29 (1990) (3) Lyman WJ; p. 31 in Environmental Exposure From Chemicals Vol I, Neely WB, Blau GE, eds, Boca Raton, FL: CRC Press (1985)] **PEER REVIEWED**

Environmental Standards & Regulations:

FIFRA Requirements:
Residues of **ascorbyl palmitate** are exempted from the requirement of a tolerance when used in accordance with good agricultural practice as inert (or occasionally active) ingredients in

pesticide formulations applied to growing crops or to raw agricultural commodities after harvest. Use: preservative.
[40 CFR 180.910 (USEPA); U.S. National Archives and Records Administration's Electronic Code of Federal Regulations. Available from, as of July 8, 2010: http://www.gpoaccess.gov/ecfr **PEER REVIEWED**

Residues of **ascorbyl palmitate** are exempted from the requirement of a tolerance when used in accordance with good agricultural practice as inert (or occasionally active) ingredients in pesticide formulations applied to animals. Use: preservative.
[40 CFR 180.930 (USEPA); U.S. National Archives and Records Administration's Electronic Code of Federal Regulations. Available from, as of August 4, 2010: http://www.gpoaccess.gov/ecfr **PEER REVIEWED**

FDA Requirements:
Ascorbyl palmitate used as a chemical preservative in food for human consumption is generally recognized as safe when used in accordance with good manufacturing practice.
[21 CFR 182.3149; U.S. National Archives and Records Administration's Electronic Code of Federal Regulations. Available from, as of August 4, 2010: http://www.gpoaccess.gov/ecfr **PEER REVIEWED**

Ascorbyl palmitate used as a chemical preservative in animal drugs, feeds, and related products is generally recognized as safe when used in accordance with good manufacturing or feeding practice.
[21 CFR 582.3149; U.S. National Archives and Records Administration's Electronic Code of Federal Regulations. Available from, as of August 4, 2010: http://www.gpoaccess.gov/ecfr **PEER REVIEWED**

Allowable Tolerances:
Residues of **ascorbyl palmitate** are exempted from the requirement of a tolerance when used in accordance with good agricultural practice as inert (or occasionally active) ingredients in pesticide formulations applied to growing crops or to raw agricultural commodities after harvest. Use: preservative.
[40 CFR 180.910 (USEPA); U.S. National Archives and Records Administration's Electronic Code of Federal Regulations. Available from, as of July 8, 2010: http://www.gpoaccess.gov/ecfr **PEER REVIEWED**

Residues of **ascorbyl palmitate** are exempted from the requirement of a tolerance when used in accordance with good agricultural practice as inert (or occasionally active) ingredients in pesticide formulations applied to animals. Use: preservative.
[40 CFR 180.930 (USEPA); U.S. National Archives and Records Administration's Electronic Code of Federal Regulations. Available from, as of August 4, 2010: http://www.gpoaccess.gov/ecfr **PEER REVIEWED**

Chemical/Physical Properties:

Molecular Formula:
C22-H38-O7
PEER REVIEWED

Molecular Weight:
414.533
[Lide, D.R. CRC Handbook of Chemistry and Physics 88TH Edition 2007-2008. CRC Press, Taylor & Francis, Boca Raton, FL 2007, p. 3-28] **PEER REVIEWED**

Color/Form:
White or yellowish white powder
[Lewis, R.J. Sr.; Hawley's Condensed Chemical Dictionary 15th Edition. John Wiley & Sons, Inc. New York, NY 2007., p. 103] **PEER REVIEWED**

Odor:
Citrus-like
[Lewis, R.J. Sr.; Hawley's Condensed Chemical Dictionary 15th Edition. John Wiley & Sons, Inc. New York, NY 2007., p. 103] **PEER REVIEWED**

Melting Point:
112 deg C
[Lide, D.R. CRC Handbook of Chemistry and Physics 88TH Edition 2007-2008. CRC Press, Taylor & Francis, Boca Raton, FL 2007, p. 3-28] **PEER REVIEWED**

Octanol/Water Partition Coefficient:
log Kow = 6.00 (est)
[US EPA; Estimation Program Interface (EPI) Suite. Ver. 4.0. Jan, 2009. Available from, as of May 21, 2010: http://www.epa.gov/oppt/exposure/pubs/episuitedl.htm **PEER REVIEWED**

Solubilities:
Soluble in alcohol, animal oil, and vegetable oil; slightly soluble in water
[Lewis, R.J. Sr.; Hawley's Condensed Chemical Dictionary 15th Edition. John Wiley & Sons, Inc. New York, NY 2007., p. 103] **PEER REVIEWED**

In water, 7.44X10-2 mg/L at 25 deg C (est)
[US EPA; Estimation Program Interface (EPI) Suite. Ver. 4.0. Jan, 2009. Available from, as of May 21, 2010: http://www.epa.gov/oppt/exposure/pubs/episuitedl.htm **PEER REVIEWED**

Spectral Properties:
Specific optical rotation: +23 deg at 20 deg C, c = 1 in ethanol
[Aldrich; Handbook of Fine Chemicals and Laboratory Equipment. 2009-2010.

Milwaukee, WI: Aldrich Chem Co. p. 2057 (2009)] **PEER REVIEWED**

Vapor Pressure:
2.09X10-15 mm Hg at 25 deg C (est)
[US EPA; Estimation Program Interface (EPI) Suite. Ver. 4.0. Jan, 2009. Available from, as of May 21, 2010: http://www.epa.gov/oppt/exposure/pubs/episuitedl.htm **PEER REVIEWED**

Other Chemical/Physical Properties:
Weight/volume conversion: 16.92 mg/cu m approximately equal to 1 ppm
[Clayton, G. D. and F. E. Clayton (eds.). Patty's Industrial Hygiene and Toxicology: Volume 2A, 2B, 2C: Toxicology. 3rd ed. New York: John Wiley Sons, 1981-1982., p. 2284] **PEER REVIEWED**

Henry's Law constant = 1.40X10-7 atm-cu m/mol at 25 deg C (est)
[US EPA; Estimation Program Interface (EPI) Suite. Ver. 4.0. Jan, 2009. Available from, as of May 21, 2010: http://www.epa.gov/oppt/exposure/pubs/episuitedl.htm **PEER REVIEWED**

Base-catalyzed second-order hydrolysis reaction rate constant = 2.85X10-2 L/mol-sec at 25 deg C (est)
[US EPA; Estimation Program Interface (EPI) Suite. Ver. 4.0. Jan, 2009. Available from, as of May 21, 2010: http://www.epa.gov/oppt/exposure/pubs/episuitedl.htm **PEER REVIEWED**

Chemical Safety & Handling:

Disposal Methods:
SRP: Criteria for land treatment or burial (sanitary landfill) disposal practices are subject to significant revision. Prior to implementing land disposal of waste residue (including waste sludge), consult with environmental regulatory agencies for guidance on acceptable disposal practices.
PEER REVIEWED

Occupational Exposure Standards:

Manufacturing/Use Information:

Major Uses:
Ascorbyl palmitate is an antioxidant. It is used as a chemical preservative food additive and as an antioxidant in pharmaceuticals. ...Its use as a preservative in margarine is limited to 0.02% percent by weight of the finished food. **Ascorbyl palmitate** in foods prevents rancidity and the

browning of cut apples. It is also used in meat curing, to preserve canned and frozen foods.
[Cosmetic Ingredient Review; Final Report of the Cosmetic Ingredient Review Expert Panel; Final Report on the Safety Assessment of Ascorbyl Palmitate, Ascorbyl Dipalmitate, Ascorbyl Stearate, Erythorbic Acid, and Sodium Erythorbate; Scientific Regulatory Reference CD-ROM (2006). Cosmetic, Toiletry, and Fragrance Association, Washington D.C.] **PEER REVIEWED**

Source of vitamin C; stabilizer; emulsifier
[Lewis, R.J. Sr.; Hawley's Condensed Chemical Dictionary 15th Edition. John Wiley & Sons, Inc. New York, NY 2007., p. 103] **PEER REVIEWED**

ANTIOXIDANT SYNERGIST IN FATS & OILS
[SRI] **PEER REVIEWED**

Medication
PEER REVIEWED

Manufacturers:
A.M. Todd Company, 1717 Douglas Avenue, Kalamazoo, MI 49007, U.S.A.
[Directory of World Chemical Producers, Chemical Information Services, 9101 LBJ Frwy., Suite 310, Dallas, TX 75243, (214) 349-6200. Date downloaded: September 2009. Available from, as of May 24, 2010: http://www.chemicalinfo.com/products/dwcp/dwcp_overview.htm **PEER REVIEWED**

ChemPacific Corporation, 6200 Freeport Center, Baltimore, MD 21224, U.S.A.
[Directory of World Chemical Producers, Chemical Information Services, 9101 LBJ Frwy., Suite 310, Dallas, TX 75243, (214) 349-6200. Date downloaded: September 2009. Available from, as of May 24, 2010: http://www.chemicalinfo.com/products/dwcp/dwcp_overview.htm **PEER REVIEWED**

Crystal Chemie Pvt. Ltd., 3810/09/11 GIDC Industrial Estate Ankleshwar Bharuch, Gujarat 393002, India
[Directory of World Chemical Producers, Chemical Information Services, 9101 LBJ Frwy., Suite 310, Dallas, TX 75243, (214) 349-6200. Date downloaded: September 2009. Available from, as of May 24, 2010: http://www.chemicalinfo.com/products/dwcp/dwcp_overview.htm **PEER REVIEWED**

Danisco A/S, Langebrogade 1 1001 Copenhagen, Denmark
[Directory of World Chemical Producers, Chemical Information Services, 9101 LBJ Frwy., Suite 310, Dallas, TX 75243, (214) 349-6200. Date downloaded: September 2009. Available from, as of May 24, 2010: http://www.chemicalinfo.com/products/dwcp/dwcp_overview.htm **PEER REVIEWED**

Danisco Brasil Ltda., Rodovia Raposo Tavares km 27.2 06707-000 Cotia (SP), Brazil
[Directory of World Chemical Producers, Chemical Information Services, 9101 LBJ Frwy., Suite 310, Dallas, TX 75243, (214) 349-6200. Date downloaded: September 2009. Available from, as of May 24, 2010: http://www.chemicalinfo.com/products/dwcp/dwcp_overview.htm **PEER REVIEWED**

Gangwal Chemicals Pvt. Ltd., 306, Business Classic, Chincholi Bunder Road, Malad West Mumbai 400.064, India

[Directory of World Chemical Producers, Chemical Information Services, 9101 LBJ Frwy., Suite 310, Dallas, TX 75243, (214) 349-6200. Date downloaded: September 2009. Available from, as of May 24, 2010: http://www.chemicalinfo.com/products/dwcp/dwcp_overview.htm **PEER REVIEWED**

Hangzhou Fuyuan Fabric Material Co., Ltd. (Hangzhou Garden Trading Co), Sanxin Mansion, 7/F, 33-35, Xintang Road Hangzhou, Zhejiang 310020, China
[Directory of World Chemical Producers, Chemical Information Services, 9101 LBJ Frwy., Suite 310, Dallas, TX 75243, (214) 349-6200. Date downloaded: September 2009. Available from, as of May 24, 2010: http://www.chemicalinfo.com/products/dwcp/dwcp_overview.htm **PEER REVIEWED**

Hawkins, Inc., 3100 East Hennepin Ave., Minneapolis, MN 55413, U.S.A.
[Directory of World Chemical Producers, Chemical Information Services, 9101 LBJ Frwy., Suite 310, Dallas, TX 75243, (214) 349-6200. Date downloaded: September 2009. Available from, as of May 24, 2010: http://www.chemicalinfo.com/products/dwcp/dwcp_overview.htm **PEER REVIEWED**

Huzhou Longs Biochem Co., Ltd., Room C213, 699 Qingtong Road Huzhou City, Zhejiang Province 313000, China
[Directory of World Chemical Producers, Chemical Information Services, 9101 LBJ Frwy., Suite 310, Dallas, TX 75243, (214) 349-6200. Date downloaded: September 2009. Available from, as of May 24, 2010: http://www.chemicalinfo.com/products/dwcp/dwcp_overview.htm **PEER REVIEWED**

Jiangxi Liming Pharmaceutical Factory, Liming Road Jingdezhen City, Jiangxi Province 333032, China
[Directory of World Chemical Producers, Chemical Information Services, 9101 LBJ Frwy., Suite 310, Dallas, TX 75243, (214) 349-6200. Date downloaded: September 2009. Available from, as of May 24, 2010: http://www.chemicalinfo.com/products/dwcp/dwcp_overview.htm **PEER REVIEWED**

Kaiyuan Hengtai Fine Chemicals Factory, 33 Zhaogong North Street Shengyang City 110026, China
[Directory of World Chemical Producers, Chemical Information Services, 9101 LBJ Frwy., Suite 310, Dallas, TX 75243, (214) 349-6200. Date downloaded: September 2009. Available from, as of May 24, 2010: http://www.chemicalinfo.com/products/dwcp/dwcp_overview.htm **PEER REVIEWED**

Liaoyang Zhongnuo Chemical Industry Co., Ltd., 248 Zhenxing Road, Taizihe District Liaoyang City, Liaoning Province 111000, China
[Directory of World Chemical Producers, Chemical Information Services, 9101 LBJ Frwy., Suite 310, Dallas, TX 75243, (214) 349-6200. Date downloaded: September 2009. Available from, as of May 24, 2010: http://www.chemicalinfo.com/products/dwcp/dwcp_overview.htm **PEER REVIEWED**

Merck KGaA - Performance & Life Science Chemicals, Frankfurter Strasse 250 34271 Darmstadt, Germany
[Directory of World Chemical Producers, Chemical Information Services, 9101 LBJ Frwy., Suite 310, Dallas, TX 75243, (214) 349-6200. Date downloaded: September 2009. Available from, as of May 24, 2010: http://www.chemicalinfo.com/products/dwcp/dwcp_overview.htm **PEER REVIEWED**

Nikko Chemicals Co. Ltd., 1-4-8 Nihonbashi-Bakurocho, Chuoku Tokyo 103-0002, Japan
[Directory of World Chemical Producers, Chemical Information Services, 9101 LBJ Frwy., Suite 310, Dallas, TX 75243, (214) 349-6200. Date downloaded: September 2009. Available from, as of May 24, 2010: http://www.chemicalinfo.com/products/dwcp/dwcp_overview.htm **PEER REVIEWED**

Shanghai Sunve Pharmaceutical Co. Ltd., 22/F, Sunve Building, 356 Aomen Road Shanghai 200060, China
[Directory of World Chemical Producers, Chemical Information Services, 9101 LBJ Frwy., Suite 310, Dallas, TX 75243, (214) 349-6200. Date downloaded: September 2009. Available from, as of May 24, 2010: http://www.chemicalinfo.com/products/dwcp/dwcp_overview.htm **PEER REVIEWED**

Spec-Chem Industries, 90 East Zhongshan Road Nanjing 210002, China
[Directory of World Chemical Producers, Chemical Information Services, 9101 LBJ Frwy., Suite 310, Dallas, TX 75243, (214) 349-6200. Date downloaded: September 2009. Available from, as of May 24, 2010: http://www.chemicalinfo.com/products/dwcp/dwcp_overview.htm **PEER REVIEWED**

Urmila Chemopharma (P) Ltd., 1 Kiran, Dada Patil Road, Opp. Pethe, Jewellers, Naupada Thane, Mumbai 400.602, India
[Directory of World Chemical Producers, Chemical Information Services, 9101 LBJ Frwy., Suite 310, Dallas, TX 75243, (214) 349-6200. Date downloaded: September 2009. Available from, as of May 24, 2010: http://www.chemicalinfo.com/products/dwcp/dwcp_overview.htm **PEER REVIEWED**

Yasho Industries Pvt. Ltd., 31-H, Laxmi Industrial Estate, New Link Road, Andheri West Mumbai, Maharashtra 400.053, India
[Directory of World Chemical Producers, Chemical Information Services, 9101 LBJ Frwy., Suite 310, Dallas, TX 75243, (214) 349-6200. Date downloaded: September 2009. Available from, as of May 24, 2010: http://www.chemicalinfo.com/products/dwcp/dwcp_overview.htm **PEER REVIEWED**

Zhejiang Ruibang Laboratories, 48 Feixia Road Wenzhou 325027, China
[Directory of World Chemical Producers, Chemical Information Services, 9101 LBJ Frwy., Suite 310, Dallas, TX 75243, (214) 349-6200. Date downloaded: September 2009. Available from, as of May 24, 2010: http://www.chemicalinfo.com/products/dwcp/dwcp_overview.htm **PEER REVIEWED**

Zhejiang Tianxin Pharmaceutical Co,. Ltd., 215 Fengze Road Tiantai County, Zhejiang Province 317200, China
[Directory of World Chemical Producers, Chemical Information Services, 9101 LBJ Frwy., Suite 310, Dallas, TX 75243, (214) 349-6200. Date downloaded: September 2009. Available from, as of May 24, 2010: http://www.chemicalinfo.com/products/dwcp/dwcp_overview.htm **PEER REVIEWED**

Methods of Manufacturing:
Ascorbyl palmitate is prepared by condensing palmitoyl chloride and ascorbic acid in the presence of a dehydrochlorinating agent such as pyridine. It is also formed in the reaction of L-

ascorbic acid and palmitic acid.
[Cosmetic Ingredient Review; Final Report of the Cosmetic Ingredient Review Expert Panel; Final Report on the Safety Assessment of Ascorbyl Palmitate, Ascorbyl Dipalmitate, Ascorbyl Stearate, Erythorbic Acid, and Sodium Erythorbate; Scientific Regulatory Reference CD-ROM (2006). Cosmetic, Toiletry, and Fragrance Association, Washington D.C.] **PEER REVIEWED**

General Manufacturing Information:
Ascorbyl palmitate is an antioxidant in foods containing vegetable oil and animal fats; more recently it has appeared in the neutraceutical pantheon under the name "ester-C."
[Block JH; Kirk-Othmer Encyclopedia of Chemical Technology. (2006). New York, NY: John Wiley & Sons; Vitamins, Survey. Online Posting Date: June 16, 2006.] **PEER REVIEWED**

Active compounds can be protected against degradation by incorporation into colloidal carrier systems. The stabilizing effect of carrier systems for **ascorbyl palmitate** (AP) was investigated using microemulsions (ME), liposomes and solid lipid nanoparticles (SLN). Analysis of chemical stability by HPLC showed that AP is most resistant against oxidation in non-hydrogenated soybean lecithin liposomes, followed by SLN, w/o and o/w ME, and hydrogenated soybean lecithin liposomes...
[Kristl J et al; Eur J Pharm Sci 19 (4): 181-9 (2003)] **PEER REVIEWED** PubMed Abstract

Ascorbic acid (AA), also known as vitamin C, is a very popular skin-whitening agent used in cosmetics. However, the use of AA (and also its sodium or magnesium salts) in cosmetic products is limited owing to its labile oxidative properties. In order to avoid its early degradation, different derivatives have been designed, such as ascorbyl phosphate (APH; as magnesium or sodium salts) and **ascorbyl palmitate** (AP), and more recently the ascorbyl glucoside (AG).
[Balaguer A et al; J Sep Sci 31 (2): 229-36 (2008)] **PEER REVIEWED** PubMed Abstract

Formulations/Preparations:
Grade: FCC (Foods Chemical Codex).
[Lewis, R.J. Sr.; Hawley's Condensed Chemical Dictionary 15th Edition. John Wiley & Sons, Inc. New York, NY 2007., p. 103] **PEER REVIEWED**

Impurities:
The National Formulary states that **ascorbyl palmitate** must contain between 95.0% and 100.5% of C22H3807, based on the dried weight. Depending on the method of manufacture, **ascorbyl palmitate** could contain stearic acid, because palmitic acid samples contain large quantities of stearic acid.
[Cosmetic Ingredient Review; Final Report of the Cosmetic Ingredient Review Expert Panel; Final Report on the Safety Assessment of Ascorbyl Palmitate, Ascorbyl Dipalmitate, Ascorbyl Stearate, Erythorbic Acid, and Sodium Erythorbate; Scientific Regulatory Reference CD-ROM (2006). Cosmetic, Toiletry, and Fragrance Association, Washington D.C.] **PEER REVIEWED**

Consumption Patterns:
100% AS AN ANTIOXIDANT SYNERGIST IN FATS & OILS (1973)
[SRI] **PEER REVIEWED**

U. S. Production:
(1972) LESS THAN 4.54X10+5 GRAMS
[SRI] **PEER REVIEWED**

(1975) LESS THAN 4.54X10+5 GRAMS
[SRI] **PEER REVIEWED**

U. S. Imports:
(1972) No Data
[SRI] **PEER REVIEWED**

(1975) No Data
[SRI] **PEER REVIEWED**

U. S. Exports:
(1972) No Data
[SRI] **PEER REVIEWED**

(1975) No Data
[SRI] **PEER REVIEWED**

Laboratory Methods:

Special References:

Synonyms and Identifiers:

Related HSDB Records:
818 [Ascorbic acid] (METABOLITE)

Synonyms:
L-Ascorbic acid, 6-hexadecanoate
PEER REVIEWED

Ascorbic acid palmitate
PEER REVIEWED

L-Ascorbic acid, 6-palmitate
PEER REVIEWED

Ascorbic acid palmitate (ester)
PEER REVIEWED

Ascorbic palmitate
PEER REVIEWED

Ascorbyl monopalmitate
PEER REVIEWED

L-Ascorbyl monopalmitate
PEER REVIEWED

L-**Ascorbyl palmitate**
PEER REVIEWED

L-Ascorbyl 6-palmitate
PEER REVIEWED

Ascorbylpalmitic acid
PEER REVIEWED

Cetyl ascorbate
PEER REVIEWED

6-Hexadecanoyl-L-ascorbic acid
PEER REVIEWED

6-Monopalmitoyl-L-ascorbate
PEER REVIEWED

Ondascora
PEER REVIEWED

Palmitoyl-L-ascorbic acid
PEER REVIEWED

6-O-Palmitoylascorbic acid
PEER REVIEWED

6-Palmitoylascorbic acid
PEER REVIEWED

Quicifal
PEER REVIEWED

Formulations/Preparations:
Grade: FCC (Foods Chemical Codex).
[Lewis, R.J. Sr.; Hawley's Condensed Chemical Dictionary 15th Edition. John Wiley & Sons, Inc. New York, NY 2007., p. 103] **PEER REVIEWED**

Administrative Information:

Hazardous Substances Databank Number: 418

Last Revision Date: 20110104

Last Review Date: Reviewed by SRP on 9/23/2010

Update History:
Complete Update on 2011-01-04, 37 fields added/edited/deleted
Complete Update on 03/05/2003, 1 field added/edited/deleted.
Field Update on 01/14/2002, 1 field added/edited/deleted.
Field Update on 08/08/2001, 1 field added/edited/deleted.
Complete Update on 03/28/2000, 1 field added/edited/deleted.
Complete Update on 02/02/2000, 1 field added/edited/deleted.
Complete Update on 09/21/1999, 1 field added/edited/deleted.
Complete Update on 08/26/1999, 1 field added/edited/deleted.
Complete Update on 06/03/1999, 1 field added/edited/deleted.
Complete Update on 06/02/1998, 1 field added/edited/deleted.
Complete Update on 10/17/1997, 1 field added/edited/deleted.
Complete Update on 03/11/1997, 2 fields added/edited/deleted.
Complete Update on 01/19/1996, 1 field added/edited/deleted.
Complete Update on 08/29/1995, 15 fields added/edited/deleted.
Field Update on 05/26/1995, 1 field added/edited/deleted.
Field Update on 12/21/1994, 1 field added/edited/deleted.
Complete Update on 03/25/1994, 1 field added/edited/deleted.
Complete Update on 02/05/1993, 1 field added/edited/deleted.
Field update on 12/12/1992, 1 field added/edited/deleted.
Complete Update on 12/14/1984
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Complete nutrition for the 1st year	For babies with fussiness, gas, & spit-up	For babies needing extra TLC
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Organic	Spit-Up	NeoSure®
	Soy	Diarrhea

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IMMUNE SUPPORT — Early Shield® — BRAIN & EYE — STRONG BONES

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USDA ORGANIC

Organic
Complete Nutrition

For Your Baby's 1st Year

Infant Formula with Iron

U-D 1 QT (946 mL)

NUTRIENTS PER 100 CALORIES (5 FL OZ)

PROTEIN	2.07	G	WATER	133	G
FAT	5.40	G	LINOLEIC ACID	860	MG
CARBOHYDRATE	10.9	G			

VITAMINS

VITAMIN A	300	IU	NIACIN	1050	MCG
VITAMIN D	60	IU	FOLIC ACID (FOLACIN)	15	MCG
VITAMIN E	1.5	IU	PANTOTHENIC ACID	450	MCG
VITAMIN K	8	MCG	BIOTIN	4.4	MCG
THIAMIN (VIT. B_1)	100	MCG	VITAMIN C (ASCORBIC ACID)	9	MG
RIBOFLAVIN (VIT. B_2)	150	MCG	CHOLINE	16	MG
VITAMIN B_6	60	MCG	INOSITOL	4.7	MG
VITAMIN B_{12}	0.25	MCG			

MINERALS

CALCIUM	78	MG	COPPER	90	MCG
PHOSPHORUS	42	MG	IODINE	6	MCG
MAGNESIUM	6	MG	SELENIUM	1.8	MCG
IRON	1.8	MG	SODIUM	24	MG
ZINC	0.75	MG	POTASSIUM	106	MG
MANGANESE	5	MCG	CHLORIDE	65	MG

INGREDIENTS: WATER, **ORGANIC** NONFAT MILK, **ORGANIC** MALTODEXTRIN, **ORGANIC** SUGAR, **ORGANIC** HIGH OLEIC SUNFLOWER OIL, **ORGANIC** SOY OIL, **ORGANIC** COCONUT OIL; **LESS THAN 0.5% OF:** C. COHNII OIL*, M. ALPINA OIL†, BETA-CAROTENE, LUTEIN, LYCOPENE, FRUCTOOLIGOSACCHARIDES, POTASSIUM CITRATE, CALCIUM CARBONATE, ASCORBIC ACID, SOY LECITHIN, CARRAGEENAN, MAGNESIUM CHLORIDE, SALT, FERROUS SULFATE, CHOLINE CHLORIDE, CHOLINE BITARTRATE, TAURINE, m-INOSITOL, d-ALPHA-TOCOPHERYL ACETATE, L-CARNITINE, ZINC SULFATE, NIACINAMIDE, CALCIUM PANTOTHENATE, RIBOFLAVIN, VITAMIN A PALMITATE, CUPRIC SULFATE, THIAMINE CHLORIDE HYDROCHLORIDE, PYRIDOXINE HYDROCHLORIDE, FOLIC ACID, MANGANESE SULFATE, PHYLLOQUINONE, BIOTIN, POTASSIUM IODIDE, SODIUM SELENATE, VITAMIN D_3, CYANOCOBALAMIN, POTASSIUM HYDROXIDE AND NUCLEOTIDES (ADENOSINE 5'-MONOPHOSPHATE, CYTIDINE 5'-MONOPHOSPHATE, DISODIUM GUANOSINE 5'-MONOPHOSPHATE, DISODIUM URIDINE 5'-MONOPHOSPHATE).
CONTAINS MILK AND SOY INGREDIENTS.
*SOURCE OF DOCOSAHEXAENOIC ACID (DHA) †SOURCE OF ARACHIDONIC ACID (ARA)

USE AS DIRECTED BY A DOCTOR
Directions for Preparation and Use

USE BY DATE ON BOTTLE • DO NOT ADD WATER
DO NOT USE IF BAND AROUND CAP OR INNER FOIL SEAL IS DAMAGED.

Your baby's health depends on carefully following these directions. Failure to follow these directions could result in severe harm. Ask your baby's doctor if you need to boil (sterilize) bottles, nipples and rings before use.

Use

Shake very well before each use
Remove protective band; twist off and clean cap

Invert cap; press down to pierce foil, then turn cap a half turn
Remove foil

Pour formula into bottle; attach nipple
Once feeding begins, use within 1 hour or discard

Prepare and feed all formula in this container within 3 days after opening.

Storage Once opened, store quart bottle in refrigerator. Store prepared bottles in refrigerator and **feed to baby within 48 hours.** Store unopened containers at room temperature; avoid extreme temperatures. Do not reuse container.

Warning Do not use this container to warm formula. **Never use a microwave to warm formula.** Serious burns can result.

Abbott Nutrition, Abbott Laboratories, Columbus, Ohio 43219-3034 USA

CERTIFIED ORGANIC BY QUALITY ASSURANCE INTERNATIONAL

NUTRIENTS PER 100 CALORIES (5 FL OZ, PREPARED AS DIRECTED)

PROTEIN	2.07	G	WATER	133	G
FAT	5.63	G	LINOLEIC ACID	860	MG
CARBOHYDRATE	10.4	G			

VITAMINS

VITAMIN A	300	IU	NIACIN	1050	MCG
VITAMIN D	60	IU	FOLIC ACID (FOLACIN)	15	MCG
VITAMIN E	1.5	IU	PANTOTHENIC ACID	450	MCG
VITAMIN K	8	MCG	BIOTIN	4.4	MCG
THIAMIN (VIT. B_1)	100	MCG	VITAMIN C (ASCORBIC ACID)	9	MG
RIBOFLAVIN (VIT. B_2)	150	MCG	CHOLINE	16	MG
VITAMIN B_6	60	MCG	INOSITOL	4.7	MG
VITAMIN B_{12}	0.25	MCG			

MINERALS

CALCIUM	78	MG	COPPER	90	MCG
PHOSPHORUS	42	MG	IODINE	6	MCG
MAGNESIUM	6	MG	SELENIUM	1.8	MCG
IRON	1.8	MG	SODIUM	24	MG
ZINC	0.75	MG	POTASSIUM	105	MG
MANGANESE	5	MCG	CHLORIDE	65	MG

INGREDIENTS: ORGANIC NONFAT MILK, **ORGANIC** MALTODEXTRIN, **ORGANIC** SUGAR, **ORGANIC** HIGH OLEIC SUNFLOWER OIL, **ORGANIC** SOY OIL, **ORGANIC** COCONUT OIL; **LESS THAN 2% OF:** C. COHNII OIL*, M. ALPINA OIL*, BETA-CAROTENE, LUTEIN, LYCOPENE, FRUCTOOLIGOSACCHARIDES, POTASSIUM CITRATE, CALCIUM CARBONATE, ASCORBIC ACID, SOY LECITHIN, ASCORBYL PALMITATE, FERROUS SULFATE, SALT, CHOLINE CHLORIDE, CHOLINE BITARTRATE, TAURINE, m-INOSITOL, MAGNESIUM CHLORIDE, ZINC SULFATE, MIXED TOCOPHEROLS, d-ALPHA-TOCOPHERYL ACETATE, NIACINAMIDE, CALCIUM PANTOTHENATE, L-CARNITINE, VITAMIN A PALMITATE, CUPRIC SULFATE, THIAMINE CHLORIDE HYDROCHLORIDE, RIBOFLAVIN, PYRIDOXINE HYDROCHLORIDE, FOLIC ACID, MANGANESE SULFATE, PHYLLOQUINONE, BIOTIN, SODIUM SELENATE, VITAMIN D_3, CYANOCOBALAMIN, POTASSIUM IODIDE, POTASSIUM HYDROXIDE AND NUCLEOTIDES (CYTIDINE 5'-MONOPHOSPHATE, DISODIUM GUANOSINE 5'-MONOPHOSPHATE, DISODIUM URIDINE 5'-MONOPHOSPHATE, ADENOSINE 5'-MONOPHOSPHATE).
CONTAINS MILK AND SOY INGREDIENTS.
*SOURCE OF DOCOSAHEXAENOIC ACID (DHA) †SOURCE OF ARACHIDONIC ACID (ARA)

Abbott Nutrition, Abbott Laboratories
Columbus, Ohio 43219-3034 USA

CERTIFIED ORGANIC BY QUALITY ASSURANCE INTERNATIONAL

USE BY DATE ON CONTAINER • USE AS DIRECTED BY A DOCTOR
Directions for Preparation and Use

Your baby's health depends on carefully following these directions. Proper hygiene, handling and storage are important when preparing infant formula. Failure to follow these directions could result in severe harm. Ask your baby's doctor if you need to use cooled, boiled water for mixing and if you need to boil (sterilize) bottles, nipples and rings before use.

1. Wash your hands, surfaces and utensils
   Pour water into clean bottle (see mixing guide)
2. Add 1 unpacked level scoop (8.6 g) to each 2 fl oz of water
   Return dry scoop to holder in lid
3. Cap bottle; shake well; attach nipple
   Once feeding begins, use within 1 hour or discard

Storage: Once mixed, store bottles in refrigerator and **feed to baby within 24 hours.** Store unopened or opened container at room temperature; avoid extreme temperatures. **Use opened container contents within 1 month.** Do not reuse container.

Warning: Powdered infant formulas are not sterile and should not be fed to premature infants or infants who might have immune problems unless directed and supervised by your baby's doctor. **Never use a microwave to warm formula.** Serious burns can result.

DO NOT USE IF OUTER QUALITY SEAL OR INNER FOIL SEAL IS DAMAGED.

U.S. Patent Nos. 5,700,590; 6,136,858; 6,596,767; 7,090,879; D576,035 and D578,401

POSITION ONLY
0 70074 50822 1

MIXING GUIDE
GUÍA DE MEZCLA
PEEL HERE Despréndase aquí

IMPORTANT NOTICE: BREAST MILK IS BEST FOR BABIES. Before using an infant formula, ask the advice of your health-care professional. If you choose to supplement breastfeeding with formula or to formula feed exclusively, there is no better formula than Vermont Organics™ ORGANIC Infant Formula DHA and ARA. **Powdered infant formulas are NOT sterile and should NOT be fed to premature infants or infants who might have immune problems unless directed and supervised by your baby's doctor.**

DIRECTIONS FOR PREPARATION AND USE

Your baby's health depends on carefully following these preparation, use and storage instructions; changes could affect your baby's nutrition and safety. Before preparing the infant formula, make sure to always wash your hands. Clean can top before opening. **Ask your baby's doctor about the need to boil or sterilize water for formula and the proper preparation of bottle and feeding utensils.**

1. Pour desired amount of warm water (approx. 100°F/40°C) into bottle. (See Feeding Chart below.)
2. Add powder. Always add powder to water.
3. Cap bottle and shake well until powder is dissolved. Feed immediately. Discard any remaining formula in bottle after 1 hour from start of feeding.

Use this Feeding Chart for proper amount of water and powder.

To Make	Water	Powder (Use scoop enclosed to measure)
2 fl oz bottle	2 fl oz	1 unpacked level **scoop** (8.7 g)
4 fl oz bottle	4 fl oz	2 unpacked level **scoops** (17.4 g)
6 fl oz bottle	6 fl oz	3 unpacked level **scoops** (26.1 g)
8 fl oz bottle	8 fl oz	4 unpacked level **scoops** (34.8 g)
1 quart	29 fl oz	1 unpacked level standard measuring **cup** & 2 unpacked level **scoops** (123 g)

Storage: Store unused prepared bottled formula in the refrigerator at 35-40°F (2-4°C); **use within 24 hours.** DO NOT FREEZE. Warm infant formula to room temperature and shake well before feeding. Prepared formula should not be without refrigeration more than 2 hours. Store open and unopened cans in a dry area at room temperature. Cover the opened can tightly with plastic cap; use contents within 1 month. Avoid any extreme temperatures.
Warning: Do not use microwave to prepare or warm formula. Serious burns may occur.
Filled by weight, not by volume. Contents may settle during shipment.
Contents yield approximately 190 fl oz of formula

Las instrucciones en Español se encuentran al dorso de esta etiqueta

Easy to Digest
Powder • Add Water

Vermont Organics™

For Babies
0-12 Months

organic infant formula with iron

Milk-Based Nutrition

Lipids – DHA & ARA
Nutrients found naturally in mother's milk

- No Antibiotics
- No Added Growth Hormones
- No Potentially Harmful Pesticides

USDA ORGANIC

NET WT 25.75 OZ (1 LB 9.75 OZ) 730 g

INGREDIENTS: **ORGANIC** REDUCED MINERALS WHEY, **ORGANIC** VEGETABLE OILS (PALM OR PALM OLEIN, HIGH OLEIC (SAFFLOWER OR SUNFLOWER), COCONUT, SOY), **ORGANIC** NONFAT MILK, **ORGANIC** LACTOSE, **AND LESS THAN 1%:** MORTIERELLA ALPINA OIL*, CRYPTHECODINIUM COHNII OIL**, VITAMIN A PALMITATE, BETA-CAROTENE, VITAMIN D (CHOLECALCIFEROL), VITAMIN E (dl-ALPHA TOCOPHERYL ACETATE), MIXED TOCOPHEROL CONCENTRATE, VITAMIN K (PHYTONADIONE), ASCORBYL PALMITATE, THIAMINE HYDROCHLORIDE, RIBOFLAVIN, PYRIDOXINE HYDROCHLORIDE, CYANOCOBALAMIN, NIACINAMIDE, FOLIC ACID, CALCIUM PANTOTHENATE, BIOTIN, ASCORBIC ACID, CHOLINE CHLORIDE, INOSITOL, CALCIUM CHLORIDE, CALCIUM HYDROXIDE, FERROUS SULFATE, ZINC SULFATE, MANGANESE SULFATE, CUPRIC SULFATE, POTASSIUM BICARBONATE, POTASSIUM CHLORIDE, POTASSIUM IODIDE, POTASSIUM HYDROXIDE, SODIUM SELENITE, SODIUM CITRATE, TAURINE, SOY LECITHIN, NUCLEOTIDES (ADENOSINE-5'-MONOPHOSPHATE, CYTIDINE-5'-MONOPHOSPHATE, DISODIUM GUANOSINE-5'- MONOPHOSPHATE, DISODIUM INOSINE-5'-MONOPHOSPHATE, DISODIUM URIDINE-5'MONOPHOSPHATE).
CONTAINS MILK AND SOY INGREDIENTS.

Diluted: Each 5 fl oz (150 mL) contains 100 Calories

NUTRIENTS:	PER 100 CALORIES:
PROTEIN g	2.2
FAT g	5.3
CARBOHYDRATE g	10.6
WATER g	134
LINOLEIC ACID mg	750
VITAMINS:	
VITAMIN A IU	300
VITAMIN D IU	60
VITAMIN E IU	2
VITAMIN K mcg	8
THIAMINE (VITAMIN B1) mcg	100
RIBOFLAVIN (VITAMIN B2) mcg	150
VITAMIN B6 mcg	63
VITAMIN B12 mcg	0.2
NIACIN mcg	750
FOLIC ACID (FOLACIN) mcg	7.5
PANTOTHENIC ACID mcg	315

VITAMINS:	PER 100 CALORIES:
BIOTIN mcg	2.3
VITAMIN C (ASCORBIC ACID) mg	9
CHOLINE mg	15
INOSITOL mg	4.1
MINERALS:	
CALCIUM mg	63
PHOSPHORUS mg	42
MAGNESIUM mg	7
IRON mg	1.8
ZINC mg	0.75
MANGANESE mcg	15
COPPER mcg	71
IODINE mcg	9
SELENIUM mcg	2.1
SODIUM mg	23
POTASSIUM mg	84
CHLORIDE mg	56

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VERMONT ORGANICS INFANT FORMULA
147 IND. PARK RD, GEORGIA, VT 05468

CERTIFIED ORGANIC BY QUALITY ASSURANCE INTERNATIONAL 02FTP

*A SOURCE OF ARACHIDONIC ACID (ARA)
**A SOURCE OF DOCOSAHEXAENOIC ACID (DHA)

Questions or Comments:
1-800-538-7615
9:00 a.m. to 5:00 p.m. EST
Monday – Friday

Produced under an ISO-9001 Quality System.

All infant formulas sold in the U.S. are required to be manufactured in accordance with, and meet the nutritional requirements of, the Federal Food, Drug and Cosmetic Act for infant formula under the regulation of the U.S. Food and Drug Administration.

lifes DHA•ARA

lifes DHA•ARA™ is a trademark of Martek Biosciences Corporation.

6 83744 13001 3

USE BEFORE DATE ON BOTTOM OF CAN

Breast milk is best. But if you decide to supplement breastfeeding with formula or formula-feed exclusively, Vermont Organics™ ORGANIC Infant Formula is a wholesome choice for your baby.

Made in the heart of the Green Mountains, Vermont Organics™ ORGANIC meets all USDA organic certification requirements. In addition to containing sources of organic fat, protein and carbohydrate, Vermont Organics™ ORGANIC is produced without the use of antibiotics, added growth hormones or potentially harmful pesticides.

L19847734-0351

IMPORTANT NOTICE: BREAST MILK IS BEST FOR BABIES. Before using an infant formula, ask the advice of your health-care professional. This organic soy infant formula powder is free of lactose and cow's milk protein. It is intended to meet the nutritional needs of term infants and babies who are sensitive to lactose or those who do not consume milk protein or milk products. **Powdered infant formulas are NOT sterile and should NOT be fed to premature infants or infants who might have immune problems unless directed and supervised by your baby's doctor.**

DIRECTIONS FOR PREPARATION AND USE

Your baby's health depends on carefully following these preparation, use and storage instructions; changes could affect your baby's nutrition and safety. Before preparing the infant formula, make sure to always wash your hands. Clean can top before opening. **Ask your baby's doctor about the need to boil or sterilize water for formula and the proper preparation of bottle and feeding utensils.**

1. Pour desired amount of warm water (approx. 100°F/40°C) into bottle. (See Feeding Chart below.)
2. Add powder. Always add powder to water.
3. Cap bottle and shake well until powder is dissolved. Feed immediately. Discard any remaining formula in bottle after 1 hour from start of feeding.

Use this Feeding Chart for proper amount of water and powder.

To Make	Water	Powder (Use scoop enclosed to measure)
2 fl oz bottle	2 fl oz	1 unpacked level **scoop** (8.8 g)
4 fl oz bottle	4 fl oz	2 unpacked level **scoops** (17.6 g)
6 fl oz bottle	6 fl oz	3 unpacked level **scoops** (26.4 g)
8 fl oz bottle	8 fl oz	4 unpacked level **scoops** (35.2 g)
1 quart	29 fl oz	1 unpacked level standard measuring **cup** & 2 unpacked level **scoops** (125 g)

Storage: Store unused prepared bottled formula in the refrigerator at 35-40°F (2-4°C); **use within 24 hours.** DO NOT FREEZE. Warm infant formula to room temperature and shake well before feeding. Prepared formula should not be without refrigeration more than 2 hours. Store open and unopened cans in a dry area at room temperature. Cover the opened can tightly with plastic cap; use contents within 1 month. Avoid any extreme temperatures.

Warning: Do not use microwave to prepare or warm formula. Serious burns may occur.

Filled by weight, not by volume. Contents may settle during shipment.

Contents yield approximately 187 fl oz of formula

Martek DHA

Las instrucciones en Español se encuentran al dorso de esta etiqueta

Easy to Digest
Powder • Add Water

Vermont Organics™

For Babies
0-12 Months

soy organic infant formula

with iron

Soy-Based Nutrition

Lipids – DHA & ARA

Nutrients found naturally in mother's milk

- Milk-Free
- Lactose-Free
- No Potentially Harmful Pesticides

USDA ORGANIC

Pareve

NET WT 25.75 OZ (1 LB 9.75 OZ) 730 g

INGREDIENTS: **ORGANIC** CORN SYRUP SOLIDS, **ORGANIC** SOY PROTEIN, **ORGANIC** PALM OLEIN OR PALM OIL, **ORGANIC** COCONUT OIL, **ORGANIC** HIGH OLEIC (SAFFLOWER OR SUNFLOWER) OIL, **ORGANIC** SOY OIL, **AND LESS THAN 1%:** MORTIERELLA ALPINA OIL*, CRYPTHECODINIUM COHNII OIL**, ASCORBYL PALMITATE, L-CARNITINE, L-METHIONINE, MIXED TOCOPHEROL CONCENTRATE, SOY LECITHIN, TAURINE, CALCIUM CHLORIDE, CALCIUM PHOSPHATE, CUPRIC SULFATE, FERROUS SULFATE, MAGNESIUM CHLORIDE, MANGANESE SULFATE, POTASSIUM BICARBONATE, POTASSIUM CHLORIDE, POTASSIUM CITRATE, POTASSIUM HYDROXIDE, POTASSIUM IODIDE, SODIUM CITRATE, SODIUM SELENITE, ZINC SULFATE, ASCORBIC ACID, BETA-CAROTENE, BIOTIN, CALCIUM PANTOTHENATE, CHOLINE BITARTRATE, CYANOCOBALAMIN, FOLIC ACID, INOSITOL, NIACINAMIDE, PYRIDOXINE HYDROCHLORIDE, RIBOFLAVIN, THIAMINE HYDROCHLORIDE, VITAMIN A PALMITATE, VITAMIN D (CHOLECALCIFEROL), VITAMIN E (DL-ALPHA TOCOPHERYL ACETATE), VITAMIN K (PHYTONADIONE). **CONTAINS SOY INGREDIENTS.**

Diluted: Each 5 fl oz (150 mL) contains 100 Calories

NUTRIENTS:	PER 100 CALORIES:
PROTEIN g	2.5
FAT g	5.3
CARBOHYDRATE g	10.6
WATER g	134
LINOLEIC ACID mg	750
VITAMINS:	
VITAMIN A IU	300
VITAMIN D IU	60
VITAMIN E IU	2
VITAMIN K mcg	8
THIAMINE (VITAMIN B_1) mcg	80
RIBOFLAVIN (VITAMIN B_2) mcg	90
VITAMIN B_6 mcg	60
VITAMIN B_{12} mcg	0.3
NIACIN mcg	1000
FOLIC ACID (FOLACIN) mcg	16
PANTOTHENIC ACID mcg	500

VITAMINS:	PER 100 CALORIES:
BIOTIN mcg	3
VITAMIN C (ASCORBIC ACID) mg	12
CHOLINE mg	24
INOSITOL mg	6
MINERALS:	
CALCIUM mg	105
PHOSPHORUS mg	69
MAGNESIUM mg	11
IRON mg	1.8
ZINC mg	1.2
MANGANESE mcg	25
COPPER mcg	75
IODINE mcg	15
SELENIUM mcg	2.8
SODIUM mg	36
POTASSIUM mg	120
CHLORIDE mg	80

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* A SOURCE OF ARACHIDONIC ACID (ARA) ** A SOURCE OF DOCOSAHEXAENOIC ACID (DHA)
Ⓟ PAREVE Contains no dairy ingredients. Manufactured on dairy equipment.

Questions or Comments:
1-800-538-7615
9:00 a.m. to 5:00 p.m. EST
Monday – Friday

Produced under an ISO-9001 Quality System.

All infant formulas sold in the U.S. are required to be manufactured in accordance with, and meet the nutritional requirements of, the Federal Food, Drug and Cosmetic Act for infant formula under the regulation of the U.S. Food and Drug Administration.

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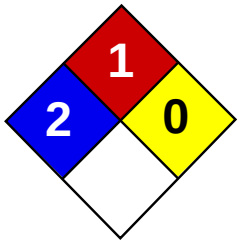
USE BEFORE DATE ON BOTTOM OF CAN

Breast milk is best. But if you decide to supplement breastfeeding with formula or formula-feed exclusively, and lactose-sensitivity is a concern, Vermont Organics™ Soy ORGANIC Infant Formula is a wholesome choice for your baby.

Made in the heart of the Green Mountains, Vermont Organics™ Soy ORGANIC meets all USDA organic certification requirements. A milk-free, lactose-free baby formula containing organic soy protein.

L18A0730-0351



Health	2
Fire	1
Reactivity	0
Personal Protection	C

Material Safety Data Sheet
Ascorbyl palmitate MSDS

Section 1: Chemical Product and Company Identification

Product Name: Ascorbyl palmitate

Catalog Codes: SLA2635, SLA4138

CAS#: 137-66-6

RTECS: CI7671040

TSCA: TSCA 8(b) inventory: Ascorbyl palmitate

CI#: Not available.

Synonym: L-Ascorbic Acid, 6-Hexadecanoate

Chemical Name: Ascorbyl Palmitate

Chemical Formula: C22H38O7

Contact Information:

Sciencelab.com, Inc.
14025 Smith Rd.
Houston, Texas 77396

US Sales: **1-800-901-7247**
International Sales: **1-281-441-4400**

Order Online: ScienceLab.com

CHEMTREC (24HR Emergency Telephone), call:
1-800-424-9300

International CHEMTREC, call: 1-703-527-3887

For non-emergency assistance, call: 1-281-441-4400

Section 2: Composition and Information on Ingredients

Composition:

Name	CAS #	% by Weight
Ascorbyl palmitate	137-66-6	100

Toxicological Data on Ingredients: Ascorbyl palmitate: ORAL (LD50): Acute: 25000 mg/kg [Mouse]. DERMAL (LD50): Acute: >3000 mg/kg [Guinea pig].

Section 3: Hazards Identification

Potential Acute Health Effects:
Hazardous in case of eye contact (irritant), of inhalation. Slightly hazardous in case of skin contact (irritant), of ingestion.

Potential Chronic Health Effects:
CARCINOGENIC EFFECTS: Not available. MUTAGENIC EFFECTS: Not available. TERATOGENIC EFFECTS: Not available. DEVELOPMENTAL TOXICITY: Not available. Repeated or prolonged exposure is not known to aggravate medical condition.

Section 4: First Aid Measures

Eye Contact:
Check for and remove any contact lenses. In case of contact, immediately flush eyes with plenty of water for at least 15 minutes. Cold water may be used. WARM water MUST be used. Get medical attention.

Skin Contact: Wash with soap and water. Cover the irritated skin with an emollient. Get medical attention if irritation develops.

Serious Skin Contact: Not available.

Inhalation:
If inhaled, remove to fresh air. If not breathing, give artificial respiration. If breathing is difficult, give oxygen. Get medical attention.

Serious Inhalation: Not available.

Ingestion:
Do NOT induce vomiting unless directed to do so by medical personnel. Never give anything by mouth to an unconscious person. Loosen tight clothing such as a collar, tie, belt or waistband. Get medical attention if symptoms appear.

Serious Ingestion: Not available.

Section 5: Fire and Explosion Data

Flammability of the Product: May be combustible at high temperature.

Auto-Ignition Temperature: Not available.

Flash Points: CLOSED CUP: Higher than 93.3°C (200°F).

Flammable Limits: Not available.

Products of Combustion: These products are carbon oxides (CO, CO2).

Fire Hazards in Presence of Various Substances: Slightly flammable to flammable in presence of heat.

Explosion Hazards in Presence of Various Substances:
Risks of explosion of the product in presence of mechanical impact: Not available. Risks of explosion of the product in presence of static discharge: Not available.

Fire Fighting Media and Instructions:
SMALL FIRE: Use DRY chemical powder. LARGE FIRE: Use water spray, fog or foam. Do not use water jet.

Special Remarks on Fire Hazards: Not available.

Special Remarks on Explosion Hazards: Not available.

Section 6: Accidental Release Measures

Small Spill:
Use appropriate tools to put the spilled solid in a convenient waste disposal container. Finish cleaning by spreading water on the contaminated surface and dispose of according to local and regional authority requirements.

Large Spill:
Use a shovel to put the material into a convenient waste disposal container. Finish cleaning by spreading water on the contaminated surface and allow to evacuate through the sanitary system.

Section 7: Handling and Storage

Precautions:
Keep away from heat. Keep away from sources of ignition. Empty containers pose a fire risk, evaporate the residue under a fume hood. Ground all equipment containing material. Do not ingest. Do not breathe dust. Avoid contact with eyes. Wear suitable protective clothing. In case of insufficient ventilation, wear suitable respiratory equipment. If ingested, seek medical advice immediately and show the container or the label.

Storage: Keep container tightly closed. Keep container in a cool, well-ventilated area.

Section 8: Exposure Controls/Personal Protection

Engineering Controls:
Use process enclosures, local exhaust ventilation, or other engineering controls to keep airborne levels below recommended exposure limits. If user operations generate dust, fume or mist, use ventilation to keep exposure to airborne contaminants below the exposure limit.

Personal Protection: Safety glasses. Synthetic apron. Gloves (impervious).

Personal Protection in Case of a Large Spill:
Splash goggles. Full suit. Boots. Gloves. Suggested protective clothing might not be sufficient; consult a specialist BEFORE handling this product.

Exposure Limits: Not available.

Section 9: Physical and Chemical Properties

Physical state and appearance: Solid. (Powdered solid.)

Odor: Citrus-like

Taste: Not available.

Molecular Weight: 414.54 g/mole

Color: White to yellowish.

pH (1% soln/water): Not available.

Boiling Point: Not available.

Melting Point: 116°C (240.8°F)

Critical Temperature: Not available.

Specific Gravity: Not available.

Vapor Pressure: Not applicable.

Vapor Density: Not available.

Volatility: Not available.

Odor Threshold: Not available.

Water/Oil Dist. Coeff.: Not available.

Ionicity (in Water): Not available.

Dispersion Properties: Not available.

Solubility: Very slightly soluble in cold water.

Section 10: Stability and Reactivity Data

Stability: The product is stable.

Instability Temperature: Not available.

Conditions of Instability: Excess heat, incompatible materials

Incompatibility with various substances: Not available.

Corrosivity: Not available.

Special Remarks on Reactivity: Not available.

Special Remarks on Corrosivity: Not available.

Polymerization: Will not occur.

Section 11: Toxicological Information

Routes of Entry: Inhalation. Ingestion.

Toxicity to Animals:
Acute oral toxicity (LD50): 25000 mg/kg [Mouse]. Acute dermal toxicity (LD50): >3000 mg/kg [Guinea pig].

Chronic Effects on Humans: Not available.

Other Toxic Effects on Humans:
Hazardous in case of inhalation. Slightly hazardous in case of skin contact (irritant), of ingestion.

Special Remarks on Toxicity to Animals: Not available.

Special Remarks on Chronic Effects on Humans: Not available.

Special Remarks on other Toxic Effects on Humans:
Acute Potential Health Effects: Skin: May cause skin irritation. Eyes: May cause eye irritation. Inhalation: May cause respiratory tract irritation. Ingestion: May cause gastrointestinal (digestive) tract irritation. May affect metabolism and urinary system. Chronic Potential Health Effects: no information found

Section 12: Ecological Information

Ecotoxicity: Not available.

BOD5 and COD: Not available.

Products of Biodegradation:
Possibly hazardous short term degradation products are not likely. However, long term degradation products may arise.

Toxicity of the Products of Biodegradation: The product itself and its products of degradation are not toxic.

Special Remarks on the Products of Biodegradation: Not available.

Section 13: Disposal Considerations

Waste Disposal:
Waste must be disposed of in accordance with federal, state and local environmental control regulations.

Section 14: Transport Information

DOT Classification: Not a DOT controlled material (United States).

Identification: Not applicable.

Special Provisions for Transport: Not applicable.

Section 15: Other Regulatory Information

Federal and State Regulations: TSCA 8(b) inventory: Ascorbyl palmitate

Other Regulations: EINECS: This product is on the European Inventory of Existing Commercial Chemical Substances.

Other Classifications:

WHMIS (Canada): Not controlled under WHMIS (Canada).

DSCL (EEC):
R36- Irritating to eyes. S2- Keep out of the reach of children. S46- If swallowed, seek medical advice immediately and show this container or label.

HMIS (U.S.A.):

Health Hazard: 2

Fire Hazard: 1

Reactivity: 0

Personal Protection: C

National Fire Protection Association (U.S.A.):

Health: 2

Flammability: 1

Reactivity: 0

Specific hazard:

Protective Equipment:
Gloves (impervious). Synthetic apron. Not applicable. Safety glasses.

Section 16: Other Information

References: Not available.

Other Special Considerations: Not available.

Created: 10/09/2005 04:16 PM

Last Updated: 11/01/2010 12:00 PM

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The EFSA Journal (2004) 59, 1-21

Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a request from the Commission related to the Tolerable Upper Intake Level of Vitamin C (L-Ascorbic acid, its calcium, potassium and sodium salts and L-ascorbyl-6-palmitate)

(Request N° EFSA-Q-2003-018)

(adopted on 28 April 2004)

SUMMARY

The European Food Safety Authority is asked to derive an upper level for the intake of vitamin C from food that is unlikely to pose a risk of adverse health effects.

Vitamin C is a water soluble vitamin that is an important anti-oxidant in the body. Insufficient intake results in the deficiency condition scurvy.

The vitamin is of low acute toxicity as indicated by the limited data available from studies in animals and humans. Despite the extensive use of high doses of vitamin C in some vitamin supplements, there have been few controlled studies that specifically investigated adverse effects. Overall, acute gastrointestinal intolerance (e.g., abdominal distension, flatulence, diarrhoea, transient colic) is the most clearly defined adverse effect at high intakes, but there are limited data on the dose-response relationship for adults or for groups such as children or the elderly. While there is uncertainty whether high intakes of vitamin C increase renal excretion of oxalate which could increase the risk of renal stones, an increased risk of kidney stones was not found in individuals with habitual intakes of 1.5 g/day. There are insufficient data to establish a tolerable upper intake level for vitamin C.

The available human data suggest that supplemental daily doses of vitamin C up to about 1 g, in addition to normal dietary intakes, are not associated with adverse gastrointestinal effects, but that acute gastrointestinal effects may occur at higher intakes (3-4 g/day). The absorption of vitamin C is saturated at high doses, and therefore intakes above 1 g/day would be associated with negligible increased uptake and tissue levels, but an increased risk of adverse gastrointestinal effects.

The average daily intakes reported in surveys in European countries are above the recommended daily intakes, with the 95th percentile intakes from food and supplements ranging up to about 1 g/day. These dietary intakes do not represent a cause for concern.

There has not been a systematic assessment of the safety of the long-term use of high dose vitamin C supplements.

KEY WORDS

Vitamin C, ascorbic acid, tolerable upper intake level, gastrointestinal effects, food safety.

BACKGROUND

In 2002, the European Parliament and the Council adopted Directive 2002/46/EC[1] related to food supplements containing vitamins and minerals.

In addition, and as announced in its White Paper on Food Safety, the Commission aims to put forward a proposal for harmonising legislation concerning the addition of vitamins and minerals to foods.

With a view to provide scientific support to the European Commission's legislative work in this field, the Scientific Committee on Food (SCF) issued, from October 2000 to April 2003, a series of opinions on tolerable upper intake levels of individual vitamins and minerals and safety factors in relation to their use in fortified foods and food supplements (available on the Internet at: http://europa.eu.int/comm/food/fs/sc/scf/out80_en.html).

The SCF opinions covered 22 out of the 29 nutrients, which were considered to be within their mandate for this task. The SCF did not have sufficient time to adopt opinions for the following vitamins and minerals: vitamin C, chloride, fluoride, iron, phosphorus, potassium and sodium. In addition, during the decision making process for the adoption of Directive 2000/46/EC on food supplements the Parliament requested that boron, nickel, silicon, vanadium and tin should be allowed to be used in food supplements. Therefore, the European Food Safety Authority is asked to provide scientific opinions on the remaining 12 vitamins and minerals in accordance with the present terms of reference.

TERMS OF REFERENCE

With respect to the outstanding 12 vitamins and minerals, the European Food Safety Authority is asked 1) to review the upper levels of daily intakes that are unlikely to pose a risk of adverse health effects; 2) to provide the basis for the establishment of safety factors, where necessary, which would ensure the safety of fortified foods and food supplements containing the aforementioned nutrients.

ASSESSMENT

1. INTRODUCTION

Vitamin C (3-oxo-L-gulofuranolactone or L-threo-hex-2-enonic acid) is a 6-carbon hydroxy-lactone that is structurally related to glucose. It is a micronutrient essential to humans, primates and guinea pigs, but which is synthesised by other mammalian species from glucose and galactose. It is readily oxidised to L-dehydroascorbic acid, in which the unsaturated 2,3-dihydroxy group is replaced by a saturated 2,3-diketone function; L-dehydroascorbic acid can be reduced back to ascorbic acid.

Vitamin C is highly water soluble, and in solution can be oxidised by atmospheric oxygen to give an equilibrium mixture of ascorbic and dehydroascorbic acids. Vitamin C has important

[1] Directive 2002/46/EC of the European Parliament and of the Council on the approximation of the laws of the Member States relating to food supplements. OJ L 183. 12.7.2002, p. 51.

anti-oxidant properties, and protects cells against oxidative stress. Because of this general cytoprotective role, its importance has been investigated in a variety of clinical conditions, including cancer, vascular disease, and cataracts.

Vitamin C deficiency in humans leads to clinical syndromes known as scurvy in adults and Moeller-Barlow disease in children (SCF, 1993), conditions which are associated with intakes of less than 10 mg/day. Early or prescorbutic symptoms in adults include fatigue, weakness, anaemia and aching joints and muscles, while there are important effects on bone tissue in children. Later stages of deficiency are characterised by capillary fragility causing bleeding from the gums and haemorrhages, and delayed wound healing due to impaired collagen synthesis.

Advice by Linus Pauling that daily intakes of 1 g or more of vitamin C can protect against the common cold (see Miller and Hayes, 1982) was followed by other claims of beneficial effects on a variety of conditions. Because of the media attention given to these claims and the apparently low toxicity of vitamin C there has been extensive human exposure to intakes up to 10 g/day (Miller and Hayes, 1982). However despite this extensive human exposure, there are only limited data that are appropriate for use in risk assessment.

Recent reviews of vitamin C by the Food and Nutrition Board in the USA (FNB, 2000) and the Expert Group on Vitamins and Minerals in the UK (EGVM, 2003) have recommended an upper level of 2 g/day and a guidance level of 1 g/day, as supplemental intake, respectively.

2. NUTRITIONAL BACKGROUND, FUNCTION, METABOLISM AND INTAKE

Major food sources of vitamin C are plants such as citrus fruits, soft fruits and green vegetables. Animal tissues also contain vitamin C, with kidney and liver representing good sources. The amounts of vitamin C present in the food when consumed may be reduced, because it is readily lost due to dissolution in water and oxidation during cooking processes such as boiling.

Ascorbic acid is a permitted anti-oxidant additive in food, with no specified limits on the level of use. Vitamin C is present in numerous dietary supplements with manufacturer recommended daily intakes of 60-3000 mg in single vitamin preparations and 10-1000 mg/day in multi-vitamin preparations (EGVM, 2003).

In 1992, the Scientific Committee for Food (SCF, 1993) recommended a Population Reference Intake of 45 mg/day for adults, with an increase to 55 mg/day in pregnancy, and to 70 mg/day during lactation.

Vitamin C has a number of biochemical roles in the body (Basu and Dickerson, 1996). It is a strong reducing agent and antioxidant, which is important in preventing the damaging effects of free radicals. Vitamin C is an enzyme co-factor for many biochemical reactions, especially those involving oxidations, such as the synthesis of hydroxyproline from proline for collagen biosynthesis, mono-oxygenases, dioxygenases and mixed function oxygenases. It is important in the synthesis and stabilisation of neurotransmitters and carnitine, and increases the gastrointestinal absorption of non-haem iron by reducing ferric to ferrous iron (SCF, 1993).

Gastrointestinal absorption of low doses of vitamin C is efficient, and occurs in the small intestine via a sodium-dependent active transport mechanism. The extent of absorption of vitamin C is 80-90% at the usual intakes from food of 30-180 mg/day (SCF, 1993), but because the transporter is saturable, absorption efficiency gradually decreases at higher intakes (Kallner *et al.*, 1979 and 1985; Hornig and Moser, 1981; Blanchard *et al.*, 1997). There is a non-linear relationship between daily intake of vitamin C and plasma concentrations, with a 5-fold increase in intake from 0.5 g/day to 2.5 g/day producing only a 20% increase in plasma levels (Levine *et al.*, 1996 and 1999). Ascorbyl palmitate is probably hydrolysed in the lumen of the gastrointestinal tract prior to absorption, but data defining the *in vivo* fate of this synthetic form of vitamin C have not been identified.

Ascorbic acid is widely distributed in all tissues of the body, with higher levels found in the adrenal and pituitary glands and the retina, and lower levels in kidney and muscle tissue. Vitamin C can be detected in most tissues and exists as an equilibrium mixture of ascorbic acid and dehydroascorbic acid, dependent on the redox status of the cells. Plasma and urinary vitamin C are not reliable indicators of body stores of vitamin C because they are influenced by recent dietary intake. Leukocytes contain higher concentrations of vitamin C than plasma, blood or serum (Levine *et al.*, 1996), and may provide a more reliable indicator of status. A vitamin C concentration in leukocytes below 0.01 mg per 10^8 cells is generally regarded as indicative of deficiency.

Vitamin C is readily oxidised to dehydroascorbic acid, which can be reduced back to ascorbic acid or hydrolysed to diketogulonic acid and then oxidised to oxalic and threonic acid, xylose, xylonic acid and lyxonic acid (Basu and Dickerson, 1996). Some oxidation to carbon dioxide occurs at high doses, possibly due to metabolism of unabsorbed ascorbate by the intestinal microflora (Kallner *et al.*, 1985). Ascorbic acid may also undergo limited conjugation with sulphate to form ascorbate-2-sulphate, which is excreted in urine. Unchanged ascorbic acid and its metabolites are excreted in the urine. Approximately 3% of a 60 mg oral dose is eliminated in the faeces. At intakes above 80-100 mg/day, most of the additional absorbed vitamin is excreted unchanged in the urine, indicating that tissue reserves are saturated at this intake level (SCF, 1993; FNB, 2000). This increasing renal elimination of ascorbic acid with increase in dose results in an inverse relationship between the elimination half-life and the dosage (Kallner *et al.*, 1979) and probably arises from saturation of reabsorption from renal tubule (Blanchard *et al.*, 1997).

The average daily intakes in European countries are above the reference intake established by the SCF in 1993, with relatively consistent data in different countries (Table 1). The 97.5th percentiles of intake are about 5-6 times the reference intake.

3. HAZARD IDENTIFICATION

3.1 Genotoxicity

The genetic toxicology of ascorbic acid was reviewed by Shamberger (1984) at which time there was evidence for indirect mutagenic effects via the generation of oxidative damage in the presence of transition metals, and also for anti-mutagenic effects in a variety of systems.

Vitamin C would be expected to be anti-mutagenic, because of its antioxidant properties, and there are data consistent with this. For example, ascorbic acid reduces the spontaneous

mutation rate in mismatch repair-defective cells (Glaab *et al.*, 2001), protects against gamma-ray induced damage (Konopacka and Rzeszowska-Wolny, 2001) and reduces the activity of some genotoxic compounds (Blasiak *et al.*, 2001; Nefic, 2001; Rao *et al.*, 2001; Kaya *et al.*, 2002; Chang *et al.*, 2002), including important food-borne mutagens such as patulin (Alves *et al.*, 2000) and toxins such as zearalenone and ochratoxin A (Grosse *et al.*, 1997 - based on a reduction in DNA adducts measured by ^{32}P-post labelling).

Table 1. The daily intakes of vitamin C in EU countries (mg/day)

	Population	N	Method	Supplements	Mean	97.5%
Austria[a]	men + women	2488	24 h recall	Not defined	88	276
Germany[b]	men	854	7-day record	Not defined	70	270
	women	1134		Not defined	83	282
Germany[c]	men	1268	Computer-	-	150	180
	women	1540	assisted	-	151	176
	men	240	dietary	+	168	309
	women	347	interview	+	156	285
Italy[d]	household	2734	7-day record	+	113	268
Ireland[e]	men	662	7-day record	-	81	212
	women	717		-	72	187
	men	662		+	116	588
	women	717		+	108	588
Netherlands[f]	household	5958	2-day record	-	78	204
Sweden[g]	men	1897	8-day record	-	87	201
	women	2223		-	103	224
	men	770		+	151	1056
	women	1655		+	169	1117
UK[h]	men	833	7-day record	-	83 (71)	217
	women	891		-	81 (69)	205
	men	833		+	101 (74)	329
	women	891		+	112 (76)	473

[a] Elmadfa *et al.* (1998)
[b] Heseker *et al.* (1992) - median not mean value
[c] Mensink and Ströbel (1999); Mensink *et al.* (2002) - values are the mean and 75th percentile
[d] Turrini (INRAN)
[e] IUNA (2001)
[f] Hulshof and Kruizinga (1999)
[g] Elmstahl *et al.* (1994) - values are the median and 95th percentile
[h] Henderson *et al.* (2003) - values are the mean (with the median in parentheses)

Although ascorbic acid is an antioxidant via its conversion to dehydroascorbic acid, the reversibility of the reaction can lead to the generation of reactive oxygen species via redox cycling (Ballin *et al.*, 1988; Stadtman, 1991). This may be involved in some positive genotoxic effects reported with vitamin C *in vitro*, such as single strand breaks produced by sodium ascorbate (Singh, 1997), weak sister chromatid exchange (SCE) activity (Galloway and Painter, 1979; Speit *et al.*, 1980; Best and McKenzie, 1988) and activity in the comet assay (Blasiak *et al.*, 2000). Ascorbic acid has been reported to increase the genotoxicity of mitomycin C (Krishnaja and Sharma, 2003), cadmium chloride (Blasiak *et al.*, 2000) and cobalt chloride (Kaya *et al.*, 2002). The results obtained may depend on the concentrations of

vitamin C studied, with protective activity at low concentrations but cytotoxicity and an increase in genotoxic activity at concentrations more than 200 μg/mL (Antunes and Takahashi, 1999). Oral and intraperitoneal doses of up to 10 g/kg in hamsters did not induce SCEs (Speit *et al.*, 1980).

Positive genotoxicity results tended to occur *in vitro* when vitamin C was tested in the presence of metal ions such as iron and copper, which may be related to its reduction of the metal followed by the formation of highly reactive hydroxyl radicals via a Fenton reaction (Carr and Frei, 1999). However, DNA-reactive species can be generated by interaction between vitamin C and lipid hydroperoxide decomposition in the absence of transition metal ions (Lee *et al.*, 2001); the *in vitro* concentrations used in this study were similar to those present in plasma after doses of 200 mg/day, but the toxicological significance of this observation is unclear.

Podmore *et al.* (1998a) reported that the administration of 500 mg/day of vitamin C supplements to 28 human volunteers for 6 weeks caused an increase in 8-oxoadenine but a decrease in 8-oxoguanine in the DNA of isolated lymphocytes measured by gas chromatography-mass spectrometry (GC-MS), possibly due to its pro-oxidant effect. Two letters were published as a consequence of this report, which pointed out that the dosage given would not have increased the intracellular concentrations of ascorbate in lymphocytes, and that the increased oxidation could be an artefact formed by monocytes in the lymphocyte preparation (Levine *et al.*, 1998), that artefacts were not adequately excluded, the study was not a randomised double-blind placebo controlled investigation, and the authors did not give information about smoking habits or cite previous publications (Poulsen *et al.*, 1998). In their reply to these letters, Podmore *et al.* (1998b) provided further support for the validity of their findings and pointed out that because 8-oxoadenine is 10-times less mutagenic than 8-oxoguanine, their results are consistent with an “overall profound protective effect”.

An increase in total damage to lymphocyte DNA bases (but not in 8-hydroxyadenine or 8-hydroxyguanine) was reported in a study in which one group of 20 volunteers who were given 14 mg iron plus either 60 or 260 mg of vitamin C, but not in a second group of 18 subjects who were treated in the same way but had slightly lower pre-treatment plasma levels of ascorbic acid (Rehman *et al.*, 1998). In a subsequent paper by the same research group, treatment of 20 healthy adults with ascorbate (280 mg/day), with or without supplemental iron (14 mg/day), for periods of 6 weeks in a cross-over design showed no significant rise in oxidative DNA damage as measured by GC-MS (Proteggente *et al.*, 2000): significant decreases in 8-oxo-7,8-dihydroguanaine and 5-hydroxymethyl uracil were found during treatment with ascorbate and the authors concluded that there was no compelling evidence of a pro-oxidant effect resulting in DNA damage. *In vivo* administration of 1g vitamin C daily for 42 days to human volunteers did not influence the extent of endogenous DNA damage in peripheral lymphocytes measured using an Elisa technique, but reduced the extent of *ex vivo* peroxide-induced damage (Brennan *et al.*, 2000). The significance of these observations is unclear and currently under further study.

Overall, the data currently available do not allow an adequate evaluation of the genotoxic potential of high intakes of vitamin C, and in particular its capacity to induce gene and chromosomal mutations. The significance of oxidative DNA damage observed *in vitro* or *in vivo* at high concentrations is unclear.

3.2 Animal toxicity data

Vitamin C has low acute toxicity. High doses of vitamin C (100 mg per 160 g animal per day) are associated with decreased growth rates in guinea pigs fed a nutritionally inadequate diet of unfortified wheat flour, but weight gain was not altered if the treated animals were fed a wheat flour diet fortified with casein (Nandi *et al.*, 1973). No effects on reproductive or developmental parameters were found in guinea pigs, rats and hamsters given oral doses of up to 400 mg/kg body weight/day during pregnancy (Alleva *et al.*, 1976) or in rats and mice given up to 1000 mg/kg body weight/day (Frohberg *et al.*, 1973). A conditioned increase in vitamin C requirements has been reported in guinea pigs (Sorensen *et al.*, 1974).

There have been a number of studies in which rats have been given high dietary concentrations of the sodium salt of ascorbic acid and the free acid in relation to the role of sodium ions in the generation of bladder hyperplasia and cancer in male rats. Using a 2-stage model of bladder carcinogenesis, in which male rats were treated with possible promoters of bladder carcinogenesis for 6 weeks, Cohen *et al.* (1991) showed that sodium ascorbate at 5% in the diet (equivalent to about 2500 mg/kg body weight/day) increased the incidence of bladder cancers, but that an equimolar dietary concentration of ascorbic acid (4.44%) was inactive. In a subsequent study in which sodium ascorbate was given in the diet to rats without pre-treatment with a carcinogen, significant increases in simple, papillary and nodular hyperplasia in the urinary bladder were detected in rats fed diets containing 5% or 7% sodium ascorbate, but these effects were abolished by co-treatment with ammonium chloride which acidified the urine (Cohen *et al.*, 1998); there was a small and non-significant increase in the numbers of papillomas and carcinomas in the urinary bladder at dietary levels of 5% (n=1) and 7% (n=2) compared to control (n=0) or 1% dietary level (n=0). In 1993, the JECFA concluded that similar effects produced by the sodium salt of saccharin were related to sodium-induced changes in urine volume, osmolality and pH, and were not relevant to human health (JECFA, 1993).

Dietary administration of ascorbyl palmitate at levels of 2000 ppm and 4000 ppm (equivalent to daily intakes of about 100 and 200 mg/kg body weight per day) to male rats treated with the colon carcinogen azoxymethane caused a significant reduction in the incidence (% of animals with tumours) and the multiplicities of invasive and total adenocarcinomas of the colon (Rao *et al.*, 1995). In contrast, administration of 2% ascorbyl palmitate in the diet of mice (equivalent to daily intakes of about 2000 mg/kg body weight per day) did not attenuate the hyperplastic and dysplastic effects of azoxymethanol in the colon (Huang *et al*., 1992).

3.3 Human data

Despite a number of clinical studies in which high doses of vitamin C (up to 1 g or more per day) have been given, there is a limited database on tolerability or adverse effects. A number of studies with different doses and durations have not reported adverse effects, but it is difficult to determine the significance of these because it is frequently unclear how any adverse effects were investigated (reviewed in Carr and Frei, 1999) (EGVM, 2003). In addition many studies have used a combination of vitamins and minerals, and identifying any effect of vitamin C *per se* is not possible because other parts of the treatment could mask adverse effects.

Adverse effects were not reported in recent studies in which 12 healthy adult volunteers received 500 mg/day for 8 weeks (McArdle *et al.*, 2002), 19 patients with hypertension

received 500 mg/day for 30 days (Duffy *et al.*, 1999), 28 male smokers received 500 mg/day for 4 weeks (Aghdassi *et al.*, 1999), 18 healthy male adults given 2 g/day for 6 weeks (Tofler *et al.*, 2000), 130 healthy adults given 250 mg of slow release vitamin C for 3 years (Salonen *et al.*, 2000), 8 adults received increasing daily doses up to a maximum of 2 g/day for 2 weeks (Johnston and Cox., 2001), 5 adults received 1 g/day for 6 months (Pullin *et al.*, 2002) and 30 adults given daily doses of 500 mg for 6 weeks (Hamilton *et al.*, 2000). Most of these studies had primary endpoints related to a health benefit, and assessment of adverse effects or tolerability was not a part of the study design.

A double-blind, cross-over study on the effects of daily doses of 3 g of vitamin C, combined with very high doses of nicotinamide (3 g), calcium pantothenate (1.2 g) and pyridoxine (0.6 g), in 41 children with attention deficit disorders (Haslam *et al.*, 1984) reported an increase in serum transaminases. However, this cannot be assigned to the vitamin C component, because of the complex megavitamin regimen. There was little information reported on general tolerability, but 3 children did not complete the study because of excessive vomiting, abdominal discomfort or an inability to swallow the vitamin capsules and "some patients experienced nausea and vomiting during the course of treatment".

Vitamin C was administered to 10, 269 adults aged 40-80 with coronary disease at a daily dose of 250 mg/day (in combination with 600 mg vitamin E and 20 mg β-carotene) for up to 5 years. The subjects showed good compliance and there were no significant differences in mortality or morbidity compared with a placebo group of equal size (Heart Protection Study, 2002). No effects on inflammatory markers were reported in a recent long-term multi-vitamin study (Bruunsgaard *et al.*, 2003) in which 52 men aged 47-70 were treated for 3 years with a combination of 500 mg vitamin C and 182 mg of α-tocopherol daily, but it is unclear to what extent other effects, such as gastrointestinal problems, would have been recorded.

A retrospective cohort study of 994 women, of whom 277 were regular users of vitamin C supplements for up to 12 years, reported a significant increase in bone mineral density of the neck of the femur; no side effects were reported but no parameters other than bone mineral density were assessed (Morton *et al.*, 2001).

Adverse effect data were not reported in a 4-year double-blind, placebo-controlled study in which patients with a history of adenoma of the large bowel were given vitamin C (1 g/day) with either vitamin E (205 patients) or vitamin E plus β-carotene (175 patients) (Greenberg *et al.*, 1994). Adherence to the prescribed regimen, and information about symptoms, illnesses and hospitalisations were assessed every 6 months. The numbers of patients who withdrew from the study were similar in all groups, but 4 subjects in the two vitamin C treatment groups "stopped taking the medications because of their presumed toxicity"; no other information was provided and tolerability during the study was not reported.

No subjective side effects were reported in the study of Cook *et al.* (1984) in which 17 adults were given 2 g/day with meals for 16 weeks.

No adverse effects were reported in a randomised, double-blind, placebo-controlled study in which 21 patients with coronary artery disease were given a single dose of 2 g vitamin C followed by 500 mg/day for 30 days (Gokce *et al.*, 1999).

3.3.1. Gastrointestinal effects

Gastrointestinal effects are the most common adverse clinical events associated with acute, high doses of vitamin C (above 1 g daily), but these can be reduced by taking the vitamin after meals (reviewed in Miller and Hayes, 1982). The incidences of stomach pains, nausea and diarrhoea in children given 1 g/day for 3 months were similar to those in the control groups (Ludvigsson *et al.*, 1977). Abdominal distension, flatulence, diarrhoea and transient colic were reported as "fairly frequent" in a study in healthy human volunteers given daily doses which increased by 1000 mg per day each week, with adverse effects reported at doses of 3-4 g/day, although no details were given of the exact dosing regimen or the numbers of subjects studied or their age, sex or body weight (Cameron and Campbell, 1974). Two out of 15 volunteers experienced diarrhoea when consuming 10 g of vitamin C daily for 5 days in a clinical study on oxalate excretion, despite the fact that the subjects were advised to take the vitamin C tablets at mealtimes to minimise the potential for adverse gastrointestinal effects (Wandzilak *et al.*, 1994).

3.3.2 Renal effects

Adverse effects related to the renal system have been reported, including renal stones, renal tubular disease and oxaluria. Vitamin C consumption has been suggested to increase oxalate excretion and the risk of urinary stone formation, but the available data are both confusing and contradictory. An early report stated that there could be wide inter-subject differences in the excretion of oxalate following high doses of vitamin C (Briggs, 1976). An additional problem is that urinary oxalate can be produced from urinary ascorbic acid as an artefact of the analytical procedure, so that the validity of the analytical data depends on the extent to which this was controlled by the use of preservatives. Increased oxalate excretion would represent a risk factor for the formation of bladder stones, and there have been anecdotal case reports of kidney stones or other nephropathy (Nakamoto *et al.*, 1998) in patients who have taken high daily doses of vitamin C.

Groups of 3 patients who had unilateral nephrostomy tubes after lithotripsy for renal stones were given supplemental doses of 100, 500, 1000, or 2000 mg ascorbic acid on days 2 and 3 postoperatively (Urivetzky *et al.*, 1992). Urine specimens were collected from the nephrostomy catheter and also from the contralateral kidney directly into EDTA and sodium thimerosol preservative to stabilise ascorbic acid and oxalate; oxalate was measured following the removal of ascorbic acid with sodium nitrite. There was a statistically significant increase in urinary oxalate at doses of 1000 and 2000 mg. The authors estimated that there was a 6-13 mg/day increase in urinary oxalate excretion per 1000 mg/day ascorbic acid intake, and concluded that there was an increased risk of calcium oxalate renal stones.

Urinary excretion of oxalate was measured in 15 volunteers given ascorbic acid supplementation (1, 5 and 10 g/day for 5 days in a cross-over design) (Wandzilak *et al.*, 1994). The 24-hour urine samples were preserved by reducing the pH to 2 by adding 20 mL of concentrated hydrochloric acid. Ascorbate was reported to be converted non-enzymatically into oxalate during analytical measurement. The study did not find an increase in urinary oxalate excretion after *ex vivo* non-enzymatic conversion of ascorbate to oxalate had been taken into account.

Supplemental vitamin C intakes of 1 g/day in 7 volunteers caused statistically significant increases in urinary excretion of oxalate (determined by an enzymatic method reported to be

free from interference by ascorbic acid) (Levine *et al.*, 1996). An increase in urinary oxalate excretion, measured by an enzymatic assay on urine collections stabilised with acid, was also reported in 6 subjects given 1 g of supplemental ascorbate with 2.85 litres of orange juice containing 0.62 g of ascorbate daily for 4 days, but not in the same subject given 2 g of ascorbate per day for 4 days (Liebman *et al.*, 1997).

Auer *et al.* (1998a) investigated the urinary excretion of oxalate in the presence and absence of EDTA preservation of the urine samples in 10 healthy male volunteers (with no history of stone formation) given 4 g of vitamin C daily for 5 days. Erroneously high oxalate concentrations were found in the absence, but not in the presence of EDTA. There was no significant increase in oxalate excretion at any stage of the protocol in EDTA preserved samples and it was concluded that large doses of vitamin C did not affect the principal risk factors associated with calcium oxalate kidney stone formation. In contrast, the same authors (Auer *et al.*, 1998b) reported increased excretion of oxalate in EDTA treated urine samples from a single volunteer who took 8 g daily for a period of 8 days, at which time the study was terminated because of the detection of haematuria, which was associated with crystalluria.

A prospective study on the relationship between vitamin C intake and the risk of symptomatic kidney stones in a group of 45,251 men (Curhan *et al.*, 1996) found no association with vitamin C intake in 751 cases of kidney stones. The age-adjusted relative risk for subjects with intakes of 1.5 g/day or more compared with less than 0.25g/day was 0.78 (95% confidence intervals 0.54-1.11), indicating that even if such doses do increase oxalate excretion, it is not a clinically significant effect. A similar study in a cohort of 85,557 women in whom there were 1078 incidences of kidney stones showed a relative risk of 1.06 (95% confidence intervals 0.69-1.64) for subjects with intakes of 1.5 g/day or more compared with less than 0.25 g/day (Curhan *et al.*, 1999).

No significant relationships were found in an analysis of data from 5214 men and 5785 women between serum vitamin C concentrations and the prevalence of kidney stones, serum vitamin B_{12} levels, or serum ferritin levels in men, but a negative correlation with serum ferritin was found for women (Simon and Hudes, 1999).

Increased excretion of uric acid has also been reported after the ingestion of 4 g or 8 g of ascorbic acid (Stein *et al.*, 1976); although the available data at lower doses are limited and conflicting, in all studies hyperuricosuria was absent at doses of less than 1 g (Levine *et al.*, 1999).

3.3.3 Other effects

Other anecdotally reported adverse effects include metabolic acidosis and changes in prothrombin activity, but a double-blind trial in patients given 200 mg/day showed no significant effect on the incidence of thrombotic episodes (Hornig and Moser, 1981).

A low incidence of adverse effects was reported during a study in patients with multiple sclerosis who were randomised to receive either supplements providing 2 g/day vitamin C, together with 6 mg/day sodium selenite and 480 mg/day vitamin E, or placebo for 5 weeks. The patients were interviewed about side effects after 2 weeks and 4 weeks of treatment. One out of the 10 patients receiving the active supplement reported slight facial erythema at week 2, which subsequently subsided during continued treatment, one reported a peculiar urine smell and another reported an increased number of headaches; three of the 10 patients

receiving the placebo reported an increased number of headaches (Mai *et al.*, 1990). It cannot be determined from the data whether these were caused by the high doses of vitamin C or by the other constituents.

There is a suggestion in the literature of conditioned need-scurvy, in which scurvy-like symptoms occur soon after cessation of ingestion of high amounts of vitamin C (1 g or more per day) (Siegel *et al.*, 1982). High intakes during pregnancy may result in neonatal scurvy by conditioning the offspring to require greater than the expected or recommended daily intakes, but the evidence for this is very limited (Cochrane, 1965). The reports of conditioned scurvy in humans are anecdotal and it does not represent a significant risk (Hornig and Moser, 1981).

Vitamin C increases iron uptake considerably from the gut when given to humans in single-meal studies in amounts from 25 to 1000 mg (Hallberg, 1985; Cook and Monsen, 1977). Studies of longer duration show a less marked effect (Hunt and Roughead, 2000), but even a small increase could be important in subjects with conditions such as haemochromatosis (Gerster, 1999) or in subjects heterozygous for this condition. A dose of 2 g/day vitamin C taken with meals for 16 weeks in 17 healthy volunteers, and up to 24 months in 9 subjects, had no significant effect on body iron stores (Cook *et al.*, 1984); this study was limited by the small numbers of participants and their variable iron status.

Large amounts of vitamin C were reported to destroy the vitamin B_{12} content of food (Herbert and Jacob, 1974), and reduced vitamin B_{12} levels in serum were reported in 3 out of 90 individuals consuming more than 1000 mg/day of vitamin C over a minimum of 3 years (Hind, 1975). However, subsequent reports showed that these observations arose from inadequate assay methods (Newmark *et al.*, 1976 and 1979), and that ascorbic acid in blood can interfere with the measurement of vitamin B_{12} (Herbert *et al.*, 1978).

An increase in serum cholesterol was reported in 25 patients with atherosclerosis following treatment with 1 g vitamin C daily for 6 weeks, but not in healthy volunteers (Spittle, 1971); the authors suggested that this may have arisen due to mobilisation of arterial cholesterol deposits (which would be a benefit), but there was no direct evidence to support this. In contrast, a 10% decrease in total plasma cholesterol levels, but with no change in the cholesterol/HDL ratio, was reported in 18 healthy adult males given 2 g vitamin C daily for 6 weeks (Tofler *et al.*, 2000).

There is conflicting evidence about the relationship between vitamin C intake and breast cancer. A prospective study in a large cohort (n=62,573) of postmenopausal women had found a lower risk of breast cancer in women with the highest intakes of vitamin C from food, but not from supplements (Verhoeven *et al.*, 1997). However a recent nested case-control study found an increased risk of breast cancer among a cohort of postmenopausal Danish women (Nissen *et al.*, 2003). A significantly increased risk was observed at intakes above 300 mg/day in comparison with intakes 60-150 mg/day. The numbers of cases and controls in the high-intake comparison were 62 and 41, respectively. When women who were taking supplemental vitamin C were excluded, the association between increasing vitamin C intake and breast cancer was weaker and no longer statistically significant.

In conclusion, the effects of vitamin C on cholesterol levels, conditioned need due to high intake, iron absorption, prothrombin time and vitamin B_{12} degradation, breast cancer and the possible pro-oxidant activity of vitamin C are not sufficiently well documented or substantiated to be used as the basis for risk assessment. There have been conflicting reports

on the influence of vitamin C supplements on the presence of oxidised bases in DNA (Podmore *et al.*, 1998; Rehman *et al.*, 1998; Proteggente *et al.*, 2000). These have been performed at relatively low doses (280 mg/day, 60 or 260 mg/day and 500 mg/day for 6 weeks respectively), and there are no data currently available at higher intakes.

4. DOSE-RESPONSE ASSESSMENT

Adequate data defining the dose-response relationships for each adverse effect described above are not available, because many studies used a single dose level only. Despite the extensive use of vitamin C supplements (up to 10 g/day) for the prevention of colds and other conditions, the tolerability of such intakes has not been subject to systematic assessment. Therefore there are few data to support the widely held view that high intakes of vitamin C are safe.

There have been a small number of studies that have investigated dose-response relationships in a controlled and scientific manner.

4.1 Gastrointestinal effects

Two out of 15 volunteers experienced diarrhoea when consuming 10 g of vitamin C daily for 5 days (Wandzilak *et al.*, 1994). In a study in healthy human volunteers given increasing doses of vitamin C, abdominal distension, flatulence, diarrhoea and transient colic were reported as “fairly frequent” at doses of 3-4 g daily (Cameron and Campbell, 1974). Lower intakes appear to be tolerated without gastrointestinal effects since no subjective side effects were reported in 17 adults given 2 g/day for 16 weeks (Cook *et al.*, 1984). The Miller and Hayes (1982) review concluded that doses greater than 1 g/day could result in adverse gastrointestinal effects. The data of Ludvigsson *et al.* (1977) indicate that 1 g/day would not produce adverse gastrointestinal effects in children.

4.2 Renal effects

A review of the early investigational studies on the relationship between ascorbic acid intake and oxalate excretion (Hornig and Moser, 1981) concluded that there were methodological problems with many of the studies.

A statistically significant increase in urinary oxalate excretion was reported in groups of 3 patients with calcium oxalate renal stones given 1 g or 2 g of supplemental ascorbic acid daily. Precautions were taken to prevent artefactual formation of oxalic acid by collection of intrarenal urine specimens from a catheter into EDTA and sodium thimerosol preservative (Urivetzky *et al.*, 1992).

The more extensive cross-over study by Wandzilak *et al.* (1994) in which 15 subjects were given 1000, 5000 and 10,000 mg vitamin C each for 5 days reported no increase in oxalate excretion after correction for non-enzymatic *ex vivo* formation. However the data are difficult to interpret because of the highly acidic preservative used.

The two studies by Auer *et al.* (1998a and b) indicate no increase in the urinary excretion of oxalate in 10 healthy male volunteers (with no history of stone formation) given 4 g of

vitamin C daily for 5 days, but a marked increase associated with haematuria and crystalluria in a single individual who took 8 g daily for a period of 8 days.

In summary, one study reported that high intakes of vitamin C (1 or 2 g per day) increased the urinary excretion of oxalic acid in patients with renal stones, but this was not found in studies in healthy volunteers. Data from the cohort studies (Curhan *et al.*, 1996 and 1999) show that intakes of 1.5 g/day do not increase the risk of kidney stone formation.

CONCLUSIONS AND RECOMMENDATIONS

1. DERIVATION OF A TOLERABLE UPPER INTAKE LEVEL (UL)

The vitamin is of low acute toxicity as indicated by the limited data available from studies in animals and humans. Despite the extensive use of high doses of vitamin C in some vitamin supplements, there have been few controlled studies that specifically investigated adverse effects. Based on the limited data, acute gastrointestinal intolerance is the most clearly defined adverse effect at high intakes, but there are limited data on the dose-response relationship for adults or for groups such as children or the elderly. There are insufficient data to establish a tolerable upper intake level for vitamin C.

2. RISK CHARACTERISATION

The available human data suggest that supplemental daily doses of vitamin C up to about 1 g in addition to normal dietary intakes are not associated with adverse gastrointestinal effects, but that acute gastrointestinal effects may occur at higher intakes (3-4 g/day). While there is uncertainty whether high intakes of vitamin C increase renal excretion of oxalate, which could increase the risk of renal stones, an increased risk of kidney stones was not found in individuals with habitual intakes of 1.5 g/day. The absorption of vitamin C is saturated at high doses, and therefore intakes above 1 g/day would be associated with negligible increased uptake and tissue levels, but an increased risk of adverse gastrointestinal effects. There are no data on the gastrointestinal absorption or tolerability of esterified forms of vitamin C, such as ascorbyl palmitate, but such esters might be expected to show similar properties, and therefore this conclusion applies to these forms as well as ascorbic acid and its salts.

The average daily intakes reported in surveys in European countries (Table 1) are above the Population Reference Intake, with the 95th percentile intake from food and supplements ranging up to about 1 g/day. These dietary intakes do not represent a cause for concern.

There has not been a systematic assessment of the safety of the long-term use of high dose vitamin C supplements.

3. RECOMMENDATIONS FOR FURTHER WORK

Any future studies on possible benefits of high intakes of vitamin C should investigate the nature and incidence of adverse effects. Very few data are available on esterified forms of vitamin C, such as ascorbyl palmitate, and these forms should be included in future studies.

The potential for vitamin C to induce gene or chromosomal mutations *in vivo* in humans at high doses (1 g or more) should be investigated especially pro-oxidant effects on DNA bases, using sensitive methods, because there are inadequate data to ensure the safety of long-term high-dose intakes.

Subgroups of the population at increased risk have not been investigated; individuals who are predisposed to gastrointestinal problems, kidney stones or who are unable to regulate iron absorption, due to haemochromatosis or thalassaemia, should be included in future studies on the possible beneficial and adverse effects of vitamin C.

The conflicting evidence about vitamin C intake and breast cancer is noted and no conclusion is possible at this time. The possible association warrants further research to clarify any relationship for both dietary sources and vitamin C supplements.

REFERENCES

Aghdassi E, Royall D, Allard JP (1999). Oxidative stress in smokers supplemented with vitamin C. Int J Vit Nutr Res 69: 45-51.

Alleva FR, Alleva JJ, Balazs T (1976). Effect of large doses of ascorbic acid on pregnancy in guinea pigs, rats and hamsters. Toxicol Appl Pharmacol 35: 393-395.

Alves I, Oliveira NG, Laires A, Rodrigues AS, Rueff J (2000). Induction of micronuclei and chromosomal aberrations by the mycotoxin patulin in mammalian cells: role of ascorbic acid as a modulator of patulin clastogenicity. Mutagenesis 15: 229-234.

Antunes LM and Takahashi CS (1999). Protection and induction of chromosomal damage by vitamin C in human lymphocyte cultures. Teratog Carcinog Mutagen 19: 53-59.

Auer BL, Auer D, Rodgers AL (1998a). The effect of ascorbic acid ingestion on the biochemical and physiochemical risk factors associated with calcium oxalate kidney stone formation. Clin Chem Lab Med 36: 143-148.

Auer BL, Rodgers AL, Auer D (1998b). Relative hyperoxaluria, crystalluria and haematuria after megadose ingestion of vitamin C. Eur J Clin Invest 28: 1695-700.

Ballin A, Brown EJ, Koren G, Zipursky A (1988). Vitamin C-induced erythrocyte damage in premature infants. J Pediatr 113: 114-120.

Basu TK and Dickerson JWT (1996). Vitamin C (Ascorbic Acid). In Vitamins in Health and Disease. Cab International, Oxford, UK, pp 125-147.

Best RG and McKenzie WH (1988). Sister chromatid exchange in human lymphocytes exposed to ascorbic acid and the cancer chemotherapeutic agent 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea. Teratog Carcinog Mutagen 8: 339-346.

Blanchard J, Tozer TN, Rowland M (1997). Pharmacokinetic perspectives on megadoses of ascorbic acid. Am J Clin Nutr 66: 1165-1171.

Blasiak J and Kowalik J (2001). Protective action of vitamin C against DNA damage induced by selenium-cisplatin conjugate. Acta Biochim Pol 48: 233-240.

Blasiak J, Trzeciak A, Dziki A, Ulanska J, Pander B (2000). Synergistic effect of vitamin C on DNA damage induced by cadmium. Gen Physiol Biophys 19: 373-379.

Brennan LA, Morris GM, Wasson GR, Hannigan BM, Barnett YA (2000). The effect of vitamin C or vitamin E supplementation on basal and H_2O_2-induced DNA damage in human lymphocytes. Br J Nutr 84: 195-202.

Briggs M (1976). Vitamin-C-induced hyperoxaluria. The Lancet: January 17th 1976: 154.

Bruunsgaard H, Poulsen HE, Pedersen BK, Nyyssonen K, Kaikkonen J, Salonen JT (2003). Long-term combined supplementations with α-tocopherol and vitamin C have no detectable anti-inflammatory effects in healthy men. J Nutr 133: 1170-1173.

Cameron E and Campbell A (1974). The ortho-molecular treatment of cancer. II. Clinical trial of high dose ascorbic acid supplements in advanced human cancer. Chem Biol Interact 9: 285-315.

Carr AC and Frei B (1999) Toward a new recommended dietary allowance for vitamin C based on antioxidant and health effects in humans. Am J Clin Nutr 69: 1086-1107.

Chang MC, Ho YS, Lee JJ, Kok SH, Hahn LJ, Jeng JH (2002). Prevention of the areca nut extract-induced unscheduled DNA synthesis of gingival keratinocytes by vitamin C and thiol compounds. Oral Oncol 38: 258-265.

Cochrane WA (1965). Overnutrition in prenatal and neonatal life: A problem? J Can Med Assoc 93: 893-899

Cohen SM, Ellwein LB, Okamura T, Masui T, Johansson SL, Smith RA, Wehner JM, Khachab M, Chappel CI and Schoenig GP (1991). Comparative bladder tumor promoting activity of sodium saccharin, sodium ascorbate, related acids, and calcium salts in rats. Cancer Res 51: 1766-1777.

Cohen SM, Anderson TA, de Oliveira LM, Arnold LL (1998). Tumorigenicity of sodium ascorbate in male rats. Cancer Res 58: 2557-2561.

Cook JD and Monsen ER (1977). Vitamin C, the common cold, and iron absorption. Am J Clin Nutr 30: 235-241.

Cook JD, Watson SS, Simpson KM, Lipschitz DA, Skikne BS (1984). The effect of high ascorbic acid supplementation on body iron stores. Blood 64: 721-726.

Curhan GC, Willett WC, Speizer FE, Stampfer MJ (1999). Intakes of vitamins B6 and C and the risk of kidney stones in women. Am Soc Nephrol 10: 840-845.

Curhan GC, Willett WC, Rimm EB, Stampfer MJ (1996). A prospective study of the intake of vitamins C and B6, and risk of kidney stones in men. J Urol 155: 1847-1851.

Duffy SJ, Gokce N, Hlbrook M, Huang A, Frei B, Keaney, Jf, Vita JA (1999). Treatment of hypertension with ascorbic acid. The Lancet 354: 2048 -2049.

Elmadfa I, Burger P, Derndorfer E, Kiefer I, Kunze M, König J, Leimüller G, Manafi M, Mecl M, Papathanasiou V, Rust P, Vojir F, Wagner K-H, Zarfl B (1998). Austrian Study on Nutritional Status (ASNS). Österreichischer Ernährungsbericht. Bundesministerium für Gesundheit, Arbeit und Soziales. Wien 1999.

Elmstahl S, Wallstrom P, Berglund G, Janzon L, Johansson U, Larsson SA, Mattison I (1994). The use of dietary supplements in relation to dietary habits in a Swedish middle-aged population. Scand J Nutr 38: 94-97.

EGVM (Expert Group on Vitamins and Minerals) (2003). Report on safe upper levels for vitamins and minerals. London. May 2003. Available on the Internet at: http://www.foodstandards.gov.uk/multimedia/pdfs/vitmin2003.pdf

FNB (Food and Nutrition Board) (2000). Dietary Reference Intakes for vitamin C, vitamin E, selenium, and carotenoids. Institute of Medicine. National Academy Press, Washington D.C., USA.

Frohberg VH, Gleich J, Kieser H (1973). Reproduktionstoxikologische studien mit ascorbinsäure and mässen und ratten. Arzneim Forschung 23: 1081-1082.

Galloway SM and Painter RB (1979). Vitamin C is positive in the DNA synthesis inhibition and sister-chromatid exchange tests. Mutat Res 60: 321-327.

Gerster H (1999). High-dose vitamin C: A risk for persons with high iron stores? Int J Vit Nutr Res 69: 67-82.

Glaab WE, Hill RB, Skopek TR (2001). Suppression of spontaneous and hydrogen peroxide-induced mutagenesis by the antioxidant ascorbate in mismatch repair-deficient human colon cancer cells. Carcinogenesis 22: 1709-1713.

Gokce N, Keaney JF Jr, Frei B, Holbrook M, Olesiak M, Zachariah BJ, Leeuwenburgh C, Heinecke JW, Vita JA (1999). Long-term ascorbic acid administration reverses endothelial vasomotor dysfunction in patients with coronary artery disease. Circulation 99: 3234-3240.

Greenberg ER, Baron JA, Tosteson TD, Freeman DH, Beck GJ, Bond JH, Colacchio TA, Coller JA, Frankl HD, Haile RW, Mandel JS, Nierenberg DW, Rothstein R, Snover DC, Stevens MM, Summers RW, van Stolk RU (1994). A clinical trial of antioxidant vitamins to prevent colorectal adenoma. New Engl Med J 331: 141-147.

Grosse Y, Chekir-Ghedira L, Huc A, Obrecht-Pflumio S, Dirheimer G, Bacha H, Pfohl-Leszkowicz A (1997). Retinol, ascorbic acid and alpha-tocopherol prevent DNA adduct formation in mice treated with the mycotoxins ochratoxin A and zearalenone. Cancer Lett 114: 225-229.

Hallberg L (1985). The role of vitamin C in improving the critical iron balance situation in women. Int J Vitam Nutr Res 27: 177-187.

Hamilton IMJ, Gilmore WS, Benzie IFF, Mulholland CW, Strain JJ (2000). Interactions between vitamins C and E in human subjects. Br J Nutr 84: 261-267.

Haslam RHA, Dalby JT, Rademaker AW (1984). Efects of megavitamin therapy on children with attention deficit disorders. Pediatrics 74: 103-111.

Heart Protection Study (2002). MRC/BHF Heart Protection Study of antioxidant vitamin supplementation in 20536 high-risk individuals: a randomised placebo-controlled trial. The Lancet 360: 23-33.

Henderson L, Irving K, Gregory J (2003). The National Diet and Nutrition Survey: adults aged 19 to 64 years. Her majesty's Stationery Office, Norwich, UK.

Herbert V and Jacob E (1974). Destruction of vitamin B12 by ascorbic acid. JAMA 230:241-242.

Herbert V, Jacob E, Wong KTJ, Scott J, Pfeffer RD (1978). Low serum vitamin B12 levels in patients receiving ascorbic acid in megadoses: Studies concerning the effect of ascorbate on radioisotope vitamin B12 assay. Am J Clin Nutr 31: 253-258.

Heseker H, Adolf T, Eberhardt W, Hartmann S, Herwig A, Kübler W, Matiaske B, Moch KJ, Nitsche A, Schneider R, Zipp A (1994). Lebensmittel- und Nährstoffaufnahme Erwachsener in der Bundesrepublik Deutschland. VERA- Schriftenreihe Band III, Wiss. Fachverlag Dr. Fleck, Niederkleen.

Hind JD (1975). Ascobic acid and vitamin B12 deficiency. JAMA 234: 24.

Hornig DH and Moser U (1981). The safety of high vitamin C intakes in man. In Vitamin C (ascorbic acid). Ed Counsell JN and Hornig DH. New Jersey Applied Science Publishers, pp. 225-248.

Huang MT, Deschner EE, Newmark HL, Wang ZY, Ferraro TA, Conney AH (1992). Effect of dietary curcumin and ascorbyl palmitate on azoxymethanol-induced colonic epithelial cell proliferation and focal areas of dysplasia. Cancer Lett 64: 117-21.

Hulshof KFAM and Kruizinga AG (1999). TNO Report 99.516, Zeist, The Netherlands.

Kallner A, Hartmann D, Hornig D (1977). On the absorption of ascorbic acid in man. Int J Vit Nutr Res 47: 383-388.

IUNA (Irish Universities Nutrition Alliance) (2001). The North-South Ireland Food Consumption Survey, Food Safety Promotion Board, Dublin. http://www.iuna.net

JECFA (1993). Evaluation of certain food additives and contaminants. Forty-first report of the Joint FAO/WHO Expert Committee on Food Additives. WHO Technical Report Series, 837. World Health Organisation, Geneva. (http://whqlibdoc.who.int/trs/WHO_TRS_837.pdf)

Johnston CS and Cox SK (2001). Plasma-saturating intakes of vitamin C confer maximal antioxidant protection to plasma. J Am College Nutr 20: 623-627.

Kallner A, Hartmann D, Hornig D (1979). Steady-state turnover and body pool of ascorbic acid in man. Am J Clin Nutr 32: 530-539.

Kallner A, Hornig D, Pellika R (1985). Formation of carbon dioxide from ascorbate in man. Am J Clin Nutr 41: 609-613.

Kaya B, Creus A, Velazquez A, Yanikoglu A, Marcos R (2002). Genotoxicity is modulated by ascorbic acid. Studies using the wing spot test in Drosophila. Mutat Res 520: 93-101.

Konopacka M and Rzeszowska-Wolny J (2001). Antioxidant vitamins C, E and beta-carotene reduce DNA damage before as well as after gamma-ray irradiation of human lymphocytes in vitro. Mutat Res 491: 1-7.

Krishnaja AP and Sharma NK (2003). Ascorbic acid potentiates mitomycin C-induced micronuclei and sister chromatid exchanges in human peripheral blood lymphocytes in vitro. Teratog Carcinog Mutagen 23 (Suppl 1): 99-112.

Lee SH, Oe T, Blair IA (2001). Vitamin C-induced decomposition of lipid hydroperoxides to endogenous genotoxins. Science 292: 2083-2086.

Levine, M. Conry-cantilena, C. Wang, Y. Welch RW, Washko PW, Dhariwal KR, Park JB, Lazarev A, Graumlich JF, King J, Cantilena LR. (1996). Vitamin C pharmacokinetics in healthy volunteers. Proceedings of the National Academy of Sciences 93: 3704-3709.

Levine M, Rumsey SC, Daruwala R, Park JB, Wang Y (1999). Criteria and Recommendations for Vitamin C Intake. J Am Med Assoc 281: 1415-1423.

Levine M, Daruwala RC, Park JB, Rumsey SC, Wang Y, (1998). Does vitamin C have a pro-oxidant effect? Letter. Nature 395: 231.

Liebman M, Chai W, Harvey E, Boenisch L (1997). Effect of supplemental ascorbate and orange juice on urinary oxalate. Nutr Res 17: 415-425.

Ludwigsson J, Hansson LO, Tibbling G (1977). Vitamin C as a preventive medicine against common colds in children. Scand J Infect Dis 9: 91-98.

Mai J, Sorensen PS, Hansen JC (1990). High dose antioxidant supplementation to MS patients. Effects on glutathione peroxidase, clinical safety, and absorption of selenium. Biol Trace Element Res 24: 109-117.

McArdle F, Rhodes LE, Parslew R, Jack CIA, Friedmann PS, Jackson MJ (2002). UVR-Induced oxidative stress in human skin in vivo: effects of oral vitamin C supplementation. Free Radical Biol and Med 33: 1355-1362.

Mensink GBM and Ströbel A (1999). Einnahme von Nahrungsergänzungspräparaten und Ernährungsverhalten. Gesundheitswesen 61; S132-S137.

Mensink G, Burger M, Beitz R, Henschel Y, Hintzpeter B (2002) Was essen wir heute? Ernaehrungsverhalten in Deutschland. Beitraege zur Gesundheitsberichterstattung des Bundes. Robert Koch-Institut, Berlin.

Miller DR and Hayes KC (1982).Vitamin excess and toxicity. Nutr Toxicol 1: 81-133.

Morton DJ, Barrett-Connor EL, Schneider DL. Vitamin C supplement use and bone mineral density in postmenopausal women. J Bone Mineral Res 16: 135-140.

Nandi BK, Majumder AK, Suramanian N, Chatterjee IB (1973). Effects of large doses of vitamin C in guinea pigs and rats. J Nutr 103: 1688-1695.

Nakamoto Y, Motohashi S, Kasahara H, Numazawa K (1998). Irreversible tubulointerstitial nephropathy associated with prolonged massive intake of vitamin C. Nephrol Dial Transplant 13: 754-756.

Nefic H (2001). Anticlastogenic effect of Vitamin C on cisplatin induced chromosome aberrations in human lymphocyte cultures. Mutat Res 498: 89-98.

Newmark HL, Scheiner J, Marcus M, Prabhudesai M (1976). Stability of vitamin B12 in the presence of ascorbic acid. Am J Clin Nutr 29: 645-649.

Newmark HL, Scheiner JM, Marcus M, Prabhudesai M (1979). Ascorbic acid and vitamin B12. JAMA 242: 2319-2320.

Podmore ID, Griffiths HR, Herbert KE, Mistry N, Mistry P, Lunec J (1998a). Vitamin C exhibits pro-oxidant properties. Nature 392: 559.

Podmore ID, Griffiths HR, Herbert KE, Mistry N, Mistry P, Lunec J (1998b). Podmore *et al.*, reply. Nature 395: 232.

Poulsen HE, Weimann A, Salonen JT, Nyyssonen K, Loft S, Cadet J, Douki T, Ravanat J-L (1998). Does vitamin C have a pro-oxidant effect? Letter. Nature 395: 231-232.

Proteggente AR, Rehman A, Halliwell B, Rice-Evans CA (2000). Potential problems of ascorbate and iron supplementation: Pro-oxidant effect in vivo? Biochem Biophys Res Commun 277: 535-540.

Pullin CH, Bonham JR, McDowell IFW, Lee PJ, Powers HJ, Wilson JF, Lewis MJ, Moat SJ (2002). Vitamin C therapy ameliorates vascular endothelial dysfunction in treated patients with homocystinuria. J Inherit Metab Dis 25:107-118.

Rao CV, Rivenson A, Kelloff GJ, Reddy BS (1995). Chemoprevention of azoxymethane-induced colon cancer by ascorbylpalmitate, carbenoxolone, dimethylfumarate and p-methoxyphenol in male F344 rats. Anticancer Res. 15:1199-204.

Rao MV, Chinoy NJ, Suthar MB, Rajvanshi MI (2001). Role of ascorbic acid on mercuric chloride-induced genotoxicity in human blood cultures. Toxicol In Vitro 15: 649-654.

Rehman A, Collis CS, Yang M, Kelly M, Diplock AT, Halliwell B, Rice-Evans C (1998). The effects of iron and vitamin C co-supplementation on oxidative damage to DNA in healthy volunteers. Biochem Biophys Res Coomun 246: 293-298.

Salonen JT, Nyyssonen K, Salonen R, Lakka HM, Kaikkonen J, Porkkala-Sarataho E,

Voutilainen S, Lakka TA, Rissanen T, Leskinen L, Tuomainen TP, Valkonen VP, Ristonmaa U, Poulsen HE (2000). Antioxidant supplementation in atherosclerosis prevention (ASAP) study: a randomised trial of the effect of vitamins E and C on 3-year progression of carotid atherosclerosis. J Intern Med 248: 377-386.

SCF (Scientific Committee for Food) (1993). Nutrient and energy intakes for the European Community. Reports of the Scientific Committee for Food (Thirty-first series). European Commission, Luxembourg.

Shamberger RJ (1984). Genetic toxicology of ascorbic acid. Mutat Res 133: 135-159.

Siegel C, Barker B, Kundstadter M (1982). Conditioned oral scurvy due to megavitamin C withdrawal. J Periodontol 53: 453-455.

Simon JA and Hudes ES (1999). Relation of serum ascorbic acid to serum vitamin B12, serum ferritin and kidney stones in US adults. Arch Intern Med 159: 619-624.

Singh NP (1997). Sodium ascorbate induces DNA single-strand breaks in human cells in vitro. Mutat Res 375: 195-203.

Sorensen DI, Devine MM, Rivers JM (1974). Catabolism and tissue levels of ascorbic acid following long-term massive doses in the guinea pig. J Nutr: 104, 1041-1048.

Speit G, Wolf M, Vogel W (1980). The SCE-inducing capacity of vitamin C: Investigations in vitro and in vivo. Mut Res 78: 273-278.

Spittle CR (1971). Atherosclerosis and vitamin C. Lancet Dec 11th, 1280-1281.

Stadtman ER (1991). Ascorbic acid and oxidative inactivation of proteins. Am J Clin Nutr 54: 1125S-1128S.

Stein HB, Hasan A, Fox IH (1976). Ascorbic acid induced uricosuria: a consequence of megavitamin therapy. Ann Intern Med 84: 385-388.

Tofler GH, Stec JJ, Stubbe I, Beadle J, Feng D, Lipinska I, Taylor A (2000). The effect of vitamin C supplementation on coagulability and lipid levels in healthy male subjects. Thrombosis Res 100: 35-41.

Turrini A. National Survey 1994-1996. INRAN, Rome.

Urivetsky M, Kessaris D and Smith AD (1992). Ascorbic acid overdosing: a risk for calcium oxalate nephrolithiasis. J Urol 147: 1215-1218.

Verhoeven DT, Assen N, Goldbohm RA, Dorant E, van 't Veer P, Sturmans F, Hermus RJ, van den Brandt PA (1997). Vitamins C and E, retinol, beta-carotene and dietary fibre in relation to breast cancer risk: a prospective cohort study. Br J Cancer 75: 149-155.

Wandzilak TR, D'Andre SD, Davis PA, Williams HE (1994). Effect of high dose vitamin C on urinary oxalate levels. J Urol 151: 834-837.

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ACKNOWLEDGEMENT

The Scientific Panel on Dietetic Products, Nutrition and Allergies wishes to thank Jan Alexander, Angelo Carere, Werner Grunow, Andrew Renwick and Gerrit Speijers for their contributions to the draft opinion.